FINAL REPORT ON THE SAFETY ASSESSMENT OF GLYCOLIC ACID, AMMONIUM, CALCIUM, POTASSIUM, AND SODIUM GLYCOLATES, METHYL, ETHYL, PROPYL, AND BUTYL GLYCOLATES, AND LACTIC ACID, AMMONIUM, CALCIUM, POTASSIUM, SODIUM, AND TEA-LACTATES, METHYL, ETHYL, ISOPROPYL, AND BUTYL LACTATES, AND LAURYL, MYRISTYL, AND CETYL LACTATES

This report provides a review of the safety of Glycolic Acid, Ammonium, Calcium, Potassium, and Sodium Glycolates, Methyl, Ethyl, Propyl, and Butyl Glycolates, Lactic Acid, Ammonium, Calcium, Potassium, Sodium, and TEA-Lactates, and Lauryl, Myristyl, and Cetyl Lactates. These ingredients belong to a group known as alpha-hydroxy acids (AHAs). Products containing these ingredients may be for consumer use, salon use, or medical use. This report does not address the medical use. In consumer and salon use, AHAs can function as mild exfoliants, but are also used as pH adjusters and skin-conditioning agents. AHAs are absorbed by the skin; the lower the pH, the greater the absorption. Metabolism and distribution studies show expected pathways and distribution. Consistent with these data, acute oral animal studies show oxalate-induced renal calculi, an increase in renal oxalate, and nephrotoxic effects. No systemic effects in animals were seen with dermal application, but irritation at the sight of application was produced. While many animal studies were performed to evaluate AHA-induced skin irritation, it was common for either the AHA concentration or the pH of the formulation to be omitted, limiting the usefulness of the data. Clinical testing using AHA formulations of known concentration and pH was done to address the issue of skin irritation as a function of concentration and pH. Skin irritation increased with AHA concentration at a given pH. Skin irritation increased when the pH of a given AHA concentration was lowered. Repeat insult patch tests using lotions and creams containing up to 10% Glycolic or Lactic Acid were negative. Glycolic Acid at concentrations up to 10% was not comedogenic and Lactic Acid at the same concentrations did not cause immediate urticarial reactions. Glycolic Acid was found to be nonirritating to minimally irritating in animal ocular tests, while Lactic Acid was found to be nonirritating to moderately irritating. In vitro testing to predict ocular irritation suggested Glycolic Acid would be a minimal to moderate–severe ocular irritant, and that Lactic Acid would be a minimal to moderate ocular irritant. Developmental and maternal toxicity were reported in rats dosed by gavage at the highest dose level used in a study

Reviewed by the Cosmetic Ingredient Review Expert Panel.

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that exposed the animals on days 7–21 of gestation. No developmental toxicity was reported at levels that were not maternally toxic. AHAs were almost uniformly negative in genotoxicity tests and were not carcinogenic in rabbits or rats. Clinical reports suggested that AHAs would enhance the penetration of hydroquinone and lidocaine. Animal and clinical tests were done to further evaluate the potential of AHAs to enhance the skin penetration of other chemical agents. Pretreatment of guinea pig skin with Glycolic Acid did not affect the absorption of hydroquinone or musk xylol. Clinical tests results indicated no increase in penetration of hydrocortisone or glycerin with Glycolic Acid pretreatment. Because AHAs can act to remove a portion of the stratum corneum, concern was expressed about the potential that pretreatment with AHAs could increase skin damage produced by UV radiation. Clinical testing was done to determine the number of sunburn cells (cells damaged by UV radiation that show distinct morphologic changes) produced by 1 MED of UV radiation in skin pretreated with AHAs. A statistically significant increase in the number of sunburn cells was seen in skin pretreated with AHAs compared to controls. These increases, however, were less than those seen when the UV dose was increased from 1 MED to 1.56 MED. The increase in UV radiation damage associated with AHA pretreatment, therefore, was of such a magnitude that it is easily conceivable that aspects of product formulation could eliminate the effect. Based on the available information included in this report, the CIR Expert Panel concluded that Glycolic and Lactic Acid, their common salts and their simple esters, are safe for use in cosmetic products at concentrations ≤10%, at final formulation pH ≥3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection. These ingredients are safe for use in salon products at concentrations ≤30%, at final formulation pH ≥3.0, in products designed for brief, discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals, and when application is accompanied by directions for the daily use of sun protection.

INTRODUCTION

A group of ingredients, known as alpha-hydroxy acids (AHAs) (organic carboxylic acids in which there is a hydroxy group at the two, or alpha [α], position of the carbon chain [Rosan, 1994]), have sparked the interest of a number of groups, including the cosmetic industry and the Food and Drug Administration (FDA). Because of the interest in AHAs and their possible effects, the cosmetic industry requested that the Cosmetic Ingredient Review (CIR) accelerate its review of these ingredients. The CIR Expert Panel agreed to this request at its May 1994 meeting. Since Glycolic and Lactic Acids are two of the most commonly used AHAs in retail cosmetic products (Kavanaugh, 1994), it was decided that these two acids, along with some of their salts and esters, would be the AHAs included in the accelerated review.

Many AHAs are naturally occurring products (Yu and Van Scott, 1994). Glycolic Acid, a constituent of sugar cane juice, and Lactic Acid, which occurs in sour milk, molasses, apples and other fruits, tomato

juice, beer, and wines (Budavari, 1989), are carboxylic acid that function as pH adjusters (Wenninger and McEwen, 1995a) and mild exfoliants (Cosmetic, Toiletry, and Fragrance Association [CTFA], 1995a) in various types of cosmetic formulations. In addition, Lactic Acid functions as a humectant–skin conditioning agent.

This report summarizes published and unpublished chemical, cosmetic, toxicological, mutagenic, clinical, and general data available on Glycolic Acid, Ammonium, Calcium, Potassium, Sodium, Methyl, Ethyl, Propyl, and Butyl Glycolates, Lactic Acid, and Ammonium, Calcium, Potassium, Sodium, TEA-, Methyl, Ethyl, Isopropyl, Butyl, Lauryl, Myristyl, and Cetyl Lactates.

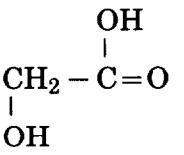
Myristyl and Cetyl Lactate have previously been reviewed by CIR (Elder, 1982), but updated information is included in this review. It is assumed that all data submitted citing testing with Glycolic Acid are for cosmetic-grade (70%) Glycolic Acid unless otherwise stated. The Expert Panel considered that the lack of specific data on the salts and esters did not preclude the review of the safety of these ingredients via extrapolation of existing data.

CHEMISTRY

DEFINITION AND STRUCTURE

Glycolic Acid

Glycolic Acid (CAS No. 79-14-1) is the organic acid that generally conforms to the following formula (Wenninger and McEwen, 1995b):



Glycolic Acid is also known as Hydroxyacetic Acid (Wenninger and McEwen, 1995b; Budavari, 1989; Gosselin et al., 1984; Grant, 1972); Acetic Acid, Hydroxy- (Wenninger and McEwen, 1995b); Hydroxyethanoic Acid (Budavari, 1989; Gosselin et al., 1984; Sax, 1979; Grant, 1972); Alpha-Hydroxyacetic Acid (Hazardous Substances Database, 1994); Acetoacetic Acid; Ethylethanoic Acid (Elson, 1993), and Glycolic Acid, (Grant, 1972).

Calcium Glycolate. Calcium Glycolate (CAS No. 26257-13-6) is also known as Glycolic Acid, Calcium Salt (Registry of Toxic Effects of Chemical Substances [RTECS], 1995).

Sodium Glycolate. Sodium Glycolate is also known as Sodium Hydroxyacetic Acid (Lewis, 1993a).

Methyl Glycolate. Methyl Glycolate is also known as Hydroxyacetic Acid, Methyl Ester (Lide, 1993).

Ethyl Glycolate. Ethyl Glycolate (CAS No. 623-50-7) is also known as Glycolic Acid, Ethyl Ester (RTECS, 1995); Hydroxyacetic Acid, Ethyl Ester (Lide, 1993); and Ethyl Hydroxyacetate (Grant, 1972).

Propyl Glycolate. Propyl Glycolate is also known as Hydroxyacetic Acid, Propyl Ester (Lide, 1993).

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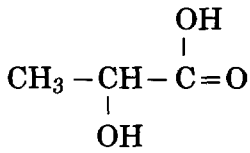
Lactic Acid

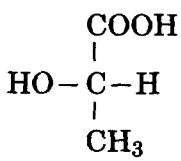
Lactic Acid (CAS No. 50-21-5) is the organic acid that generally conforms to the following formula (Wenninger and McEwen, 1995b):



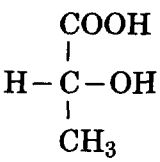
Lactic Acid can exist in a DL-, D-, or L- form. The L- and the D- forms are enantiomorphic isomers (mirror images). The L- form, which is dextrorotatory, is sometimes referred to as *d*-Lactic Acid in the literature and the D- form, which is levorotatory, is sometimes referred to as *l*-Lactic Acid in the literature. For the purpose of this review, the terms L- or D- will be used, as appropriate. The DL- or L- form is likely to be used in cosmetic formulations (Akerson, personal communication, 1994).

Lactic Acid is also known as 2-Hydroxypropanoic Acid (Wenninger and McEwen, 1995b; Lewis, 1993b; Grant, 1972); 2-Hydroxypropionic Acid (Wenninger and McEwen, 1995b; Lewis, 1993b; Gennaro, 1990); Propanoic Acid, 2-Hydroxy (Wenninger and McEwen, 1995b; Gennaro, 1990); Propionic Acid, 2-Hydroxy (RTECS, 1994); α-Hydroxypropionic Acid (Lewis, 1993a,b); alpha-Hydroxypropionic Acid (Budavari, 1989); DL-Lactic Acid (Lewis, 1993b); Ethylidenelactic Acid (Lewis, 1993b; Grant, 1972); 1-Hydroxyethanecarboxylic Acid; DL-1-Hydroxyethane Carboxylic Acid; DL-2-Hydroxy Propionic Acid (FAO/WHO, 1967); Racemic Lactic Acid; Acetonic Acid (Lewis, 1993b); Propanoloic Acid (Gennaro, 1990); Ethylidene Lactic Acid (Sax, 1979); Milk Acid (Lewis, 1993a,b; Gennaro, 1990); Acid of Milk (Grant, 1972) and Ordinary Lactic Acid (Budavari, 1989).

L-Lactic Acid conforms to the following formula (Budavari, 1989):



D-Lactic Acid conforms to the following formula (Budavari, 1989):



L-Lactic Acid is also known as (*S*)-2-Hydroxypropanoic Acid; L(+)-Lactic Acid; Dextrorotatory Lactic Acid; *d*-Lactic Acid; Paralactic Acid (Budavari, 1989); and Sarcolactic Acid (Rosan, 1994; Budavari, 1989).

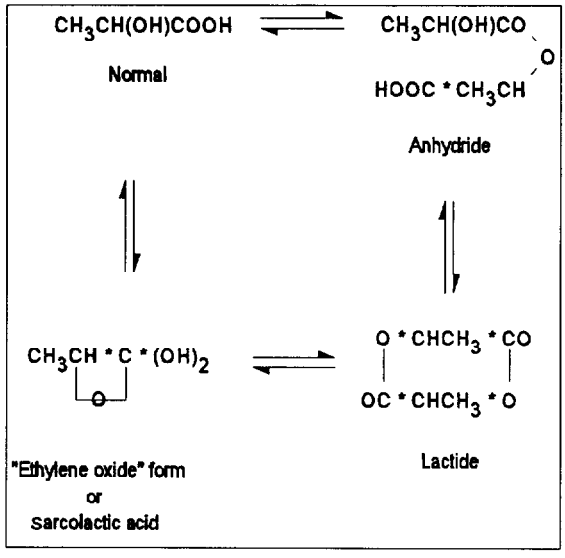


Figure 1. Equilibrium forms of Lactic Acid in water.

D-Lactic Acid is also known as 2-Hydroxypropanoic Acid (Rosan, 1994); D-2-Hydroxypropionic Acid (Lide, 1993); (*R*)-2-Hydroxypropanoic Acid; D(−)-Lactic Acid; levorotatory Lactic Acid; and *l*-Lactic Acid (Budavari, 1989). An aqueous solution of Lactic Acid consists of an equilibrium of four forms, as presented in Figure 1 (Grant, 1972).

Ammonium Lactate. Ammonium Lactate (CAS No. 52003-58-4) is the ammonium salt of Lactic Acid (Wenninger and McEwen, 1995b). Ammonium Lactate is also known as DL-Lactic Acid, Ammonium Salt (Budavari, 1989).

Calcium Lactate. Calcium Lactate (CAS No. 814-80-2) is the calcium salt of Lactic Acid (Wenninger and McEwen, 1995b). Calcium Lactate is also known as Calcium 2-Hydroxypropanoate; 2-Hydroxypropanoic Acid, Calcium Salt (2:1); Propanoic Acid, 2-Hydroxy-, Calcium Salt (2:1) (Wenninger and McEwen, 1995b); Lactic Acid Calcium Salt (2:1); Propanoic Acid, 2-Hydroxy-, Calcium Salt (RTECS, 1995); and 2-Hydroxypropanoic Acid, Calcium Salt (RTECS, 1995; Budavari, 1989).

Potassium Lactate. Potassium Lactate (CAS No. 996-31-6) is the potassium salt of Lactic Acid (Wenninger and McEwen, 1995b) that is also known as Lactic Acid, Monopotassium Salt; Monopotassium 2-Hydroxypropanoate Acid; Propanoic Acid, 2-Hydroxy-, Monopotassium Salt; and Potassium alpha-Hydroxypropionate (RTECS, 1995).

Sodium Lactate. Sodium Lactate (CAS No. 72-17-3) is the sodium salt of Lactic Acid (Wenninger and McEwen, 1995c). Sodium Lactate is also known as 2-Hydroxypropanoic Acid, Monosodium Salt; Propanoic Acid, 2-Hydroxy-, Monosodium Salt (Wenninger and McEwen, 1995c);

Lactic Acid, Monosodium Salt; and Lactic Acid Sodium Salt (Lewis, 1993b).

TEA-Lactate. TEA-Lactate (CAS No. 20475-12-1) is the triethanolamine salt of Lactic Acid (Wenninger and McEwen, 1995c). TEA-Lactate is also known as Lactic Acid compd., with 2,2′,2″-Nitrilotris [Ethanol] (1:1) and Triethanolamine Lactate (Wenninger and McEwen, 1995c).

Methyl Lactate. The methyl ester of Lactic Acid is also known as DL-, D-, or L-Lactic Acid, methyl ester (Lide, 1993). D-Lactic Acid, methyl ester is also known as D-Methyl Lactate. Additionally, Methyl Lactate (CAS No. 547-64-8) is also known as Lactic Acid, Methyl Ester (RTECS, 1995) and 2-Hydroxypropanoic Acid Methyl Ester (Budavari, 1989).

Ethyl Lactate. Ethyl Lactate (97-64-3) is also known as Lactic Acid, Ethyl Ester (Opdyke and Letizia, 1982); 2-Hydroxypropanoic Acid Ethyl Ester (Budavari, 1989); Ethyl α-Hydroxypropionate (Opdyke and Letizia, 1982; Budavari, 1989); and Ethyl-2-Hydroxypropionate (Opdyke and Letizia, 1982; Gosselin et al., 1984; Sax, 1979). The ethyl ester of the different forms of Lactic Acid is also known as DL-, D-, or L-Lactic Acid, Ethyl Ester, and D-Lactic Acid. Ethyl ester is also known as D-Ethyl Lactate (Lide, 1993).

Isopropyl Lactate. Isopropyl Lactate (CAS No. 617-51-6) is also known as Lactic Acid, Isopropyl Ester (RTECS, 1995; Lide, 1993); 1-Methylethyl 2-Hydroxypropanoate; Propanoic Acid, 2-Hydroxy, 1-Methylethyl Ester (RTECS, 1995); and Isopropyl-2-Hydroxypropanoate (Sax, 1979).

Butyl Lactate. Butyl Lactate (CAS No. 138-22-7) is also known as *n*-Butyl Lactate; Lactic Acid, Butyl Ester; Butyl alpha-Hydroxypropionate; Propanoic Acid, 2-Hydroxy-, Butyl Ester; Butyl 2-Hydroxypropanoate (RTECS, 1995); Butyl α-Hydroxypropionate; and 2-Hydroxypropanoic Acid, Butyl Ester (Lewis, 1993b). The butyl ester of the different forms of Lactic Acid is also known as DL- or D-Lactic Acid, Butyl Ester; DL-Butyl Lactate; D-Lactic Acid, Butyl Ester; and D-Butyl Lactate (Lide, 1993).

Lauryl Lactate. Lauryl Lactate (CAS No. 6283-92-7) is the ester of lauryl alcohol and Lactic Acid (Wenninger and McEwen, 1995b). Lauryl Lactate is also known as Dodecyl 2-Hydroxypropanoate; 2-Hydroxypropanoic Acid, Dodecyl Ester; and Propanoic Acid, 2-Hydroxy-, Dodecyl Ester (Wenninger and McEwen, 1995b).

Myristyl Lactate. Myristyl Lactate (CAS No. 1323-03-1) is the ester of myristyl alcohol and Lactic Acid (Wenninger and McEwen, 1995b). Myristyl Lactate is also known as Tetradecyl 2-Hydroxypropanoate; 2-Hydroxypropanoic Acid, Tetradecyl Ester; and Propanoic Acid, 2-Hydroxy-, Tetradecyl Ester (Wenninger and McEwen, 1995b).

Cetyl Lactate. Cetyl Lactate (CAS No. 35274-05-6) is the ester of cetyl alcohol and Lactic Acid (Wenninger and McEwen, 1995b). Cetyl Lactate is also known as *n*-Hexadecyl Lactate; *n*-Hexadecyl-2-Hydroxypropanoate; Propanoic Acid, 2-Hydroxy-, Hexadecyl Ester (Wenninger and McEwen, 1995b); 2-Hydroxypropanoic Acid Hexadecyl Ester, 1-Hexadecanol Lactate; Lactic Acid Cetyl Ester, and Lactic Acid Hexadecyl Ester (Budavari, 1989).

Physical and Chemical Properties

The chemical and physical properties of Glycolic Acid and its salts and esters are summarized in Table 1. The chemical and physical properties of Lactic Acid and its common salts and simple esters are summarized in Table 2.

There is a relationship between the total concentration of AHAs in a solution, the pH of the solution, and the amount of free Glycolic Acid or Lactic Acid in the solution because of dissociation of the AHA (CTFA, 1996a). This relationship is described by the Henderson–Hasselbalch equation:

$$\mathrm{pH} = \mathrm{p}K_a + \frac{[\mathrm{A}^-]}{[\mathrm{HA}]}$$

where [HA] represents the concentration of the free acid, $[A^-]$ is the concentration of the salt, and pK_a is the dissociation constant of the particular AHA. The dissociation constant, as its name implies, is a constant value for a given ionic strength at 25°C in water.

The pK_a, however, is directly influenced by the partition of the AHA between the oil and water phases in an emulsion, suggesting that cosmetic formulations containing AHAs in oil/water emulsions will have pK_a values different from published dissociation constants. These variations could drastically change the distribution of weak acids in the pH region close to the pK_a. An equation has been developed that purports to take into consideration both partitioning and dissociation in calculating the concentration of free acid:

$$[\mathrm{HA}]_W = \frac{C}{Kq + 1 + K_a/[\mathrm{H_3O^+}]}$$

where C is the total concentration of Lactic or Glycolic Acid; K is the partition coefficient of the AHA (solubility in the oil phase divided by the solubility in the water phase); q is the ratio of the oil phase and aqueous phase volumes; K_a is the dissociation constant of the acid in the aqueous phase; and $[H_3O^+]$ is the hydrogen ion concentration of the water phase.

Table 1. Physical and chemical properties of Glycolic Acid and Calcium, Sodium, Methyl, Ethyl, Propyl, and Butyl Glycolates

Property	Description		Reference
	Glyolic Acid		
Physical properties	Rhombic needles from water and leaflets from ether		Lide, 1993
	Crystalline solid		Patty et al., 1963
	Colorless		Lewis, 1993a
	Odorless		Budavari, 1989
Molecular weight	76.05		Lide, 1993
Solubility	Soluble in water, methanol, alcohol, acetone, acetic acid, ether		Budavari, 1989
Melting point	75–80°C		Rosan, 1994
	80°C		Lide, 1993
	78–79°C		Lewis, 1993a
Boiling point	Decomposes		Lide, 1993
pH of aq. solution	0.5%: 2.5	5.0%: 1.91	Budavari, 1989
	1.0%: 2.33	10%: 1.73	
	2.0%: 2.16		
	5%: 1.7	40%: 1.3	Yu and Van Scott, 1994
	10%: 1.6	50%: 1.2	
	20%: 1.5	60%: 1.0	
	30%: 1.4	70%: 0.6	
pK_a (pH of 50% dissociation)	3.83 (25°C)		Rosan, 1994
	Technical grade (70%) Glycolic Acid		
Physical properties	Clear, light amber-colored liquid with a mild (burnt sugar) odor		Elson, 1993
	Light, straw-colored liquid having an odor similar to burnt sugar		Lewis, 1993a
Melting point	10°C		Elson, 1993
Boiling point	112°C		Elson, 1993
Density	1.25 g/mL (26°C)		Elson, 1993
Reactivity	Stable, will not decompose, polymerize, or burn		Elson, 1993
	Combustible		Lewis, 1993a
	Calcium Glycolate		
Molecular formula	$(CH_3OHCOO)_2Ca$		Lewis, 1993a
	$Ca(C_2H_3O_3)\cdot H_2O$		Grant, 1972
Molecular weight	190.18		RTECS, 1995
	208.1		Grant, 1972
Physical properties	White solid		Lewis, 1993a
	White crystals		Grant, 1972
Solubility	Slightly soluble in water		Grant, 1972

Table 1. Physical and chemical properties of Glycolic Acid and Calcium, Sodium, Methyl, Ethyl, Propyl, and Butyl Glycolates (*Continued*)

Property	Description	Reference
	Sodium Glycolate	
Molecular formula	$NaOOCCH_2OH$	Lewis, 1993a
Molecular weight	98.04 (calculated)	
Physical properties	White powder	Lewis, 1993a
	Methyl Glycolate	
Molecular formula	$HOCH_2CO_2CH_3$	Lide, 1993
Molecular weight	90.08	Lide, 1993
Boiling point	151.1°C	Lide, 1993
Solubility	Soluble in water, alcohol, ether	Lide, 1993
Density	1.1677 (18°C/4°C)	Lide, 1993
	Ethyl Glycolate	
Molecular formula	$HOCH_2CO_2C_2H_5$	Lide, 1993
Physical properties	Colorless liquid	Grant, 1972
Molecular weight	104.07	Grant, 1972
Boiling point	160°C (760 mm Hg); 69°C (25 mm Hg)	Lide, 1993
	160°C	Grant, 1972
Solubility	Soluble in alcohol, ether	Lide, 1993
	Soluble in alcohol	Grant, 1972
Density	1.0826 (23°C/4°C)	Lide, 1993
Refractive index	1.4180 (20°C)	Lide, 1993
	Propyl Glycolate	
Molecular formula	$HOCH_2CO_2C_3H_7$	Lide, 1993
Molecular weight	118.14	Lide, 1993
Boiling point	170-1°C	Lide, 1993
Density	1.0631 (18°C/4°C)	Lide, 1993
Index of refraction	1.4231 (18°C)	Lide, 1993
	Butyl Glycolate	
Molecular formula	$C_6H_{12}O_3$	Sax, 1979
Molecular weight	132.2	Sax, 1979
Boiling point	184°	Sax, 1979
Flash point	142°	Sax, 1979
Density	1.01	Sax, 1979

From the above information, it is clear that the relationship between the concentration of free acid, the pH, and the total concentration of AHA may not be calculated simply on the basis of the Henderson–Hasselbalch equation. The influence of the partitioning of the AHA between phases in an emulsion must also be considered. Overall, the relationship between the pH and the concentration of free acid is a complicated one.

Table 2. Physical and chemical properties of Lactic Acid, and Ammonium, Calcium, Potassium, Sodium, Methyl, Ethyl, Isopropyl, Butyl, Myristyl, and Cetyl Lactates

Property	Description	Reference
	Lactic Acid	
Physical properties	Colorless or slightly yellow viscous, odorless or almost odorless, hygroscopic liquid	ESLUR, 1994a
	Crystal	Budavari, 1989
	Yellow	Lide, 1993
	Crystalline form; food grade is a colorless or yellowish, nearly odorless, syrupy liquid	Informatics, Inc., 1975
Molecular weight	90.08	Lide, 1993
Melting point	18°C	Lide, 1993
	16.8°C	Budavari, 1989
Boiling point	122°C (15 mm Hg)	Lide, 1993
	119°C (12 mm Hg)	Grant, 1972
	82–85°C (0.5–1 mm Hg)	Budavari, 1989
pH	<1 (concentrated acid)	ESLUR, 1994a
	2.28 (1%); 1.75 (10%)	Shelef, 1994
Chemical characterization	Mixture of Lactic Acid and Lactic Acid Lactate equiv. to a total of 85–90% by weight Lactic Acid	USP, 1994
	When concentrated above 50%, it is partially converted to lactic anhydride	Lewis, 1993a
	Not less than 95.0% and not more than 105.0% of the labeled concentration of $C_3H_6O_3$	Informatics, Inc., 1975
	Grades: Technical, 22 and 44%; Food, 50–80%; USP, 85–90%	Lewis, 1993a
	Food grade—a mixture consisting of Lactic Acid and Lactic Acid Lactate usually containing the equivalent of 50–90% Lactic Acid	Informatics, Inc., 1975
Density	1.2060 (21°C/4°C)	Lide, 1993
	1.240	Grant, 1972
	1.14 (60% solution)	Shelef, 1994
Refractive index	1.4392 (20°C)	Lide, 1993
Solubility	Soluble in water, alcohol, and ether	Lide, 1993
	Soluble in water, alcohol, and furfurol, less soluble in ether; practically insoluble in chloroform, petroleum ether, and carbon disulfide	Budavari, 1989

Table 2. Physical and chemical properties of Lactic Acid, and Ammonium, Calcium, Potassium, Sodium, Methyl, Ethyl, Isopropyl, Butyl, Myristyl, and Cetyl Lactates (*Continued*)

Property	Description	Reference
	Lactic Acid	
Specific rotation	between −0.05° and +0.05° (racemic)	USP, 1994
pK_a	3.03 (100°C) 3.86 (25°C)	Rosan, 1994
Ionization constant	1.38×10^{-4} at 25°C	Informatics, Inc., 1975
Reactivity	Volatile with superheated steam	Budavari, 1989
	Incompatible with oxidizing agents, iodides, nitric acid, and albumin in pharmaceuticals	Informatics, Inc., 1975
	L-Lactic Acid	
Physical properties	Hygroscopic prisms obtained from ether solvent	Lide, 1993
	Crystals formed from acetic acid or chloroform	Budavari, 1989
Melting point	53°C	Budavari, 1989
Boiling point	103°C (2 mm Hg)	Rosan, 1994
Solubility	Soluble in water and alcohol	Lide, 1993
Specific rotation	$[\alpha]_D^{15/} = +3.8$ (w,c = 10.5)	Lide, 1993
pK	3.86 (25°C)	Yu and Van Scott, 1994
	3.79 (25°C)	Budavari, 1989
	D-Lactic Acid	
Physical properties	Plates obtained from chloroform and acetic acid solvents	Lide, 1993
	Crystals from ether + isopropyl ether	Budavari, 1989
	Solid	Grant, 1972
Melting point	53°C	Lide, 1993
Boiling point	103°C (2 mm Hg)	Rosan, 1994; Lide, 1993
Solubility	Soluble in water and alcohol	Lide, 1993
	Soluble in water, alcohol, acetone, ether, and glycerol; practically insoluble in chloroform	Budavari, 1989
Specific rotation	$[\alpha]'_D = -2.26$ (w,c = 1.24)	Lide, 1993
pK	3.83	Budavari, 1989

(*Table continued on next page.*)

Table 2. Physical and chemical properties of Lactic Acid, and Ammonium, Calcium, Potassium, Sodium, Methyl, Ethyl, Isopropyl, Butyl, Myristyl, and Cetyl Lactates (*Continued*)

Property	Description	Reference
	Ammonium Lactate	
Molecular formula	$C_3H_9NO_3$	Budavari, 1989
Physical properties	Crystals from propanol	Budavari, 1989
	Colorless syrup	Grant, 1972
Molecular weight	107.11	Budavari, 1989
Melting point	91–94°C	Budavari, 1989
pH	5.0–5.5 (12% solution)	FDA, 1988
Solubility	Soluble in water, glycerol, 95% alcohol; slightly soluble in methanol; practically insoluble in ethyl, n-butyl alcohols, ether acetone, ethyl acetate	Budavari, 1989
	Miscible with water	Grant, 1972
Density	1.2006 (20°C/4°C); 1.1984 (25°C/4°C); 1.1904 (40°C/4°C)	Budavari, 1989
Refractive index	1.4543 (20°C; 1.4536 (25°C); 1.4503 (40°C)	Budavari, 1989
	Calcium Lactate	
Empirical formula	$C_6H_{10}CaO_6$	Budavari, 1989
Structural formula	$Ca(C_3H_5O_3)_2 \cdot 5H_2O$	Sax, 1979
	$Ca(CH_3CH(OH)COO)_2 \cdot xH_2O$	Informatics, Inc., 1975
Physical properties	Available as dry powder, mono-, or pentahydrate	Shelef, 1994
	Pentahydrate, almost odorless, slightly efflorescent granules or powder	Budavari, 1989
	White, almost odorless powder	Sax, 1979
	White to cream colored, almost odorless, crystalline powder or granules containing up to 5 molecules of water of crystallization; the pentahydrate is some what efflorescent	Informatics, Inc., 1975
Molecular weight	218.22	Budavari, 1989
	308	Sax, 1979
Melting point	$-5H_2O$ @ 120°C	Sax, 1979

Table 2. Physical and chemical properties of Lactic Acid, and Ammonium, Calcium, Potassium, Sodium, Methyl, Ethyl, Isopropyl, Butyl, Myristyl, and Cetyl Lactates (*Continued*)

Property	Description	Reference
Solubility	Slowly soluble in cold water; quickly soluble in hot water; almost insoluble in alcohol	Budavari, 1989
Chemical characterization	Commercially prepared Calcium Lactate usually contains approx. 25% water; on the anhydrous basis, it is at least 98% pure	Budavari, 1989
	Not less than 98.0% and not more than 101.0% of $C_6H_{10}CaO_6$ after drying	Informatics, Inc., 1975
pH	6–7	Budavari, 1989
Loss on drying	Pentahydrate: 24–30% Trihydrate: 15–20% Monohydrate: 5–8% Dried form: ≤3%	Informatics, Inc., 1975
	Potassium Lactate	
Molecular formula	$C_3H_5O_3K$	Rothschild, 1990
Molecular weight	129.17 (calculated)	Rothschild, 1990
Physical properties	Hydroscopic, white, odorless solid	Rothschild, 1990
	Sodium Lactate	
Molecular formula	$C_3H_5NaO_3$	Budavari, 1989
Physical properties	Colorless or almost colorless, thick, odorless liquid	Budavari, 1989
	Colorless or yellowish syrupy liquid; very hygroscopic	Lewis, 1993a
Molecular weight	112.07	Budavari, 1989
Melting point	17°C	Lewis, 1993a
Boiling point	Decomposes at 140°C	Lewis, 1993a
Solubility	Miscible with water, alcohol	Budavari, 1989
	Soluble in water	Lewis, 1993a
Chemical characterization	Commercially prepared Sodium Lactate is a mixture with water containing 70–80% Sodium Lactate	Budavari, 1989
pH	Neutral	Budavari, 1989
	6.0–7.3 (USP, solution)	Lewis, 1993a
Reactivity	Combustible	Lewis, 1993a

(*Table continued on next page.*)

Table 2. Physical and chemical properties of Lactic Acid, and Ammonium, Calcium, Potassium, Sodium, Methyl, Ethyl, Isopropyl, Butyl, Myristyl, and Cetyl Lactates (*Continued*)

Property	Description	Reference
	Methyl Lactate	
Molecular formula	$C_4H_8O_3$	Budavari, 1989
Physical properties	Colorless, transparent liquid	Budavari, 1989
	Colorless liquid	Sax, 1979
Molecular weight	104.1	Lide, 1993; Budavari, 1989; Sax, 1979
Specific rotation		Lide, 1993
D-	$[\alpha]_D^{20/} = +7.5$	
L-	$[\alpha]_D^{20/} = -8.3$	
Boiling point	144–145°C	Budavari, 1989
	144°C	Sax, 1979
DL-	144.8°C	Lide, 1993
D-	40°C (11 mm Hg)	
L-	58°C (19 mm Hg)	
Solubility	Soluble in alcohol, ether; decomposes in water	Budavari, 1989
	Decomposes in water	Sax, 1979
DL-, D-	Soluble in water, alcohol, ether	Lide, 1993
Specific gravity	1.09 (19°C/4°C)	Budavari, 1989; Sax, 1979
DL-	1.0928 (20°C/4°C)	Lide, 1993
D-	1.0857 (25°C/4°C)	
L-	1.0895 (20°C/4°C)	
Refractive index	1.4156 (16°C)	Budavari, 1989
DL-	1.4141 (20°C)	Lide, 1993
L-	1.4139 (20°C)	
Flash point	121°F	Sax, 1979
	Ethyl Lactate	
Molecular formula	$C_5H_{10}O_3$	Budavari, 1989
Physical characteristics	Colorless liquid; mild odor	Lewis, 1993a
	Colorless liquid; characteristic odor	Budavari, 1989
Chemical characterization	Grade: technical (96%)	Lewis, 1993a
Molecular weight	118.13	Lide, 1993; Budavari, 1989

Table 2. Physical and chemical properties of Lactic Acid, and Ammonium, Calcium, Potassium, Sodium, Methyl, Ethyl, Isopropyl, Butyl, Myristyl, and Cetyl Lactates (*Continued*)

Property	Description	Reference
Specific rotation		Lide, 1993
D-	$[\alpha]_D^{19/} = +14.5$	
L-	$[\alpha]_D^{19/} = -11.3$	
Melting point	−25°C	Browning, 1965
Boiling point	154°C	Lewis, 1993a; Budavari, 1989
DL-	154.5°C; 58°C (19 mm Hg)	Lide, 1993
D-	58°C (20 mm Hg)	
L-	69–70°C (36 mm Hg)	
Solubility	Miscible with water, alcohols, ketones, esters, hydrocarbons, oil	Lewis, 1993a
	Miscible with water (with partial decomposition), alcohol, ether	Budavari, 1989
	Very soluble in water; miscible with gasoline	Browning, 1965
DL-, D-, L-	Soluble in water, alcohol, ether	Lide, 1993
Specific gravity	1.020–1.036 (20°C/20°C)	Lewis, 1993a
	1.042 (14°C/4°C)	Budavari, 1989
DL-	1.0302 (20°C/4°C)	Lide, 1993
D-	1.0324 (20.4°C/4°C)	
L-	1.0314 (20°C/4°C)	
Refractive index		Lide, 1993
DL-	1.4124 (20°C)	
D-	1.4125 (20°C)	
L-	1.4156 (20°C)	
Flash point	115°F (closed cup)	Lewis, 1993a
	117°F (closed cup)	Budavari, 1989
	115°F (closed cup); 131°F (technical)	Sax, 1979
Reactivity	Combustible	Lewis, 1993a
	Isopropyl Lactate	
Molecular formula	$CH_3CH(OH)CO_2CH(CH_3)_2$	Lide, 1993
Molecular weight	132.16	Lide, 1993
Boiling point	166–8°C; 75–80°C (12 mm Hg)	Lide, 1993
Solubility	Soluble in water, alcohol, ether, benzene	Lide, 1993
Specific gravity	0.9980 (20°C/4°C)	Lide, 1993
Refractive index	1.4082 (25°C)	Lide, 1993
Flash point	130°F (open cup)	Sax, 1979

(*Table continued on next page.*)

Table 2. Physical and chemical properties of Lactic Acid, and Ammonium, Calcium, Potassium, Sodium, Methyl, Ethyl, Isopropyl, Butyl, Myristyl, and Cetyl Lactates (*Continued*)

Property	Description	Reference
	Butyl Lactate	
Molecular formula	$C_7H_{14}O_3$	Lewis, 1993b
Physical properties	Water-white, stable liquid; mild odor	Lewis, 1993a
Chemical characterization	Grade: technical (95% min.)	Lewis, 1993a
Specific rotation		Lide, 1993
D-	$[\alpha]_D^{27/} = +13.6$	
Molecular weight	146.19	Lide, 1993
	146.21	Lewis, 1993b
	146.18	Sax, 1979
Melting point	−43°C	Lewis, 1993a,b; Sax, 1979
DL-	−49°C	Lide, 1993
Boiling point	188°C	Lewis, 1993a,b; Sax, 1979
DL-	83°C (13 mm Hg)	Lide, 1993
D-	77°C (10 mm Hg)	
Solubility	Miscible with many lacquer solvents, diluents, oils; slightly soluble in water; hydrolyzed in acids and alkalies	Lewis, 1993a
	Miscible in alcohol and ether; slightly soluble in water	Lewis, 1993b
DL-, D-	Soluble in alcohol and ether	Lide, 1993
Specific gravity	0.974–0.984 (20°C/20°C)	Lewis, 1993a
	0.986	Sax, 1979
DL-	0.9807 (22°C/4°C)	Lide, 1993
D-	0.9744 (27°C/4°C)	
Refractive index	1.4126 (20°C)	Lewis, 1993a
DL-	1.4217 (°C)	Lide, 1993
Flash point	168°F	Lewis, 1993a
	160°F (open cup)	Lewis, 1993b; Sax, 1979
Reactivity	Combustible	Lewis, 1993a
	Myristyl Lactate	
Physical properties	White to yellow liquid or soft solid	Elder, 1982
Molecular formula	$C_{17}H_{34}O_3$	

Table 2. Physical and chemical properties of Lactic Acid, and Ammonium, Calcium, Potassium, Sodium, Methyl, Ethyl, Isopropyl, Butyl, Myristyl, and Cetyl Lactates (*Continued*)

Property	Description	Reference
Molecular weight	286.46 (calculated)	
Solubility	Soluble in ethyl alcohol and propylene glycol; dispersible in mineral oil; insoluble in water and glycerine	Elder, 1982
Specific gravity	0.892–0.904 (25°C)	Elder, 1982
Titer	11–14°C	Elder, 1982
Saponification value	166–185	Elder, 1982
Ester value	166–185	Elder, 1982
Acid value	3 max	Elder, 1982
Iodine value	1.0 max	Elder, 1982
	Cetyl Lactate	
Molecular formula	$C_{19}H_{38}O_3$	Budavari, 1989
Physical properties	Waxy solid	Budavari, 1989
	White to yellow soft waxy solid with a slight, characteristic, pleasant odor	Elder, 1982
Molecular weight	314.49	Budavari, 1989
Melting point	41°C	Budavari, 1989
	23–25°C	Elder, 1982
Boiling point	132°C (0.1 mm Hg) 170°C (1 mm Hg) 219°C (10 mm Hg)	Budavari, 1989
Solubility	Soluble in ethyl alcohol and propylene glycol	Elder, 1982
Specific gravity	0.893–0.905 (25°C)	Elder, 1982
Refractive index	1.4410 (40°C) 1.4370 (50°C)	Budavari, 1989
Titer	23–26°C	Elder, 1982
Saponification value	155–195	Elder, 1982
Ester value	155–195	Elder, 1982
Acid value	3.5 max	Elder, 1982
Iodine value	1.0 max	Elder, 1982

MANUFACTURE AND PRODUCTION

AHAs that are used in dermatologic and cosmetic products can be produced synthetically (Rosan, 1994). A common methodology utilizes base or, preferably, acid hydrolysis of cyanohydrins available from appropriate ketones. A limitation of this method is the lack of reactivity of certain hindered ketones. AHAs are often sold and generally utilized in the form of their carboxylate salts.

In 1993, there were more than 20 manufacturers and distributors of over 60 AHA-type products (Jackson, 1993). In 1994, there were over 75 manufacturers that introduced over 100 AHA products, some of which were sold only to dermatologists (Jackson, 1994).

Glycolic Acid

Glycolic Acid can be manufactured by bubbling carbon monoxide through formaldehyde (Elson, 1993), by the action of sodium hydroxide on monochloroacetic acid (Budavari, 1989), and by the electrolytic reduction of oxalic acid. Glycolic Acid is available pure and in aqueous solution (Rosan, 1994).

The pH and concentration of Glycolic Acid can be adjusted by the utilization of a base, such as ammonium hydroxide (Elson, 1993). Instead of totally neutralizing the product, resulting in Ammonium Glycolate, the acid–base reaction is stopped to allow varying concentrations of free Glycolic Acid and Ammonium Glycolate in order to change the concentration of the free acid and to adjust the pH.

Glycolic Acid is available as a technical grade 70% solution and as higher purity grade solutions of 70% (Glypure 70) and 99% (Glypure 99) (DuPont, 1995). Because of the amount of impurities, DuPont prohibits the use of its technical-grade Glycolic Acid in personal care applications (DuPont Specialty Chemicals, 1995, 1996).

Calcium Glycolate. Calcium Glycolate is available as a technical grade (Lewis, 1993a).

Lactic Acid

Lactic Acid can be prepared by inoculating a solution of glucose or starch that was previously hydrolyzed with diluted sulfuric acid with *Bacillus lactis* after the addition of suitable nitrogen compounds and mineral salts (Gennaro, 1990). Calcium carbonate is added to neutralize the Lactic Acid as soon as it is formed so that the fermentation process does not stop (which would happen if the amount of acid is greater than 0.5%). When fermentation is complete, as indicated with a test for glucose, the solution is filtered, concentrated, and allowed to stand; the Calcium

Lactate that crystallizes is hydrolyzed with dilute sulfuric acid and filtered with charcoal.

The Lactic Acid in the filtrate is then extracted with ethyl or isopropyl ether, the ether is distilled off, and the aqueous solution of the acid is concentrated under reduced pressure. Lactic Acid (DL-) can also be prepared technically by "Lactic Acid fermentation" of carbohydrates, such as glucose, sucrose, and lactose, with *Bacillus acidi lacti* or other related organisms, such as *Lactobacillus delbrueckii* and *L. bulgaricus*, at very high temperatures (Budavari, 1989). Commercially, Lactic Acid is produced by fermentation of whey, cornstarch, potatoes, and molasses.

D- and L-Lactic Acid can be obtained by the resolution of DL-Lactic Acid (Budavari, 1989). Additionally, in the laboratory, D- and L-Lactic Acid can be produced from glucose using *L. leichmannii* and *L. delbrueckii*, respectively. Grant (1972) states that D-Lactic Acid is produced by the action of *Micrococcus acidi paralactici* and that L-Lactic Acid is formed by the action of *Bacillus acidi levolactica*. Another source (USP, 1994) states that Lactic Acid can be prepared by the lactic fermentation of sugars or synthetically (synthetic production methods not described); that which is obtained from the fermentation of sugars is levorotatory, whereas that prepared synthetically is racemic. However, Lactic Acid prepared by fermentation becomes dextrorotatory on dilution, which hydrolyzes L(−)-Lactic Acid lactate (believed to be the anhydride form) to L(+)-Lactic Acid.

Lactic Acid is hygroscopic, and when concentrated by boiling, the acid condenses to form Lactic Acid Lactate, 2-(lactoloxy) propanoic acid, which upon dilution and heating hydrolyzes to Lactic Acid (National Academy of Science, 1981).

Lactic Acid is most commonly available as an 85% aq. solution which contains varying amounts of esterification products (Rosan, 1994) (see Figure 5). Other grades available include technical, 22 and 44%; food grade, 50–80%; plastic grade, 50–80%; and USP, 85–90% (Lewis, 1993a).

Ammonium Lactate. Ammonium Lactate is prepared by neutralizing DL-Lactic Acid with ammonium hydroxide (Budavari, 1989).

Calcium Lactate. Calcium Lactate can be prepared commercially by neutralization of Lactic Acid from fermentation of dextrose, molasses, starch, sugar, or whey with calcium carbonate (Budavari, 1989). It can also be neutralized with calcium hydroxide (Rothschild, 1990).

Potassium Lactate. Potassium Lactate can be prepared commercially by the neutralization of Lactic Acid with potassium hydroxide (Rothschild, 1990).

Sodium Lactate. Sodium Lactate can be prepared commercially by the neutralization of Lactic Acid with sodium hydroxide (Rothschild,

1990). There are two grades of Sodium Lactate available, technical and USP (solution with pH 6.0–7.3) (Lewis, 1993a).

Methyl Lactate. Methyl Lactate can be prepared by heating 1 mol Lactic Acid condensation polymer with 2.5–5 mol of methanol and a small quantity of sulfuric acid at 100°C for 1–4 h in a heavy-walled bottle (Budavari, 1989).

Ethyl Lactate. Ethyl Lactate can be prepared by the esterification of Lactic Acid with ethanol (Lewis, 1993a). It can also be prepared by combining acetaldehyde with hydrogen cyanide to form acetaldehyde cyanohydrin, which is converted into Ethyl Lactate by treatment with ethanol and an inorganic acid. Another reported method of preparation of Ethyl Lactate is to biologically optically inactive Lactic Acid with ethyl alcohol in carbon tetrachloride for 24 h (Opdyke and Letizia, 1982). Ethyl Lactate is available as a technical grade, 96% (Lewis, 1993a).

Butyl Lactate. Butyl Lactate can be prepared by direct esterification of Lactic Acid with butyl alcohol (Browning, 1965). Butyl Lactate is available as a technical grade, 95% minimum (Lewis, 1993a).

ANALYTICAL METHODS

Glycolic Acid

Glycolic Acid can be determined by the Eegriwe method; however, caution is required with this method, especially if formaldehyde or EDTA are present. Glycolic Acid can also be assayed by thin-layer chromatography (McChesney et al., 1972).

Urinary Glycolic Acid can be determined by gas chromatography (GC) (McChesney et al., 1972; Niederwieser et al., 1978), a colorimetric method using 2,7-dihydroxynaphthalene (Chow et al., 1978), or by automated ion chromatography (Wandzilak et al., 1991). Isotope dilution and a combination of ion-exchange chromatography and paper chromatography (Niederwieser et al., 1978) or gradient ion-exchange chromatography (Johansson and Tabova, 1974) can also be used to assay for urinary Glycolic Acid. A chromotropic acid–sulfuric acid assay in which the sample is precleaned by filtering through strongly acidic and strongly basic ion exchangers and compared with a standard can also be used (Niederwieser et al., 1978).

Isotachophoretic determination has been used to separate and quantify Glycolic Acid in blood metabolized from ethylene glycol (Ovrebo et al., 1987). However, in samples with high concentrations of Glycolic Acid, the maximum injected amount had to be reduced. In the serum, the presence of Glycolic Acid has been demonstrated by preparing a derivative with *O*-*p*-nitrobenzyl-*N*,N^1-diisopropyl urea followed by

quantitation on a normal-phase liquid-chromatography system and by gas chromatography–mass spectrometry, colorimetric procedures, gas chromatography (Fraser and MacNeil, 1993), and gas–liquid chromatography (GLC) and mass spectrometry (Perier et al., 1988).

Glycolic Acid in natural water can be determined by an enzyme (glycolate oxidase) assay (Hackney and Hensley, 1987). High-performance liquid chromatography (HPLC) has been applied to determine Glycolic Acid in sugar cane process juice (Blake et al., 1987).

Lactic Acid

The method for determining Lactic Acid in whole or skim milk, ice cream, or butter involves the extraction of Lactic Acid with ether (Informatics, Inc., 1975). Ferric chloride is added to produce a color change, and then a spectrophotometer is used to compare the solution to a standard curve.

Lactic Acid has been measured by spectrophotometry (Kageyama et al., 1992) and nuclear magnetic resonance (Hurd and Freeman, 1991). Isotachophoretic determination can be used to separate and quantify Lactic Acid (Ovrebo et al., 1987). In erythrocytes, plasma, and Ehrlich ascites tumor cells, Lactic Acid was measured by GLC (Kageyama et al., 1992). HPLC has been used to determine Lactic Acid in sugar cane process juice (Blake et al., 1987).

D-Lactic Acid. D-Lactic Acid can be measured by chromatography but cannot be measured by a standard enzymatic method (details not provided) (Evans, 1986).

CHEMICAL REACTIVITY

AHAs display chemical reactivity common to both alcohols and carboxylic acids (Rosan, 1994). AHAs undergo an intermolecular acid-catalyzed, bimolecular dimerization (self-esterification), producing an ester that is a 4- or δ-hydroxy acid (Rosan, 1994). The resultant product, a "lactide," is a dimeric cyclic diester composed of two molecules of the original AHA.

Glycolic Acid

Glycolic Acid has a nonlinear pK_a–temperature profile with ionization increasing slightly at or near 25°C (Rosan, 1994). The heating of Glycolic Acid in the presence of sulfuric acid produces formaldehyde (Fraser and MacNeil, 1993).

Lactic Acid

Lactic Acid also has a nonlinear pK_a–temperature profile with ionization increasing slightly at or near 25°C (Rosan, 1994). Lactic Acid readily undergoes self-esterification (Informatics, Inc., 1975) (see Figure 1). Upon heating, dehydration occurs between the α-hydroxyl group of one molecule and the carboxyl of another to form several polylactic acids, e.g., lactyllactic acid. The products occur in all solutions containing greater than 18% Lactic Acid, and temperature affects the relative amounts of each moiety. Mixtures of Lactic Acid with nitric acid and hydrofluoric acid can react vigorously (Lewis, 1993b). When heated to decomposition, acrid smoke and irritating fumes are emitted. (This also occurs for its salts.)

ULTRAVIOLET ABSORPTION

Lactic Acid

Ammonium Lactate. The ultraviolet (UV) absorption of 12% Ammonium Lactate in 95% ethanol, hexanes, and 1,4-dioxane was determined (Kornreich et al., 1996). UVA (at 360 nm) and UVB (at 310 nm) absorption were low, with relative UVA and UVB absorption of Ammonium Lactate to mineral oil of 1 and 3, respectively.

IMPURITIES

AHAs may include free acid, intramolecular lactone, salt, and complex ion forms (Yu and Van Scott, 1994).

Glycolic Acid

Specifications analyses of Glypure 70, Glypure 99, and technical-grade (70%) Glycolic Acid (DuPont, 1995) are shown in Table 3. Typical analyses of these grades are shown in Table 4.

Table 3. Glycolic Acid specifications

	Glypure @99	Glypure @70	Technical (70%)
Total acid (%)	99.0 min	70.0 min	70.0 min
Total heavy metals (ppm)	<4	<4	N/A
Sulfates (ppm)	N/A	N/A	800 max
Formic acid (ppm)	N/A	N/A	4500 max
Turbidity (ntu)	N/A	N/A	6 max

Table 4. Typical analysis of Glycolic Acid

	Glypure @99%	Glypure @70	Technical (70%)
Total acid (%)	99.8–100.5	69.7–72.0	70.0–72.2
Heavy metals (ppm)	<4	<4	<4
Sulfates (ppm)	<100	<25	<150
Formic acid (ppm)	<10	<150	<3800
Turbidity (ntu)	N/A	N/A	<2.3
Formaldehyde (ppm)	<3.5	<15 (as made)	<750
Iron (ppm)	<1.0	<1.0	<7.0
Chloride (ppm)	<1.0	<1.0	<1.7
Sodium (ppm)	<10	<2.5	<32
Ammonia (ppm)	<5.0	<3.9	<110
Diglycolic acid	<115 ppm	<140 ppm	<1.1%
Methoxyacetic acid	<170 ppm	<190 ppm	<1.9%
Free acid (%)	>95.0	64.0–67.0	62.8–65.2

Lactic Acid

Commercial products contain Lactic Acid and water and can contain lactic anhydride in the more concentrated solutions (FAO/WHO, 1967). The total acid content, calculated as $C_3H_6O_3$, is not less than 95% and not more than 105% of the amount specified.

Myristyl Lactate. The original CIR Final Report on the Safety Assessment of Cetyl Lactate and Myristyl Lactate (Elder, 1982) states that depending on the purity of the starting materials, unspecified amounts of decyl, Lauryl, and/or Cetyl Lactate could be present in commercial Myristyl Lactate.

Cetyl Lactate. The original CIR Final Report on the Safety Assessment of Cetyl Lactate and Myristyl Lactate (Elder, 1982) states that unspecified amounts of Myristyl and/or stearyl Lactate could be present in commercial Cetyl Lactate and that it could also contain a maximum of 0.1% ash.

USE

COSMETIC

Glycolic and Lactic Acids are two of the most commonly used AHAs in retail cosmetic products (Kavanaugh, 1994). AHAs serve cosmetic functions by cleansing dead cells from the surface of the skin and by assisting moisturization.

Glycolic Acid

Glycolic Acid functions as a pH adjuster (Wenninger and McEwen, 1995a) and Glycolic Acid, its common salts, and its simple esters can function as a mild exfoliant in various cosmetic formulations (CTFA, 1995a). A solution containing equal moles of Glycolic Acid and Sodium Glycolate was a good and effective buffer for a pH range of 2.8–4.8 (Yu and Van Scott, 1994). However, a solution containing Glycolic Acid and Ammonium Glycolate was not an effective buffer because Ammonium Glycolate did not have the excess alkalinity that was needed to buffer the system when an external acid was added.

Product formulation data submitted to the FDA in 1997 reported that Glycolic Acid is used in 42 cosmetic formulations (FDA, 1997) (Table 5). Concentration of use values are no longer reported to the FDA by the cosmetic industry (FDA, 1992). However, data have been submitted to CIR that give the concentration of Glycolic Acid as used in products (CTFA, 1995b; Environmental Safety Laboratory–Unilever Research (ESLUR), 1994b) or as used in some formulations that have been tested for safety (Avon Products, Inc., 1995a). The use concentrations ranged from $<1\%$ in skin fresheners to $\leq 20\%$ in skin-care preparations.

Also, data submitted by FDA (FDA, 1996a) gave the results of an FDA survey that used "validated analytical methods" to determine the composition and pH of commercial products containing keratolytic agents. It was found that of the surveyed products that contained Glycolic Acid, the concentration of Glycolic Acid (or Glycolic Acid and Ammonium Glycolate) present ranged from 2 to 19% and the pH, determined on a 1:9 dilution of the product with water, ranged from 2.42 to 4.10. These data are summarized in Table 6.

FDA analyzed the pH of 12 commercial products (FDA, 1996b). The pH of the 12 products ranged from 2.68 to 8.19. The product formulation data submitted to the FDA in 1984 stated that Glycolic Acid was used in

1091-5818/98 $12.00 + .00

Table 5. Product formulation data on Glycolic Acid, Ammonium Glycolate, and Sodium Glycolate

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient		
		Gly. Acid	Amm. Gly.	Sdm. Gly.
Shampoos (noncoloring)	825	2	2	
Cuticle softeners	19	1		
Nail creams and lotions	17	1	1	
Cleansing preparations	630	8	6	
Face and neck preps. (excl. shaving)	251	7		
Body and hand preps. (excl. shaving)	776	4	3	
Moisturizing preparations	743	10	4	1
Paste masks (mud packs)	247	1		
Skin fresheners	181	1		
Other skin care preparations	683	7	3	
1997 Totals		**42**	**19**	**1**

Source. FDA, 1997.

23 hair rinse formulations (coloring) at a concentration of $\leq$0.1% (FDA, 1984).

The Esthetic Manufacturers/Distributors Alliance (EMDA) has developed guidelines for AHA professional use only product manufacturing and distribution (EMDA, 1996a). They state that salon-use professional products, AHA products developed and intended for application by a licensed esthetician or cosmetologist, should contain no more than 30% AHA and that the pH should be $\geq$3.0. EMDA has also developed professional guidelines for the AHA cosmetic chemical exfoliation procedure (EMDA, 1996b). These guidelines include a training program for licensed exfoliation practitioners, client patch testing, consultation, skin evaluation and inspection, and the use of a sunscreen with sun protection factor (SPF) 15 following the procedure.

In the FDA survey determining product composition and pH of commercial products containing keratolytic agents, the composition and pH of professional use only skin-peeling agents was also examined (FDA, 1996a). It was found that of the professional use products that contained Glycolic Acid, the concentration of Glycolic Acid (or Glycolic Acid and Ammonium Glycolate) present ranged from 3 to 67% and the pH, determined on a 1:9 dilution of the product with water, range from 0.2 to 4.38.

Ammonium Glycolate. In 1997, it was reported to the FDA that Ammonium Glycolate was used in 19 cosmetic formulations (FDA, 1997)

Table 6. Concentration of use of Glycolic Acid as submitted by industry

Products used in	Concentration	Reference
	Glycolic Acid (grade not specified)	
Facial cream/lotion	<8%	CTFA, 1995b
Skin fresheners	<1%	CTFA, 1995c
AHA drops	≤5%	CTFA, 1995c
Cleanser products	≤9.8%	CTFA, 1995c
Moisturizing products	≤10%	CTFA, 1995c
Night products	≤13%	CTFA, 1995c
Face and neck products	≤13%	CTFA, 1995c
Body and hand products	≤13%	CTFA, 1995c
Skin care preparations	≤20%	CTFA, 1995c
Preshave lotion	≤7.8%	CTFA, 1995c
Cuticle softeners	≤8%	CTFA, 1995c
Nail creams and lotions	≤8%	CTFA, 1995c
Shampoo	≤8%	CTFA, 1995c
'Skin peeling agents"	2–19% (pH 2.42–4.10)	FDA, 1996a
	99% Pure Glycolic Acid	
Face lotion	8.08% (pH 3.70–3.90)	Avon Products Inc., 1995a
	70% Aq. Glycolic Acid, nontechnical	
	<8%	ESLUR, 1994b
	70% Aq. Glycolic Acid (assumed nontechnical)	
Lipline gel	7.04–14.29% (pH 3.89–4.01)	Avon Products Inc., 1995a
Face cream	5.71–11.42% (pH 5.35–5.70)	Avon Products Inc., 1995a
Body lotion	2.86–14.29% (pH 3.5–3.80)	Avon Products Inc., 1995a
Hand and body cream	8.57–14.29% (pH 3.82–3.89)	Avon Products Inc., 1995a

(Table 5). Ammonium Glycolate was not reported to be used in 1984 (FDA, 1984).

Sodium Glycolate. In 1997, it was reported to the FDA that Sodium Glycolate was used in one cosmetic formulation (FDA, 1997) (Table 5). Sodium Glycolate was not reported to be used in 1984 (FDA, 1984).

Lactic Acid

Lactic Acid functions as a humectant, pH adjuster, and skin-conditioning agent–humectant (Wenninger and McEwen, 1995a) and as a mild

exfoliant (CTFA, 1995a) in numerous types of cosmetic formulations. One source states that it is primarily used as a moisturizer for dry skin (Elson, 1993), probably due to its pronounced affinity for water (Guillot et al., 1982a).

Astringents are a class of materials that are identified by their local effects on skin when applied topically (Wilkinson and Moore, 1982). Low molecular weight organic acids with an ionizable proton have astringent properties, and Lactic Acid is one of the most commonly encountered low molecular weight organic acids used as an astringent.

Product formulation data submitted to the FDA in 1997 reported that Lactic Acid was used in 342 cosmetic formulations (322 uses reported for Lactic Acid, 14 uses reported for L-Lactic Acid, and 6 uses in a trade-name mixture) (FDA, 1997) (Table 7). Data have been submitted to CIR that give the concentration of Lactic Acid (and some of its salts and esters) as used in products (CTFA, 1995b; ESLUR, 1994a) or as used in some formulations that have been tested for safety (Avon Products, Inc., 1995b–d). The use concentrations for Lactic Acid ranged from 0.1% in hair preparations to 11.8% in face cream preparations. Also, results from the previously described FDA survey of keratolytic agents (FDA, 1996a) report that of the surveyed products containing Lactic Acid, the concentration present ranged from 0.4 to 1% and the pH, determined on a 1:9 dilution of the product with water, ranged from 2.67 to 2.88. These data are summarized in Table 8. Upon examination of the composition and pH of professional use only skin-peeling agents, the results of this survey found that of the products that contained Lactic Acid, the concentration of Lactic Acid present ranged from 5 to 7% and the pH, determined on a 1:9 dilution of the product with water, ranged from 2.48 to 2.81.

Product formulation data submitted to the FDA in 1984 stated that Lactic Acid was used in 260 cosmetic formulations at a concentration of $\leq$25%; the concentration used with the most frequency was in the range of 0.1–1% (Table 9).

Potassium Lactate. Potassium Lactate functions as a buffering agent and a skin-conditioning agent–humectant (Wenninger and McEwen, 1995a). Product formulation data submitted to the FDA in 1997 reported that Potassium Lactate was used in three cosmetic formulations (FDA, 1997) (Table 7). Use data submitted to CIR by CTFA (1995b) stated that Potassium Lactate was used in a body lotion preparation at <0.1% (Table 8). Potassium Lactate was not reported to be used in 1984 (FDA, 1984).

Sodium Lactate. Sodium Lactate functions as a buffering agent and as a skin-conditioning agent–humectant in a number of product categories (Wenninger and McEwen, 1995a). It also functions as a mild

Table 7. Product formulation data on Lactic Acid, L-Lactic Acid, and Sodium, TEA-, Potassium, Ethyl, Lauryl, Myristyl, and Cetyl Lactate

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient								
		Lactic Acid	L-Lactic Acid	Potassium Lactate	Sodium Lactate	TEA-Lactate	Ethyl Lactate	Lauryl Lactate	Myristyl Lactate	Cetyl Lactate
Baby lotions, oils, powders, creams	51									1
Bath oils, tablets, and salts	117	1								
Bubble baths	186	1			1					
Other bath preparations	141	1								
Eyebrow pencil	89								11	
Eyeliner	499								42	
Eye shadow	501								47	
Other eye makeup preparations	116	1							5	1
Colognes and toilet waters	627	1								
Powders	234							4		4
Hair conditioners	596	33			7					
Hair sprays (aerosol fixatives)	255	8								
Permanent waves	297	9			4	4				

(Table continued on next page.)

Table 7. Product formulation data on Lactic Acid, L-Lactic Acid, and Sodium, TEA-, Potassium, Ethyl, Lauryl, Myristyl, and Cetyl Lactate (*continued*)

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient								
		Lactic Acid	L-Lactic Acid	Potassium Lactate	Sodium Lactate	TEA-Lactate	Ethyl Lactate	Lauryl Lactate	Myristyl Lactate	Cetyl Lactate
Rinses (noncoloring)	42	5			1					
Shampoos (noncoloring)	825	35			4					
Tonics/dressings/other hair grooming aids	512	32	2		5				2	
Wave sets	55	4								
Other hair preparations	311	16								
Hair dyes and colors	1478	41								
Hair bleaches	104	1								
Other hair coloring preparations	56	4								
Blushers (all types)	229								3	
Face powders	245								1	
Foundations	283	2			2	1				
Lipstick	758								53	29
Makeup bases	125		1						1	
Makeup fixatives	8	2								
Other makeup preparations	122								1	

Cuticle softeners	19	1							
Nail polish and enamel removers	33					1			
Other manicuring preparations	59					2			
Bath soaps and detergents	341	2							
Deodorants (underarm)	241			1			1		
Douches	16	2							
Other personal cleanliness products	262						1	3	
Aftershave lotion	212	7		3					
Preshave lotions (all types)	14		1						
Shaving cream	138								2
Other shaving preparation products	60		1					1	
Cleansing preparations	630	26	2	6	2		2		
Face and neck preps (excl shaving)	251	9	1	4	2		1		

(*Table continued on next page.*)

Table 7. Product formulation data on Lactic Acid, L-Lactic Acid, and Sodium, TEA-, Potassium, Ethyl, Lauryl, Myristyl, and Cetyl Lactate (*continued*)

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient								
		Lactic Acid	L-Lactic Acid	Potassium Lactate	Sodium Lactate	TEA-Lactate	Ethyl Lactate	Lauryl Lactate	Myristyl Lactate	Cetyl Lactate
Body and hand preps (excl shaving)	776	14	1	1	5	1			5	1
Moisturizing preparations	743	17	1		14			2	6	
Night preparations	185	7			1			1		
Paste masks (mud packs)	247	8	1		4				2	
Skin fresheners	181	9	1	1	4				1	
Other skin-care preparations	683	19	1	1	17	2			5	
Suntan gels, creams, and liquids	134	2			1					
Indoor tanning preparations	50	1							6	
Other suntan preparations	43	1	1		2	1				
Uses in tradename mixture		6			6					
1997 Totals		**328**	**14**	**3**	**93**	**13**	**3**	**13**	**195**	**38**

Source. FDA, 1997.

Table 8. Concentration of use of Lactic Acid and Potassium, Sodium, Ethyl, Lauryl, Myristyl, and Cetyl Lactate

Products used in	Concentration	Reference
	Lactic Acid (% aq. not specified)	
Lash and brow tint	1.2%	CTFA, 1995b
Skin care preparations	0.1–5%	CTFA, 1995b
Legs and feet lotion	1%	CTFA, 1995b
Hair preparations (on head)	0.1–1% (0.05–0.5%)	CTFA, 1995b
Hair conditioner soap	0.8%	CTFA, 1995b
Oxidative hair dyes	<1%	CTFA, 1995b
Shampoo	2%	CTFA, 1995b
Hair fixatives	5.0%	CTFA, 1995b
Cleanser products	≤2%	CTFA, 1995c
Face and neck products	≤10%	CTFA, 1995c
Moisturizing products	≤10%	CTFA, 1995c
Night products	≤10%	CTFA, 1995c
Foundations	≤8%	CTFA, 1995c
Makeup bases	≤8%	CTFA, 1995c
Body and hand products	≤10%	CTFA, 1995c
Indoor tanning preparations	≤6%	CTFA, 1995c
"Other" skin-care preparations	≤6%	CTFA, 1995c
Cuticle softeners	≤10%	CTFA, 1995c
Nail creams and lotions	≤10%	CTFA, 1995c
Bath capsules	≤6%	CTFA, 1995c
Commercial "skin peeling agents"	0.4–1.0% (pH 2.67–2.88)	CTFA, 1995c
	85% Aq. Lactic Acid	
Eye cream	0.12–3.53% (pH 4.00–6.33)	Avon Products Inc., 1995b
Face cream	0.25–11.80% (pH 2.02–4.26)	Avon Products Inc., 1995b
Face lotion	7.06% (pH 3.75)	Avon Products Inc., 1995b
Skin cream	0.60% (pH 7.50)	Avon Products Inc., 1995b
Nail strengthener	0.40% (pH 7.36–7.52)	Avon Products Inc., 1995b
Cuticle cream	11.77% (pH 3.79)	Avon Products Inc., 1995b
Shampoo	0.70–0.80% (pH 5.30–6.20)	Avon Products Inc., 1995b
	L-Lactic Acid	
Skin care product	<8%	ESLUR, 1994a
	Potassium Lactate	
Body lotion	<0.1%	CTFA, 1995b
	60% Aq. Sodium Lactate	
Face cream	0.10–0.20% (pH 7.90)	Avon Products Inc., 1995c
Facial cleanser	0.10%	Avon Products Inc., 1995c
Facial freshener	0.10–0.15%	Avon Products Inc., 1995c
Facial lotion	0.20% (pH 6.55–7.00)	Avon Products Inc., 1995c
Night cream	0.20–0.40% (pH 5.25–8.60)	Avon Products Inc., 1995c
Foundation	0.15%	Avon Products Inc., 1995c
Hair conditioner	0.20% (pH 3.20–5.00)	Avon Products Inc., 1995c
Shampoo	0.20–0.25% (pH 5.50–5.60)	Avon Products Inc., 1995c

(Table continued on next page.)

Table 8. Concentration of use of Lactic Acid and Potassium, Sodium, Ethyl, Lauryl, Myristyl, and Cetyl Lactate (*continued*)

Products used in	Concentration	Reference
	Ethyl Lactate	
Nail enamel corrector	50.00%	Avon Products Inc., 1995d
	Lauryl Lactate	
Skin-care preparations	>1.5%	CTFA, 1995b
Eye cream	0.10% (pH 5.30–6.33)	Avon Products Inc., 1995e
Face cream	3.2–5.0% (pH 3.87–4.65)	Avon Products Inc., 1995e
Body freshener	1.0–2.0% (pH 7.30)	Avon Products Inc., 1995e
	Myristyl Lactate	
Makeup preparations	>1.5%	CTFA, 1995b
Skin-care preparations	>1.5%	CTFA, 1995b
Eye shadow	5.0–15.0%	CTFA, 1995b
Lip pencil	11.54%	CTFA, 1995b
Foundation	7.65%	CTFA, 1995b
	Cetyl Lactate	
Eye cream	0.5–2.0 (pH 5.4)	Avon Products Inc., 1995g
Lipstick	3.0–9.0%	Avon Products Inc., 1995g
Lip pencil	3.0%	Avon Products Inc., 1995g
Aftershave moisturizer	0.75% (pH 7.0–8.0)	Avon Products Inc., 1995g
Face lotion	0.75% (pH 7.7–7.9)	Avon Products Inc., 1995g
Moisturizing cream	1.0–1.5 (pH 6.1–7.8)	Avon Products Inc., 1995g
Moisture cream	1.0 (pH 6.5)	Avon Products Inc., 1995g
Moisture lotion	1.0 (pH 7.0)	Avon Products Inc., 1995g
Night cream	1.0 (pH 6.2)	Avon Products Inc., 1995g
Cleansing cream	1.0 (pH 7.15–8.0)	Avon Products Inc., 1995g
Foundation	3.0–5.0% (pH 6.0–7.5)	Avon Products Inc., 1995g
Body cream	0.5–2.0% (pH 5.4)	Avon Products Inc., 1995g
Body refresher	1.0 (pH 7.3)	Avon Products Inc., 1995g
Body lotion	1.1 (pH 7.0)	Avon Products Inc., 1995g

exfoliant (CTFA, 1995a). Product formulation data submitted to the FDA in 1997 reported that Sodium Lactate was used in 93 cosmetic formulations (87 uses reported for Sodium Lactate and 6 uses in a tradename mixture) (FDA, 1997). Product safety testing data reported concentrations of 60% aq. Sodium Lactate that ranged from 0.10% in face creams, cleansers, and fresheners to 0.40% in night creams (Avon Products Inc., 1995c) (see Table 8). Product formulation data submitted to the FDA in 1984 (FDA, 1984) stated that Sodium Lactate was used in 76 cosmetic formulations at a concentration of ≤50%; the concentration used with the most frequency was in the range of 0.1–1% (see Table 9).

TEA-Lactate. TEA-Lactate functions as a skin-conditioning agent–humectant (Wenninger and McEwen, 1995a) and as a mild exfoliant (CTFA, 1995a). Product formulation data submitted to the FDA in 1997 reported that TEA-Lactate was used in 13 cosmetic formulations (FDA,

1997) (see Table 7). Product formulation data submitted to the FDA in 1984 (FDA, 1984) stated that TEA-Lactate was used in 33 cosmetic formulations at a concentration of ≤0.1% (see Table 9).

Ethyl Lactate. Product formulation data submitted to the FDA in 1997 reported that Ethyl Lactate was used in three cosmetic formulations (FDA, 1997) (Table 7). Product safety test data reported a nail enamel formulation containing 50% Ethyl Lactate (Avon Products Inc., 1995d) (Table 8). Ethyl Lactate was not reported to be used in 1984 (FDA, 1984). Opdyke and Letizia (1982) reported that Ethyl Lactate has been in public use since the 1940s and that the usual concentration in the final product is 0.01% for soaps, 0.001% for detergents, and 0.005% for creams and lotions, with maximum concentrations of 0.2, 0.02, and 0.07%, respectively.

Butyl Lactate. Butyl Lactate has been in public use since the 1930s (Opdyke, 1979). The usual concentration in the final product is reported to be 0.005% for soaps, 0.0005% for detergents, and 0.0025% for creams and lotions, with maximum concentrations of 0.03, 0.003, and 0.01%, respectively.

Lauryl Lactate. Lauryl Lactate functions as a skin-conditioning agent–emollient (Wenninger and McEwen, 1995a). Product formulation data submitted to the FDA in 1997 reported that Lauryl Lactate was used in 13 cosmetic formulations (FDA, 1997) (Table 7). Use data (CTFA, 1995b) and product safety testing data (Avon Products Inc., 1995e) reported concentrations ranging from 0.10% in eye creams to 5.0% in face creams (Table 8). Product formulation data submitted to the FDA in 1984 (FDA, 1984) stated that Lauryl Lactate was used in 15 cosmetic formulations at a concentration of ≤25%; the concentration used with the most frequency was in the range of 1–5% (Table 9).

Myristyl Lactate. Myristyl Lactate functions as a skin-conditioning agent–emollient in a variety of product categories (Wenninger and McEwen, 1995a). Product formulation data submitted to the FDA in 1997 reported that Myristyl Lactate was used in 195 cosmetic formulations (FDA, 1997) (Table 7). Use data (CTFA, 1995b) and product safety testing data (Avon Products Inc., 1995f) reported concentrations ranging from >1.5% in makeup and skin-care preparations to 15% in eye shadow formulations (Table 8). Product formulation data submitted to the FDA in 1984 (FDA, 1984) stated that Myristyl Lactate was used in 292 cosmetic formulations at a concentration of ≤50%; the concentration used with the most frequency was in the range of 5–10% (Table 9).

Cetyl Lactate. Cetyl Lactate functions as a skin-conditioning agent–emollient (Wenninger and McEwen, 1995a). Product formulation data

Table 9. Concentration of use of Lactic Acid, and Sodium, TEA-, Lauryl, Myristyl, and Cetyl Lactate

Product category	Concentration of use (%)							
	25–50	10–25	5–10	1–5	0.1–1	0–0.1	Unknown	Total
				Lactic Acid				
Baby lotions/oils/ powders/creams					1			1
Bath oils/tablets/salts				1	3			4
Bubble baths					4			4
Other bath preparations					3			3
Eye makeup remover					1			1
Colognes/toilet waters					1			1
Hair conditioners			1	5	11			17
Rinses (noncoloring)						1		1
Shampoos (noncoloring)		1		11	13	2		27
Tonics/dressings/other hair grooming aids				1	4			5
Wave sets					3	3		6
Other hair preparations				1	2	1		4
Hair dyes/colors (requires caution stmts)				2		26		28
Other hair coloring preparations				1	3			4
Foundations							1	1
Makeup bases				1	2			3
Makeup fixatives					2			2
Other makeup preparations						1		1
Cuticle softeners		1						1
Bath soaps/detergents					3			3
Douches		2		4	4			10
Feminine hygiene deodorants						2		2
Other personal cleanliness products				1				1
Aftershave lotions					6		1	7
Preshave lotions							1	1
Shaving cream (aerosol/ brushless/lather)					2			2
Other shaving preparations				1				1
Skin cleansing products (cold creams/lotions/ liquids/pads)				3	6	10	3	22
Face/body/hand (excl. shaving preparations)				4	2	5	6	17
Moisturizing products					7	5	13	25
Night preparations					2		2	4
Paste masks (mud packs)				1	1			2
Skin fresheners				2	3	3	20	28
Other skin-care preparations						1	14	15

(*Table continued on next page.*)

Table 9. Concentration of use of Lactic Acid, and Sodium, TEA-, Lauryl, Myristyl, and Cetyl Lactate (*continued*)

Product category	Concentration of use (%)							
	25–50	10–25	5–10	1–5	0.1–1	0–0.1	Unknown	Total
Suntan gels/creams/liquids				1			2	3
Indoor tanning preparations							1	1
Other suntan preparations				2				2
1984 Totals (Lactic Acid)		**4**	**1**	**42**	**89**	**60**	**64**	**260**
Sodium Lactate								
Hair conditioners					1			1
Makeup bases			1		2			3
Douches	1		1		2		1	5
Aftershave lotions					3	1		4
Shaving cream (aerosol/ brushless/lather)						1		1
Skin cleansing products (cold creams/lotions/ liquids/pads)				3		2	2	7
Face/body/hand (excl. shaving preparations)				1	4	1	6	12
Moisturizing products					9	6	10	25
Night preparations				1	3		2	6
Paste masks (mud packs)					1			1
Skin fresheners				1	1	2	3	7
Other skin-care preparations							1	1
Suntan gels/creams/liquids							2	2
Indoor tanning preparations							1	1
1984 Totals (Sodium Lactate)	**1**		**2**	**6**	**26**	**13**	**28**	**76**
TEA Lactate								
Makeup bases						2		2
Face/body/hand (excl. shaving preparations)						2	5	7
Moisturizing products						5	9	14
Night preparations						1	2	3
Skin fresheners						1	3	4
Suntan gels/creams/liquids							2	2
Indoor tanning preparations							1	1
1984 Totals (TEA Lactate)						**11**	**22**	**33**
Lauryl Lactate								
Hair conditioners						3		3
Blushers (all types)		1						1
Lipstick		1		1				2
Other makeup preparations				1				1
Other personal cleanliness products				3				3
Skin cleansing products (cold creams/lotions/ liquids/pads)				2				2
Moisturizing products				2				2
Other skin-care preparations				1				1

(*Table continued on next page.*)

Table 9. Concentration of use of Lactic Acid, and Sodium, TEA-, Lauryl, Myristyl, and Cetyl Lactate (*continued*)

Product category	Concentration of use (%)							
	25–50	10–25	5–10	1–5	0.1–1	0–0.1	Unknown	Total
1984 Totals (Lauryl Lactate)		**2**		**10**		**3**		**15**
				Myristyl Lactate				
Bath oils/tablets/salts					1			1
Eye shadow		1	8	31	1		13	54
Perfumes	1				1			2
Sachets					1			1
Other fragrance preparations				4				4
Hair conditioners					1			1
Tonics/dressings/other hair grooming aids					1			1
Blushers (all types)		1	3	18				22
Foundations					1			1
Lipstick	1	35	95	35	1			167
Makeup bases				1	3			4
Rouges				1				1
Other makeup preparations			2	2				4
Other personal cleanliness products					2			2
Aftershave lotions				1	3			4
Face/body/hand (excl. shaving preparations)							3	3
Moisturizing products			1	7	3			11
Night preparations				3				3
Skin lighteners				1				1
Wrinkle smoothing products (removers)	1							1
Other skin-care preparations				1				1
Suntan gels/creams/ liquids			2	1				3
1984 Totals (Myristyl Lactate)	**3**	**37**	**111**	**106**	**19**		**16**	**292**
				Cetyl Lactate				
Baby lotions/oils/ powders/creams						1		1
Other bath preparations					1			1
Eyebrow pencil				1				1
Eye shadow		1		19		6		26
Other eye makeup preparations				4	1			5
Hair conditioners				9	1			10

(*Table continued on next page.*)

Table 9. Concentration of use of Lactic Acid, and Sodium, TEA-, Lauryl, Myristyl, and Cetyl Lactate (*continued*)

	Concentration of use (%)							
Product category	25–50	10–25	5–10	1–5	0.1–1	0–0.1	Unknown	Total
Rinses (noncoloring)				4				4
Tonics/dressings/other hair grooming aids			2					2
Other hair preparations				1				1
Blushers (all types)			1	8	9			18
Foundations				9	2			11
Lipstick			28	79	11			118
Makeup bases					10			10
Other makeup preparations					1		1	2
Skin cleansing products (cold creams/lotions/ liquids/pads)			1					1
Moisturizing products			1	1	3			5
Night preparations				3	1			4
Wrinkle smoothing products (removers)			2					2
Suntan gels/creams/ liquids		1			1			2
1984 Totals (Cetyl Lactate)		**2**	**35**	**138**	**41**	**7**	**1**	**224**

Source. FDA, 1984.

submitted to the FDA in 1997 reported that Cetyl Lactate was used in 38 cosmetic formulations (FDA, 1997) (Table 7). Product safety testing data reported concentrations ranging from 0.5% in body and eye cream preparations to 9.0% in lipstick formulations (Avon Products Inc., 1995g) (Table 8). Product formulation data submitted to the FDA in 1984 (FDA, 1984) stated that Cetyl Lactate was used in 224 cosmetic formulations at a concentration of $\leq$25%; the concentration used with the most frequency was in the range of 1–5% (Table 9).

INTERNATIONAL

Glycolic Acid

Glycolic Acid is listed in the Japanese *Comprehensive Licensing Standards of Cosmetics by Category (CLS)* (Rempe and Santucci, 1997). Glycolic Acid that conforms to the specifications of the *Japanese Cosmetic Ingredients Codex (JCIC)* has precedent for use without restriction in all *CLS* categories except eyeliner, lip, oral, and bath preparations, for which there is no precedent for use.

Lactic Acid

Lactic Acid is listed in the Japanese *CLS* (Rempe and Santucci, 1997). Lactic Acid that conforms to the specifications of the *Japanese Standards of Cosmetic Ingredients (JSCI)* has precedent for use without restriction in all *CLS* categories and that which conforms to the specifications of the *Japanese Standards of Food Additives* has precedent for use without restriction in all *CLS* categories except eyeliner preparations, for which there is no precedent for use.

Calcium Lactate. Calcium Lactate is listed in the Japanese *CLS* (Rempe and Santucci, 1997). Lactic Acid that conforms to the specifications of the *Japanese Pharmacopoeia* has precedent for use without restriction in all *CLS* categories except eyeliner preparations, for which there is no precedent for use.

Sodium Lactate. Sodium Lactate is listed in the Japanese *CLS* as Sodium Lactate Solution (Rempe and Santucci, 1997). Sodium Lactate solution that conforms to the specifications of the *JSCI* has precedent for use without restriction in all *CLS* categories.

TEA-Lactate. According to the Cosmetics Directive of the European Union (European Economic Community, 1995), trialkanolamines are allowed for use in non-rinse-off products at a maximum concentration of 2.5%; no concentration limit was given for other products. Non-rinse-off and other products containing trialkanolamines cannot be used with nitrosating systems, must have a minimum purity of 99%, can have a maximum secondary alkanolamine content of 0.5% (concerning raw materials), a maximum *N*-nitrosodialkanolamine content of 50 μg/kg, and must be kept in nitrite-free containers.

Lauryl Lactate. Lauryl Lactate is listed in the Japanese *CLS* (Rempe and Santucci, 1997). Lauryl Lactate that conforms to the specifications of the *JCIC* has precedent for use without restriction in all *CLS* categories except eyeliner preparations, for which there is no precedent for use.

Myristyl Lactate. Myristyl Lactate is listed in the Japanese *CLS* (Rempe and Santucci, 1997). Myristyl Lactate that conforms to the specifications of the *JSCI* has precedent for use without restriction in all *CLS* categories.

Cetyl Lactate. Cetyl Lactate is listed in the Japanese *CLS* (Rempe and Santucci, 1997). Cetyl Lactate that conforms to the specifications of the *JSCI* has precedent for use without restriction in all *CLS* categories.

NON-COSMETIC

Glycolic Acid

Glycolic Acid can be used as a chemical peel (Murad and Shamban, 1994a). It is claimed that unneutralized Glycolic Acid, at 5–10%, can be used for treating lamellar and X-linked ichthyosis (Van Scott and Yu, 1984) and xerosis (Wehr et al., 1991). Glycolic Acid has been approved by FDA for use as an indirect food additive (adhesives) (Rothschild, 1990). It is used in cutaneous electrodeless plating and textile finishing (Lewis, 1993a). Ethyl Glycolate is a solvent for nitrocellulose and resins (Grant, 1972).

Lactic Acid

Lactic Acid, Calcium Lactate, Potassium Lactate, and Sodium Lactate have been approved for use as direct food additives with generally recognized as safe (GRAS) status for use beyond infancy at concentrations that do not exceed good manufacturing practices (GMP) (FDA, 1980). An acceptable daily intake (ADI) was not be specified for L-Lactic Acid, but an ADI of 0–0.1 g/kg for D-Lactic Acid was established (JECFA, 1974). The OTC drug ingredient status follows (CTFA, 1991a):

Lactic Acid: ANPR Category III for use to alter vaginal pH for reasons of effectiveness; ANPR Category III for use in lowering surface tension and producing mucolytic effects for reasons of effectiveness; Final Rule Category II for use as a wart remover for reasons of safety and effectiveness.
Calcium Lactate: Final Rule, Category II for use as an anorectic for reasons of safety and effectiveness.
Sodium Lactate: ANPR Category III for use to alter vaginal pH for reasons of effectiveness.

Remington's Pharmaceutical Sciences (Gennaro, 1990) states that 16.7% Lactic Acid is used to remove warts and small cutaneous tumors and that a 10% solution is used as a bactericidal agent on neonatal skin. Lactic Acid formulations partially neutralized with ammonium hydroxide are proposed to be used in treating lamellar and X-linked ichthyosis (Van Scott and Yu, 1984). Higher doses of Lactic Acid may be used to lighten "age spots" (Van Scott and Yu, 1989b). Lactic Acid is reported to be used to treat xerosis (Wehr et al., 1991).

Lactic Acid is used as a reagent to detect glucose and pyrogallol and in the leather, textile, and tanning industries (Grant, 1972). Lactic Acid (DL-) is also used in dyeing, as a plasticizer and catalyst in the casting of phenolaldehyde resins (Budavari, 1989), and as a sizer in the felt hat

industry (Schwartz et al., 1948). Lactic Acid and sodium chlorite are the "active ingredients" that are mixed together, resulting in chlorine dioxide, to form the antimicrobial Alcide (Scatina et al., 1984).

Ammonium Lactate is approved by the FDA under the name Lac-Hydrin (ammonium lactate) 12% lotion for treatment of ichthyosis vulgaris and dry, scaly skin (xerosis) and for the temporary relief of itching associated with these conditions (FDA, 1988). Ammonium Lactate has been used for the treatment of dry skin of the heels (Jackson, 1994). It is also proposed to be effective in treating photodamaged skin (Gibson et al., date unknown). Ammonium Lactate has veterinary use for bovine ketosis (Budavari, 1989).

Calcium Lactate has veterinary use for hypocalcemic states (Budavari, 1989). It has been used to treat rachitis and scrofula (Grant, 1972).

Sodium Lactate is an "electrolyte replenisher and systemic and urinary alkalizer" (Budavari, 1989). It is sometimes compounded with Ringer's solution (Grant, 1972). Sodium Lactate has veterinary use for bovine ketosis (Budavari, 1989). It is a hygroscopic agent, glycerol substitute, a plasticizer for casein, and a corrosion inhibitor in alcohol antifreeze (Lewis, 1993a).

Methyl Lactate is used as a cellulose acetate solvent (Budavari, 1989).

Ethyl Lactate and *Butyl Lactate* are approved for use as a direct food additive (Rothschild, 1990). Ethyl Lactate is used as a solvent for nitrocellulose, cellulose acetate, and many cellulose ethers and resins (Lewis, 1993a). It is a possible vehicle for drug administration (Gosselin et al., 1984). It is also used in lacquers, paints, enamels,varnishes, stencil sheets, safety glass, and flavoring.

Butyl Lactate is used as a solvent for nitrocellulose, ethyl cellulose, oils, dyes, natural gums, many synthetic polymers, lacquers, varnishes, inks, stencil pastes, antiskinning agent, dry-cleaning fluids, and adhesives (Lewis, 1993a).

Cetyl Lactate is used as a nonionic emollient and to improve the feel and texture of pharmaceutical preparations (Budavari, 1989).

ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION

Glycolic Acid

The topical efficacy of an AHA formulation depends on the bioavailable concentration and the vehicle used (Yu and Van Scott, 1996). The bioavailability of topical AHA-containing products, defined as the fraction of the AHA that can permeate the skin, depends on the fraction of free AHA present in the formulation. The bioavailability of Glycolic Acid in a topical formulation was examined. The bioavailable concentration of Glycolic Acid was then determined by multiplying the bioavailability and the concentration of the Glycolic Acid used in the formulation. These data are summarized in Table 10.

The vehicle used for the formulation also plays a role in absorption (Yu and Van Scott, 1996). For example, because Glycolic Acid is water soluble, with an oil-in-water (o/w) emulsion in which water is a continuous outside phase, most Glycolic Acid in the water phase is in direct contact with the stratum corneum when topically applied. Additionally, certain components in a vehicle can interfere with or enhance the topical effects of AHAs. Glycerin appears to have a strong affinity with water-soluble AHAs and, "since glycerin cannot substantially penetrate the stratum corneum, it affects the permeation of the AHA molecules." In contrast, propylene glycol can enhance the penetration of an AHA by modifying the permeability of the stratum corneum.

While Yu and Van Scott (1996) calculated the bioavailability and bioavailable concentrations, and noted that vehicle plays a role, it is important to refer to the section on "Physical and Chemical Properties" in which the complications of the relationship between the pH and the concentration of free acid are discussed. In that section it was stated that the relationship between the concentration of free acid, the pH, and the total concentration of AHA cannot be calculated simply and the influence of the partitioning of the AHA between phases in an emulsion must be considered.

The deposition of Glycolic Acid in a number of vehicles was investigated using male SKH-hr-1 hairless mice (Ohta et al., 1996). Glycolic Acid solutions (40 mg/mL) with trace amounts of [^{14}C]Glycolic Acid were prepared in an aqueous solution, two nonionic formulations, Non-1 containing glyceryl dilaurate/cholesterol/polyoxyethylene-10-stearyl

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Table 10. Bioavailability of Glycolic Acid as a function of pH

		Bioavailable concentration (%) at Glycolic Acid concentration:						
pH	Bioav. @25°C	4	8	12	20	35	50	70
2.0	0.99	4	8	12	20	35	50	69
2.5	0.96	3.8	7.7	12	19	34	48	67
3.0	0.87	3.5	7.0	10	17	30	44	61
3.2	0.81	3.2	6.5	9.7	16	28	41	57
3.4	0.73	2.9	5.8	8.8	15	26	37	51
3.6	0.63	2.5	5.0	7.6	13	22	32	44
3.8	0.52	2.1	4.2	6.2	10	18	26	36
3.83	0.50	2.0	4.0	6.0	10	17.5	25	35
4.0	0.40	1.6	3.2	4.8	8	14	20	28
4.2	0.30	1.2	2.4	3.6	6	11	15	21
4.4	0.21	0.8	1.7	2.5	4.2	7.4	11	15
4.6	0.15	0.6	1.2	1.8	3	5.3	7.5	11
4.8	0.10	0.4	0.8	1.2	2.0	3.5	5.0	7.0
5.0	0.06	0.2	0.5	0.7	1.2	2.1	3.0	4.2

ether and Non-2 containing glyceryl distearate/cholesterol/polyoxyethylene-10-stearyl ether, 30% (w/w) propylene glycol in water (PG/water), an o/w emulsion (80:20 (w/w) aqueous phase to oil phase), and a water-in-oil (w/o) emulsion (45:55 (w/w) water-to-oil). Using at least three animals per formulation per time point, 25 μL of the test formulation were applied without an occlusive patch to a 4-cm^2 area of the dorsal surface. One hour after application, the site was wiped three times to remove test material. Animals were killed at the time of wiping and 2, 4, and 8 h later. Full-thickness dorsal skin was excised, and the liver and the urinary bladder were removed. The excised skin was repeatedly tape stripped until it appeared "shiny and glossy," approximately 15 times. The remaining skin, the urinary bladder, and the surface swabs and strips were assayed for Glycolic Acid content using a scintillation counter. The amount of Glycolic Acid adhering to the stratum corneum surface was defined as the first two strippings, and the amount found in the stratum corneum was defined as strippings 3–15. The accumulation of Glycolic Acid in the stratum corneum using the different vehicles at 1 and 8 h was in the following order: aqueous solution = Non-1 = Non-2 > w/o emulsion = o/w emulsion = 30% PG/water solution. The amounts of Glycolic Acid in the "living skin strata" were significantly greater with Non-1 formulations as compared to all other formulations at all time periods except after 8 h, when Non-1 was similar to Non-2 and the w/o emulsion. The remaining formulations were similar to each other at all

time points, with the exception of the 30% PG/water solution, which had the poorest deposition at all times. The amount of Glycolic Acid in the urinary bladder at 8 h was significantly greater with Non-1 as compared to the others. The distribution of Glycolic Acid (% ± standard deviation) is presented in Table 11. Approximately 1–2% of the Glycolic

Table 11. Distribution of Glycolic Acid in mice as a function of vehicle (%)

Time (h)	Swabs	Strat. corn. surface	Stratum corneum	Living skin strata	Urinary excretion	Recovery
			Aqueous solution			
0	40.0 ± 3.7	28.4 ± 1.7	16.1 ± 3.7	1.04 ± 0.14	N/A	85.7 ± 2.2
4	55.9 ± 9.1	19.9 ± 2.1	11.8 ± 2.1	0.96 ± 0.18	N/A	88.5 ± 3.8
8	40.1 ± 7.9	17.0 ± 1.1	16.3 ± 0.9	0.32 ± 0.01	N/A	73.7 ± 5.6
			Non-1 liposomes			
0	18.4 ± 4.2	49.7 ± 4.5	17.2 ± 4.0	2.59 ± 0.90	0.22 ± 0.07	88.1 ± 3.2
1	23.1 ± 4.9	32.1 ± 3.5	20.6 ± 3.4	2.83 ± 0.84	0.40 ± 0.07	79.0 ± 3.6
2	23.4 ± 5.0	26.0 ± 4.2	19.8 ± 5.8	2.95 ± 0.82	1.15 ± 0.11	72.5 ± 7.0
4	19.7 ± 4.5	29.8 ± 6.0	17.5 ± 8.1	2.02 ± 0.80	1.81 ± 0.49	69.0 ± 8.0
8	16.3 ± 2.0	28.0 ± 5.3	10.9 ± 3.9	0.81 ± 0.27	2.10 ± 0.59	58.1 ± 5.5
			Non-2 liposomes			
0	13.2 ± 2.0	52.6 ± 5.1	13.6 ± 3.8	1.92 ± 0.93	0.15 ± 0.03	81.5 ± 2.3
1	12.6 ± 3.3	48.8 ± 8.7	14.7 ± 4.0	1.45 ± 0.15	0.13 ± 0.02	77.6 ± 2.3
2	21.2 ± 2.6	41.6 ± 3.5	9.9 ± 2.6	1.02 ± 0.39	0.20 ± 0.10	73.9 ± 3.0
4	17.6 ± 3.7	33.1 ± 5.7	14.7 ± 2.5	1.15 ± 0.34	0.49 ± 0.11	67.1 ± 4.1
8	11.0 ± 0.8	34.3 ± 1.3	14.6 ± 1.2	0.95 ± 0.36	0.83 ± 0.12	61.7 ± 2.6
			30% PG/water solution			
0	62.8 ± 4.0	24.6 ± 3.2	5.3 ± 1.6	0.36 ± 0.05	0.09 ± 0.05	93.1 ± 1.2
1	68.0 ± 5.5	16.4 ± 2.2	7.2 ± 3.5	0.29 ± 0.11	0.27 ± 0.08	92.2 ± 0.3
2	68.9 ± 2.7	13.9 ± 3.1	6.6 ± 2.3	0.33 ± 0.07	0.41 ± 0.16	90.2 ± 0.5
4	61.9 ± 6.4	16.0 ± 3.0	7.4 ± 0.4	0.51 ± 0.09	0.42 ± 0.10	86.3 ± 2.8
8	68.8 ± 3.4	12.7 ± 2.6	5.3 ± 1.4	0.26 ± 0.06	0.32 ± 0.13	87.4 ± 1.7
			O/W emulsion			
0	60.8 ± 1.3	25.5 ± 0.9	2.9 ± 0.7	0.85 ± 0.28	0.04 ± 0.03	90.0 ± 2.0
1	56.1 ± 6.1	24.9 ± 2.6	4.9 ± 2.9	0.77 ± 0.27	0.06 ± 0.02	86.8 ± 2.1
2	57.2 ± 2.3	21.6 ± 0.9	6.9 ± 1.4	0.87 ± 0.30	0.10 ± 0.03	86.6 ± 0.3
4	54.0 ± 2.0	20.3 ± 4.0	7.8 ± 1.0	0.98 ± 0.23	0.14 ± 0.05	83.2 ± 1.8
8	53.9 ± 1.5	16.2 ± 1.9	8.1 ± 0.7	0.89 ± 0.26	0.36 ± 0.05	79.3 ± 1.8
			W/O emulsion			
0	46.9 ± 5.2	22.4 ± 1.5	6.0 ± 0.2	0.77 ± 0.40	0.11 ± 0.02	76.2 ± 6.7
1	54.1 ± 3.4	18.8 ± 2.0	7.6 ± 1.4	0.63 ± 0.31	0.20 ± 0.06	81.3 ± 5.2
2	50.0 ± 3.2	18.1 ± 2.5	8.2 ± 1.2	0.88 ± 0.29	0.32 ± 0.070	77.5 ± 0.7
4	57.4 ± 4.7	12.1 ± 2.6	5.0 ± 0.9	0.66 ± 0.28	.35 ± 0.15	75.6 ± 5.1
8	55.1 ± 7.2	16.2 ± 8.2	6.1 ± 0.4	0.57 ± 0.04	0.47 ± 0.33	78.5 ± 1.6

Table 12. Distribution of Glycolic Acid in vitro (mouse skin) as a function of vehicle (%)

	Formulation			
	Aqueous	Non-1	Non-2	30% PG/water
Total donor	1.2 ± 1.0	2.0 ± 0.4	3.4 ± 4.2	1.2 ± 1.0
Total swabs	79.4 ± 5.4	47.4 ± 13.7	10.0 ± 8.7	72.9 ± 2.0
Strips 1, 2	21.1 ± 3.3	17.2 ± 10.7	66.1 ± 9.2	11.5 ± 0.3
Total strips	21.2 ± 3.3	19.0 ± 12.1	66.7 ± 9.3	11.6 ± 0.3
Living skin strata	0.9 ± 0.8	3.5 ± 1.5	1.1 ± 0.6	0.8 ± 0.3
Receiver	2.9 ± 0.9	20.3 ± 6.8	13.0 ± 4.7	10.0 ± 0.9
Recovery	105.6 ± 4.3	92.2 ± 4.9	94.2 ± 0.9	96.1 ± 1.1

Acid in Non-1 was found in the liver at 8 h. The combined amounts of Glycolic Acid found in the living skin strata and urinary bladder were significantly lower at 4 and 8 h if glycerol was added to the Non-1 formulation.

The *in vitro* deposition of Glycolic Acid in aqueous solution, Non-1, Non-2, and 30% PG/water was also examined (Ohta et al., 1996). Full thickness dorsal skin was excised from male SKH-hr-1 hairless mice and mounted on Franz diffusion cells. Twenty-five microliters of each test formulation was applied to the epidermal surface (1.77 cm^2) of the skin, using at least three cells from three different animals for each solution. After 16 h, the diffusion setup was dismantled, and the epidermal side of the skin was wiped three times. The skin was then tape stripped nine times or until it appeared shiny and glossy. Recovery was >92% for all systems. Glycolic Acid distribution (% ± standard deviation) is presented in Table 12.

The *in vitro* percutaneous absorption of Glycolic Acid was determined using human abdominal skin (Kraeling and Bronaugh, 1996). The skin was mounted in flow-through diffusion cells. Skin viability was maintained and barrier integrity was confirmed prior to application of the test materials. The test formulations were prepared to give an average dose of 0.55 μCi of ^{14}C radioactivity per cell. The emulsions were applied to the skin at 3 mg/cm^2 of exposed skin in the diffusion cells (exposed skin = 0.64 cm^2). At the end of each experiment, the skin was washed and rinsed three times, and it was tape stripped 10 times to remove the stratum corneum. The remaining epidermis was separated from the dermis using heat. The absorbed radioactivity in the 6-h receptor fluid fractions and the skin layers was measured by liquid scintillation counting. Glycolic Acid was studied using two o/w emulsions, one containing 2% PEG-100 stearate and 1% laureth-4 (formulation A) and the other

Table 13. Percentage of Glycolic Acid absorbed

	5% Glycolic Acid—formulation A		5% Glycolic Acid—formulation B	
	pH 3	pH 7	pH 3	pH 7
Receptor fluid	2.6 ± 0.7	0.82 ± 0.31	12.2 ± 5.3	1.40 ± 0.74
Stratum corneum	5.8 ± 2.8	1.22 ± 0.40	2.4 ± 1.3	0.13 ± 0.04
Viable epidermis	6.6 ± 2.5	0.80 ± 0.28	11.6 ± 2.5	0.41 ± 0.15
Dermis	12.2 ± 1.4	0.63 ± 0.16	8.6 ± 2.0	0.39 ± 0.05
Total in skin	24.6 ± 4.0	2.64 ± 0.64	22.6 ± 3.2	0.93 ± 0.01
Total absorption	27.2 ± 3.3	3.47 ± 0.93	34.8 ± 3.9	2.30 ± 0.75

containing 2% PEG-100 stearate and 1% ammonium laureth sulfate (formulation B). The emulsions, containing 5% Glycolic Acid, were prepared in buffers at pH 3 and 7 and evaluated using skin samples from three subjects for each emulsion. With formulation A, a much greater amount of Glycolic Acid was absorbed at a pH of 3 versus 7. Total Glycolic Acid absorption after 24 h was 27.2% at pH 3 and 3.47% at pH 7. With the pH 3 formulation, the amount of radioactivity found in the receptor fluid, stratum corneum, viable epidermis, and dermis was 2.6, 5.8, 6.6, and 12.2%, respectively. With formulation B, the amount of Glycolic Acid absorbed at pH 3 and 7 was 34.8 and 2.3%, respectively. With the pH 3 formulation, the amount of radioactivity found in the receptor fluid, stratum corneum, viable epidermis, and dermis was 12.2, 2.4, 11.6, and 8.6%, respectively. These values are summarized in Table 13 and depicted graphically in Figure 2.

Using male hairless guinea pig skin, the permeability constant (K_p) was determined following 24 h exposure to the Glycolic Acid formulations. The test formulations were applied to the surface of the skin at 3 mg/cm^2, and the skin was washed, rinsed, and dried after 24 h. The average K_p was greater than the control value (no emulsion, approximately 0.43×10^3), but a statistically significant difference was not observed among formulation A, pH 3 and 7, and formulation B, pH 3 (approximately 0.86, 0.64, and 0.73×10^3, respectively). Viable skin was used to investigate the percutaneous absorption of a 5% Glycolic Acid o/w emulsion, pH 3.0 and 7.0, over 24 h using in vitro flow-through diffusion cell techniques (FDA, 1995). Barrier integrity of the skin was confirmed using an initial [^{3}H]water screen.

The absorbed radioactive material was examined by high-performance liquid chromatography to determine whether biotransformation occurred during percutaneous absorption. The preliminary results for 5% Glycolic Acid at a pH of 3.0, three subjects, and at a pH 7.0, two

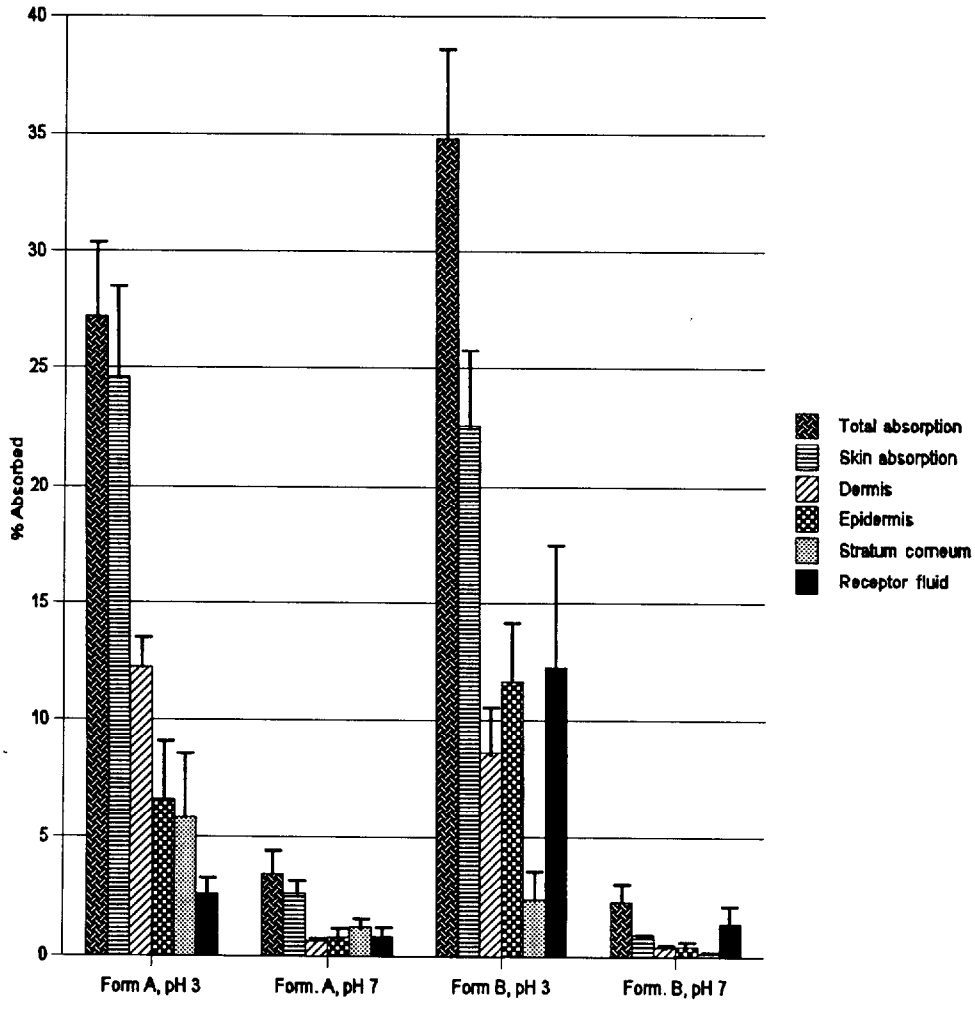

Figure 2. Percentage of applied Glycolic Acid appearing in the receptor fluid, stratum corneum, epidermis, and dermis as a function of the pH of the formulation for two formulations. Skin absorption (stratum corneum + epidermis + dermis) and total absorption (skin absorption + receptor fluid) are also shown. Samples were taken from three subjects for each emulsion. Formulation A was an oil/water emulsion with 2% PEG-100 stearate and 1% laureth-4. Formulation B was an oil/water emulsion with 2% PEG-100 stearate and 1% ammonium laureth sulfate. Both contained 5% Glycolic Acid (Kraeling and Bronaugh, 1996).

subjects, are presented in Table 14. FDA (1996c) also measured the percutaneous absorption and metabolism of 5% Glycolic Acid in the two o/w emulsion vehicles described above. Over a 24-h period through viable skin using flow-through diffusion cell techniques, the absorption of each Glycolic Acid formulation, with a tracer dose of [^{14}C]Glycolic

Table 14. Preliminary percutaneous absorption results of 5% Glycolic Acid using diffusion cell techniques

	Percent applied dose absorbed and recovered	
	pH 3.0	pH 7.0
Receptor fluid	18.9 ± 6.0	1.8 ± 1.0
Stratum corneum	3.1 ± 2.1	0.17 ± 0.04
Viable epidermis	10.3 ± 4.3	0.31 ± 0.07
Dermis	6.5 ± 1.1	0.38 ± 0.09
Total in skin	19.9 ± 4.2	0.86 ± 0.13
Total absorption	38.8 ± 4.8	2.7 ± 1.1
Unabsorbed	43.2 ± 5.5	87.7 ± 3.0
Recovery	82.0 ± 6.4	90.4 ± 1.9

Acid, was determined at pH 3.0 and 7.0. Barrier integrity of the skin was confirmed using an initial [^{3}H]water screen. The results for formulation A, two donors, and formulation B, five donors for pH 3.0 and three donors for pH 7.0, are presented in Table 15. Total Glycolic Acid absorption from formulation B at pH 3.0 varied from 24.3 to 44.6%. This reflects the normal variability in skin permeation. No metabolites of Glycolic Acid were detected in either skin or receptor fluid samples. The researchers stated that "since differences in Glycolic Acid absorption were obtained with formulations A and B, it seemed that ingredients in the emulsions (such as surfactants) might be affecting the integrity of the skin barrier." Therefore, the two formulations and two marketed cosmetic products (one containing 5% Glycolic Acid, pH 2.54, and one containing 10% Glycolic Acid, pH 3.52) were compared for their effects on the barrier properties of hairless guinea pig skin.

Steady-state [^{3}H]water absorption was measured following a 24-h exposure to the test materials, and a permeability constant (K_p) was calculated. The average K_p value for all test materials was greater than the control (no emulsion), but none of the formulations were significantly different from each other. The K_p value ($\times 10^{-4}$) was 4.64 ± 0.54 for the untreated control and 8.51 ± 0.77 for formulation A, pH 3.0 (the greatest test K_p value). The researchers noted that the Glycolic Acid absorption values they obtained were significantly greater than those reported by industry using 10% aq. solutions, pH 3.7–3.8 (believed to be An-eX Analytical Services, Ltd. [1994], which follows). They theorized that this could have been due to rapid evaporation of the aq. vehicles, "which could limit partitioning into the skin and also affect pH."

Table 15. Percutaneous absorption of 5% Glycolic Acid in two formulations using diffusion cell techniques

	Percent applied dose absorbed	
	pH 3.0	pH 7.0
	Formulation A	
Receptor fluid	3.2 ± 0.55	1.0 ± 0.39
Stratum corneum	3.0 ± 0.28	1.1 ± 0.68
Viable epidermis	7.7 ± 3.8	1.1 ± 0.11
Dermis	10.9 ± 0.96	0.72 ± 0.22
Total in skin	21.6 ± 4.5	2.9 ± 1.0
Total absorption	24.8 ± 4.0	3.9 ± 1.4
	Formulation B	
Receptor fluid	12.2 ± 5.3	1.4 ± 0.74
Stratum corneum	2.4 ± 1.3	0.13 ± 0.04
Viable epidermis	11.6 ± 2.5	0.41 ± 0.15
Dermis	8.6 ± 2.0	0.39 ± 0.05
Total in skin	22.6 ± 3.2	0.93 ± 0.10
Total absorption	34.8 ± 3.9	2.3 ± 0.75

Skin penetration of 10% aq. Glycolic Acid was determined in vitro using human female (age 87 years) abdominal skin (An-eX Analytical Services, Ltd., 1994). The aq. solution was prepared by adding 0.8 mL of 12.473% Glycolic Acid solution to 0.2 mL of [2-^{14}C]Glycolic Acid solution, 44 mCi/mmol or 250 μCi/mL, that contained 0.216 mg Glycolic Acid. (The pH of a mixture containing 0.8 mL of the 12.473% Glycolic Acid solution and 0.2 mL of water was 3.72.) Skin integrity was assessed by determining the permeability coefficient of tritiated water. Twenty microliters of 10% aq. Glycolic Acid solution, 2 mg active, was placed on the stratum corneum surface; 13 replicates were used. Samples of 200 μL, which were taken 1, 2, 4, 6, 8, and 24 h after application, were counted using a liquid scintillation counter. The skin surface was rinsed three times after the 24-h sample was taken. The average total absorption over 24 h was 2.6 ± 0.37 μg/cm^2, representing 0.15 ± 0.02% of the applied dose. A lag time of approximately 3.8 h was followed by a period of steady-state diffusion at a rate of 0.13 μg/cm^{2}h^{-1}. After 24 h, 0.48 ± 0.05% of the dose was recovered in the skin and 0.15 ± 0.02% was found in the receptor phase. Total recovery was 102 ± 2.9%.

The effect of Glycolic Acid on percutaneous absorption was examined using male hairless guinea pigs (Hood et al., 1996). Skin cell renewal

time was first estimated using the dansyl chloride staining technique performed according to the methods of Jansen et al. (1974). An o/w emulsion of 5 or 10% Glycolic Acid, pH 3.0, was applied to the backs of two guinea pigs per group once daily (excluding Sunday) for 2 weeks prior to the application of dansyl chloride. A Vaseline Intensive Care formulation was applied to three treated controls. Daily application continued until fluorescence disappeared. Stratum corneum turnover times were reduced 36 and 39% by 5 and 10% Glycolic Acid, respectively, as compared to the treated controls. Based on these data, it was determined that a 3-weeks application time was sufficient for Glycolic Acid to increase stratum corneum turnover in guinea pigs.

For the absorption study, guinea pigs received daily applications (except Sundays) of 3 mg/cm^2 of 5 or 10% Glycolic Acid, pH 3.0, to two prewashed 8 × 5-cm areas of the back for 3 weeks. Prior to each application, the area was gently rinsed and dried. A Vaseline Intensive Care lotion formulation was again used for the treated control group; an untreated control group was also used. After 3 weeks of dosing, the animals were killed. Skin was used for microscopic examination and for *in vitro* percutaneous absorption studies that were performed according to the methods of Bronaugh and Stewart (1985, 1986). All skin samples were prepared to a thickness of 250–300 μm, and skin viability was maintained throughout the study. The barrier integrity of the skin was assessed. [^{14}C(U)]Hydroquinone (specific activity 22.9 mCi/mmol) and [5-^{14}C]musk xylol (specific activity 19.76 mCi/mmol) in ethanol were applied to the skin in o/w emulsion vehicles (3 mg/cm^2) at a chemical dose of approximately 2.5 and 5.0 μg/cm^2, respectively. Receptor fluid was collected in 6-h fractions for a total of 24 h at a flow rate of 1.5 mL/h, and at 24 h, the skin surface was washed and rinsed. The amount of radioactivity in the wash, skin, and receptor fluid was determined.

Application of Glycolic Acid for 3 weeks produced some erythema and/or flaking of the skin. At microscopic examination, treated skin had a thickening of the epidermis after treatment with 5 and 10% Glycolic Acid. Application of 5% Glycolic Acid produced a twofold increase in the number of epidermal cell layers; no significant difference in the number of cell layers was found for the animals dosed with 5 versus 10% Glycolic Acid. Up to a fourfold increase in viable epidermal thickness was observed for the Glycolic Acid-treated skin as compared to the Vaseline Intensive Care-treated or untreated skin. Hypertrophy of the epithelium lining of the hair follicles of Glycolic Acid-treated skin was also observed. Although these epidermal changes were observed in Glycolic Acid-treated skin, the barrier integrity of Glycolic Acid- and control-treated skin was not significantly different. The percutaneous

absorption of hydroquinone and musk xylol were unaffected by Glycolic Acid pretreatment as compared to the Vaseline Intensive Care controls. Total absorption values for the skin treated with Glycolic Acid and Vaseline Intensive Care were significantly different from untreated skin.

Normal urinary Glycolic Acid concentrations were measured using automated ion chromatography for a group of 41 normal adults, 24 males and 17 females (Wandzilak et al., 1991). The mean urinary glycolate values were 36.6 ± 15.8 mg/24 h and 0.025 ± 0.012 mg glycolate/mg creatinine. The mean values for males were 32.1 ± 14.3 mg/24 h and 0.019 ± 0.006 mg/mg creatinine and the mean values for females were 42.9 ± 16.1 mg/24 h and 0.034 ± 0.012 mg/mg creatinine.

Normal values of excreted Glycolic Acid were measured for a control group of six male and nine female subjects using a chromotropic acid–sulfuric acid assay with 0.5-mL samples in which no correction was made for isotope dilution (Niederwieser et al., 1978). Average urinary excretion of Glycolic Acid in 24 h was 45.8 ± 11.3 mmol/mol creatinine or 602 ± 148 μmol/day (45.8 ± 11.3 mg/day). Additionally, two patients with primary hyperoxaluria type I excreted Glycolic Acid between 112 and 379 mmol/mol creatinine or 1210–5640 μmol/day (92–429 mg/day).

Two female rhesus monkeys were dosed orally with 4 mL/kg of 500 mg/kg homogenous [1-^{14}C]Glycolic Acid, 0.73 μC/mmol, in aq. solution via stomach tube (McChesney et al., 1972). Urine was collected at intervals of 0–8, 8–24, 24–48, 48–72, and, for one monkey, 72–96 h. Over a 72-h period one animal excreted, as a percentage of the dose, 53.2% ^{14}C, 51.4% of which was excreted in the urine; 51.4% of the dose was excreted in the first 24 h. The second animal excreted a total of 42.2% ^{14}C over 96 h, 36.6% of which was excreted in the urine; 34.1% of the dose was excreted in the first 24 h. (The greater amount of fecal radioactivity observed for this monkey could have been due to urinary radioactivity contamination.) Very little of the dose was converted to radioactive glyoxylic, hippuric, or oxalic acid.

The skin penetration of [^{14}C]Glycolic Acid was studied using an in vitro system in which a cream formulation was applied to pig skin at a dose of 5 mg/0.79 cm^2 skin without an occlusive patch (ESLUR, 1994b). It was determined that 3.1% of the applied Glycolic Acid penetrated the skin.

The penetration of 10% aq. Glycolic Acid, adjusted to pH 3.8 using either ammonium or sodium hydroxide, was examined using separated Yucatan minipig epidermis and full thickness hairless mouse skin (Goldstein and Brucks, 1994). A 200-μL aliquot of each formulation was applied to an area of a Franz diffusion cell, and Glycolic Acid was analyzed using liquid scintillation counting. Using an occlusive patch, penetration was linear with a lag time of less than 15 min. After 8 h, 0.8

and 1.6% of the ammonium and sodium salts penetrated, respectively, using the pig skin model and 1.8 and 2.3% of the ammonium and sodium salts penetrated, respectively, using the mouse skin model. Under open patch conditions, penetration was not linear and lag time was greater than 15 min. Using the pig skin model, 1.1 and 0.7% of the ammonium and sodium salts penetrated, respectively, and using the mouse skin model, 0.6 and 0.9% of the ammonium and sodium salts penetrated, respectively.

Glycolic Acid was injected into rabbits intramuscularly; two-thirds of the injected dose was excreted in the urine in the form of oxalic acid (Herkel and Koch, 1936).

Sodium Glycolate. Two groups of male Wistar rats, one of which was fasted, were dosed with an aq. solution of 0.51–10.2 mmol/kg sodium [1-^{14}C]glycolate (5 μC) by stomach tube (Harris and Richardson, 1980). The radioactivity recovered in the urine and the feces and as respiratory carbon dioxide was determined for the time periods 0–6, 6–24, and 24–48 h, with feed and water being withheld during the 48-h collection period. For both fasted and nonfasted rats, 2.2 ± 1.6% of the radioactivity was recovered in the feces within 48 h, indicating that glycolate was readily absorbed from the intestinal tract. The recovery of unmetabolized [1-^{14}C]glycolate in the urine was minimal at low doses and increased sharply at the greater doses, ranging from 3.1 ± 1.3 to 50.7 ± 2.2% for fasted rats and from 2.8 ± 1.0 to 49.9 ± 7.6% for nonfasted rats at doses of 0.51 to 10.2 mmol/kg, respectively. The amount of [^{14}C]oxalate recovered in the urine increased with dose up to 5.1 mmol/kg and then decreased and the amount of [^{14}C]glyoxylate recovered in the urine increased consistently. The amount of radioactivity recovered as respiratory carbon dioxide increased initially, but then decreased with increasing dose concentrations. Approximately 95% of the total radioactivity accounted for was recovered in the first 24 h.

In a General Foods Corporation 1943 study, fasted dogs were given 500–750 mg/kg Sodium Glycolate by intravenous (IV) injection (Haskell Laboratory, 1990). An increase in the blood sugar level, an increase in glucose liberation by the liver, a decrease in blood acetone body concentration, and decreased acetone body output by the liver were observed.

Male rats were dosed by intraperitoneal (IP) injection with 1 mM of sodium benzoate and 0.29 mM Sodium Glycolate (from Glycolic Acid, radiolabeled at the α-carbon and carboxyl carbon with ^{14}C) (Weinhouse and Friedmann, 1951). Five milliliters of a 2% sodium chloride solution was administered by stomach tube prior to dosing to increase urine excretion. CO_2 samples were collected at 30-min intervals for 5 h to

measure the rate of oxidation, and urine was collected for a 24-h period to determine the rates of oxalate and hippurate formation. Dosing with radioactive Sodium Glycolate resulted in 11.4% of the radioactivity as glycine being excreted as hippuric acid, 1.1% as oxalic acid, and 13% as respiratory carbon dioxide during a 5-h period. The researchers concluded that "the direct oxidation of acetate via glycolate ... is not of quantitative significance in the rat."

The absorption of 0–10 mM Sodium [1-^{14}C]glycolate by rat intestine was studied using the tissue accumulation technique and everted intestinal rings (Talwar et al., 1984). With a concentration of 4 mM glycolate, the incubation time varied from 15 to 90 min. The effects of thiol binding agents, inhibitors of respiration, and structural analogs of glycolate on glycolate absorption were also studied. The effect of substrate concentration (0–15 μmol Sodium Glycolate) on the intestinal transport of glycolate indicated that glycolate was absorbed by a carrier-mediated process. After a linear increase in the transport of up to 20 μmol glycolate, saturation was attained. Glycolate uptake was linear for a 25-min period, after which no significant increase in the uptake rate was observed, and a plateau was reached after 40 min of incubation. The jejunum and ileum, but not the duodenum, significantly absorbed more glycolate than the colon. The sulfhydryl binding agents and respiration inhibitors had no significant effect on glycolate uptake, but 6 mM of the structural analogs glyoxylate and lactate produced significant inhibition.

Lactic Acid

L-Lactic Acid is a normal metabolic intermediate produced by most mammalian cells and other organisms, such as bacteria; it is metabolized in preference to D-Lactic Acid in man, dogs, and rats (ESLUR, 1994a). Lactic Acid is converted to pyruvic acid by Lactic Acid dehydrogenase (Informatics, 1975).

In animals, lactate that is generated by anaerobic metabolism can be transported to other more aerobic tissues, such as the liver, where it can be reconverted to pyruvate. The pyruvate can then be further metabolized, reconverted to carbohydrate material as free glucose, or stored as glycogen. In the body, lactate is distributed equivalently to, or slightly less than, total body water (Kreisberg, 1972). It diffuses readily across cell membranes, primarily by passive transport; under certain conditions, the distribution could be uneven or the lactate pool could consist of several smaller pools with differing rate constants.

Kreisberg et al. (1970, 1971) examined lactate production in humans using isotopic dilution of [^{14}C]lactate administered by a primed-constant infusion technique; the lactate turnover rate was 81–2 mg/kg h^{-1} in

Table 16. Bioavailability of Lactic Acid as a function of pH

		Bioavailable concentration (%) at Lactic Acid concentration:						
pH	Bioav. @25°C	4	8	12	20	35	50	70
2.0	0.99	4	8	12	20	35	50	69
2.5	0.96	3.8	7.7	12	19	34	48	67
3.0	0.88	3.5	7.0	11	18	31	44	62
3.2	0.82	3.3	6.6	9.8	16	29	41	57
3.4	0.74	3.0	5.9	8.9	15	26	37	52
3.6	0.65	2.6	5.2	7.8	13	23	33	46
3.8	0.53	2.1	4.2	6.4	11	19	27	37
3.86	0.50	2.0	4.0	6.0	10	17.5	25	35
4.0	0.42	1.7	3.4	5.0	8.4	15	21	29
4.2	0.31	1.2	2.5	3.7	6.2	11	16	22
4.4	0.22	0.9	1.8	2.6	4.4	7.7	11	15
4.6	0.15	0.6	1.2	1.8	3	5.3	7.5	11
4.8	0.10	0.4	0.8	1.2	2.0	3.5	5.0	7.0
5.0	0.07	0.3	0.6	0.8	1.4	2.5	3.5	4.9

normal subjects. In humans, 50–60% of the lactate turnover was derived from blood glucose (Kreisberg et al., 1971), and it is theorized that 20% of the lactate turnover could be derived from alanine (Kreisberg, 1972).

The bioavailability of Lactic Acid in a topical formulation, which is the fraction of Lactic Acid in a free acid form, was examined in the manner previously described for Glycolic Acid (Yu and Van Scott, 1996). The bioavailable concentration of Lactic Acid in topical formulations was also determined. These data are summarized in Table 16. As discussed with Glycolic Acid, the vehicle of the formulation and the other components in the vehicle are important in bioavailability. As stated previously, the relationship between the concentration of free acid, the pH, and the total concentration of AHA may not be calculated simply and the influence of the partitioning of the AHA between phases in an emulsion must be considered.

The in vitro percutaneous absorption of Lactic Acid was determined using human abdominal skin (Kraeling and Bronaugh, 1996). The skin was mounted in flow-through diffusion cells. Skin viability was maintained and barrier integrity was confirmed prior to formulations that were prepared to give an average dose of 0.55 μCi of ^{14}C radioactivity per cell. The emulsions were applied to the skin at 3 mg/cm^2 of exposed skin in the diffusion cells (exposed skin = 0.64 cm^2). At the end of each experiment, the skin was washed and rinsed three times, and it was

tape stripped 10 times to remove the stratum corneum. The remaining epidermis was separated from the dermis using heat. The absorbed radioactivity in the 6-h receptor fluid fractions and the skin layers was measured by liquid scintillation counting. The percutaneous absorption of 5% Lactic Acid in 2% PEG-100 stearate and 1% laureth-4 was determined at pH 3 and 7 using skin samples from three subjects for each pH. Total absorption was 30.4 and 9.73% at pH 3 and 7, respectively. With the pH 3 formulation, the amount of radioactivity found in the receptor fluid, stratum corneum, viable epidermis, and dermis was 3.6, 6.3, 6.6, and 13.9%, respectively. These data are summarized in Table 17 and depicted graphically in Figure 3.

The effect of vehicle and pH on the absorption of Lactic Acid was examined in vitro using porcine skin (Sah et al., 1996). Lactic acid, 8%, and L-[^{14}C(U)]lactic acid, specific activity 1 mCi/mL, were prepared in w/o, o/w, and water-in-oil-in-water (w/o/w) emulsions, and for some studies, 5% propylene glycol was added to the o/w vehicle. Female porcine dermal skin, dermatomed to 510-μm thickness, was mounted on Bronaugh flow-through cells, and barrier integrity was assessed using transepidermal water loss. A finite dose, 2 μL, and an infinite dose, 75 μL, of each solution was spread over the entire surface, and the cells used with the infinite dose were covered with parafilm to avoid evaporation of the vehicle. The flow rate was controlled at 5 mL/h. After 6 h, each cell was washed three times. The stratum corneum was harvested using nine tape strippings. The total deposition and absorption of Lactic Acid as a percentage of applied dose was in the order o/w > w/o/w > w/o. The researchers stated the greater uptake of Lactic Acid in the o/w emulsion "may be attributed to a higher effective concentration in the external aqueous phase" and that from the w/o/w emulsion "may be attributed to a larger stratum corneum/vehicle partition coefficient." For the o/w emulsion, a greater amount of material was delivered to the stratum corneum from the finite dose; the amounts delivered to the epidermis

Table 17. Percentage of Lactic Acid absorbed as a function of pH

	5% Lactic Acid	
	pH 3	pH 7
Receptor fluid	3.6 ± 1.2	0.37 ± 0.09
Stratum corneum	6.3 ± 1.4	3.24 ± 0.77
Viable epidermis	6.6 ± 0.9	3.22 ± 0.84
Dermis	13.9 ± 2.3	2.90 ± 1.3
Total in skin	26.8 ± 4.5	9.36 ± 2.08
Total absorption	30.4 ± 3.3	9.73 ± 2.03

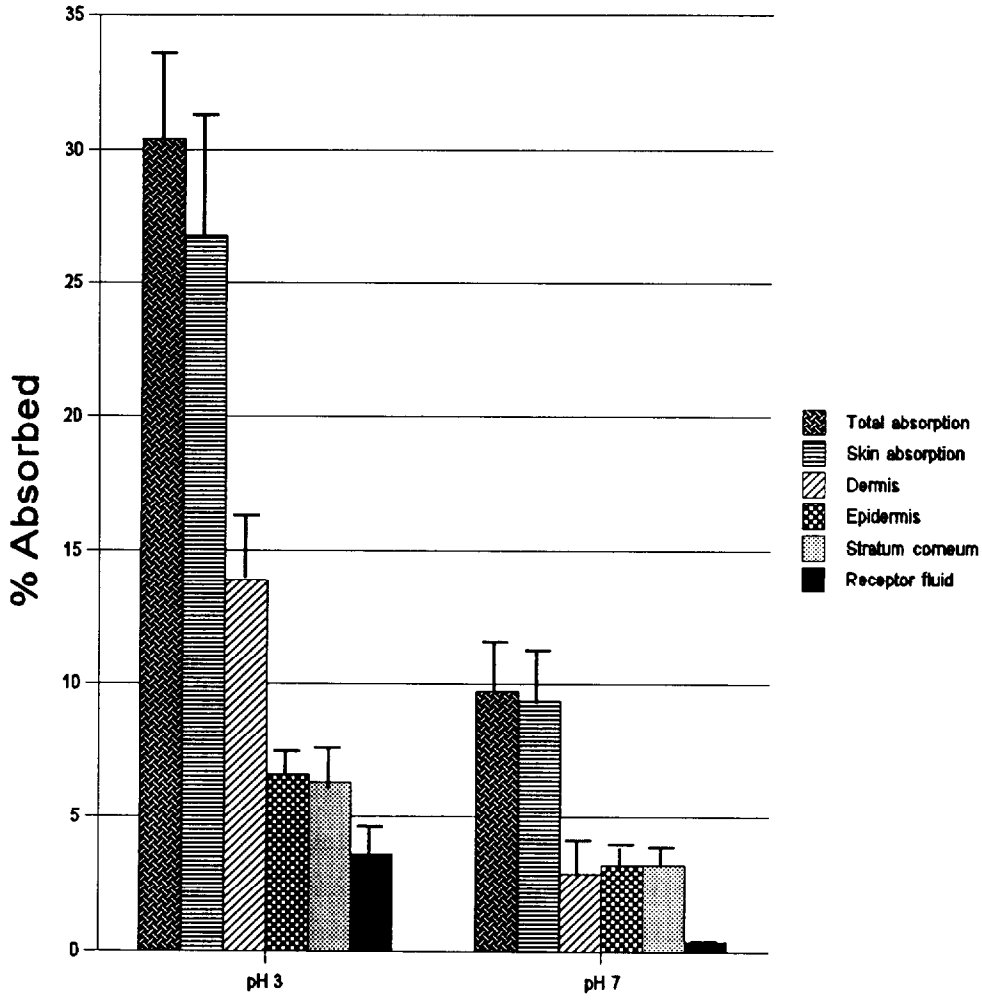

Figure 3. Percentage of applied Lactic Acid appearing in the receptor fluid, stratum corneum, epidermis, and dermis as a function of the pH of the formulation. Skin absorption (stratum corneum + epidermis + dermis) and total absorption (skin absorption + receptor fluid) are also shown. Samples were taken from three subjects for each pH. The formulation was an oil/water emulsion with 2% PEG-100 stearate and 1% laureth-4 with 5% Lactic Acid (Kraeling and Bronaugh, 1996).

were comparable for the finite and infinite doses. Decreasing the pH of the o/w emulsion from 7.0 to 3.8 increased the penetration of the finite dose 100% in 6 h. An increase in penetration was not seen when the pH of the infinite dose was lowered, and only a small fraction of the Lactic Acid penetrated the stratum corneum. The researchers stated this suggests "a coupling between pH and solubility controls skin penetration." The addition of 5% propylene glycol to the o/w emulsion enhanced

penetration for both finite and infinite doses, but was "a more efficient enhancer" at the infinite dose.

The percutaneous absorption of topically applied 5% [^{14}C]Lactic Acid in an oil-in-water cream was measured using rats (ESLUR, 1994a). After 3 days, 50% of the applied Lactic Acid had penetrated the skin.

A group of five male Fischer 344 rats was given Lactic Acid at 390 mg/200 mg body wt (30 times greater than that normally found in the rat stomach; the dose was determined by an acute study described in the "Animal Toxicology" section later in this report) with 10 μCi of L-[U-^{14}C]Lactic Acid and 10 μCi of D-[U-^{14}C]Lactic Acid by stomach tube during a 1-h period (Morotomi et al., 1981). A control group was given the same volume of water, in place of the unlabeled Lactic Acid, and radioactive Lactic Acid in the same manner. The animals were killed after 6 h, blood samples were taken, and the liver, kidneys, brain, and gastrointestinal tract were removed. Radioactivity was measured, and the remaining tissues were examined grossly and microscopically. Arterial blood pH was also determined using groups of five rats treated in the same manner as the previously described test animals with the radioactive Lactic Acid being omitted. Arterial blood was taken 6 h after dosing from the abdominal aorta, with the pH determined using a Hitachi–Horiba pH meter and a combination electrode. Six hours after dosing, the amount of the isotope that had been converted to carbon dioxide was 61.3 and 42.4% for the control and test animals, respectively. In the controls, Lactic Acid was rapidly metabolized into carbon dioxide within 3 h after administration. Approximately 78 and 91% of the radioactivity was recovered in the controls and test animals, respectively. This difference was attributed to the difference of radioactivity recovered from the gastric contents of these animals; the amount of radioactivity recovered from the stomach of the test animals was approximately 37% of the dose, which was six times greater than that of control rats. A difference in the manner of disposal of Lactic Acid was found between the experimental and control animals, although the investigators stated that "some problems may remain in comparing the fate of Lactic Acid between the test and experimental groups at 6 h after the administration, because the amount of expired CO_2 reached its plateau at 3 h after the administration in the control group." Bleeding and necrosis of the stomach and liver were seen in the rats given an excess of Lactic Acid. No obvious microscopic changes were observed in the other organs. The blood pH was significantly decreased in the test animals, 7.36 $\pm$ 0.03 as compared to 7.50 $\pm$ 0.02. The amount of Lactic Acid in the blood was 2.2-fold greater and in the brain and kidneys 3.1-fold greater for the test animals as compared to the controls; the amount of hepatic Lactic Acid was similar. No significant difference was seen in lactate dehydrogenase activity in various organs and tissues, but the

glucose-6-phosphatase, glutamic pyruvic transaminase, and glutamic oxaloacetic transaminase activities of the liver and kidneys were increased. No significant difference was observed in the L-glutaminase or monoamine oxidase activity. Liver cholesterol was significantly increased in the test group, and approximately 0.1% of the dosed amount of radioactivity was detected in the cholesterol fraction of the liver in both control and test animals. Overall, it was suggested that the excess of Lactic Acid was used as a source of energy and as precursor material for protein and lipid synthesis.

Dogs were used to determine turnover of L-[^{14}C]lactate administered by single injection and primed infusion techniques (Forbath et al., 1967). The rate of appearance in normal dogs was 39.8 and 23.9 μmol/kg min^{-1} when administered by injection and infusion, respectively.

Depocas et al. (1969) determined the rate of formation and oxidation of [^{14}C]Lactic Acid administered by a primed infusion technique using dogs. The rate of formation of Lactic Acid was 0.89 and 1.76 mg C/kg min^{-1} and the rate of oxidation was 0.38 and 1.32 mg C/kg min^{-1} in resting and running dogs, respectively. Respiratory carbon dioxide derived from lactate was 16 and 12% for resting and running dogs, respectively.

Mongrel dogs were used to examine the tubular reabsorption of Lactic Acid (Dies et al., 1969). Following rapid IV Sodium Lactate loading, tubular reabsorption of Lactic Acid was limited. Lactic Acid excretion was urine flow-dependent at low filtered loads. The researchers concluded that Lactic Acid was actively reabsorbed in the proximal tubule, that its transport rate was limited, and that it was either incompletely reabsorbed at low filtered loads or partially secreted at a distal site of the nephron.

L-Lactic Acid. L-Lactic Acid occurs in small quantities in the blood and muscle fluid of humans and animals; the concentration of Lactic Acid in these fluids increases after vigorous activity (Budavari, 1989). L-Lactic Acid is also present in the liver, kidneys, thymus gland, human amniotic fluid, and other organs and body fluids. Lactate was primarily produced through an anaerobic pathway of carbohydrate degradation (glycolysis) in skeletal muscle, or by a few select microbes (Informatics, 1975).

A primed infusion study was performed using radioactive L-Lactic Acid to estimate the turnover, oxidation, and reduction of lactate in humans (Searle and Cavalieri, 1972). The virtual volume of distribution of lactate was 49.4% of body weight. The lactate pool size and turnover time were estimated as 0.029 g/kg and 18.4 min, respectively. Turnover was approximately 96 mg/kg h^{-1}, with approximately 88% oxidation to carbon dioxide. The investigators concluded that body lactate kinetics probably reflect the total flux of carbon through pyruvate, and that the

primary fate of lactate was oxidation to carbon dioxide, not reduction to glucose in hepatic tissue.

Rabbits were used to determine the metabolism of L-[^{14}C]Lactic Acid (Drury and Wick, 1965). Circulating Lactic Acid was depleted and renewed at a rapid rate, with a turnover time of approximately 30 min. The majority of the lactate was oxidized to carbon dioxide; a small amount of the lactate was accounted for as glucose or glycogen, or by the oxidation of them. The researchers stated that since DL-lactate is practically completely metabolized, the liver might convert the D-isomer to either the L- form or to glucose and glycogen.

L-[^{14}C]Lactate produced radioactive carbon dioxide more rapidly than D-lactate in the intact rat, although the D- form is fairly well metabolized (FAO/WHO, 1967). After 2 h, both isomers were oxidized at equal rates.

L-Lactic Acid, 170 or 700 mM, was placed into unstimulated whole stomach pouches of cats to determine absorption (Frenning, 1972). After instillation, the hydrogen ion and lactate concentration decreased equally, and the net effluxes were also approximately equal. No changes in gastric mucosa exposed to 700 mM L-Lactic Acid were found in electron micrographs. Absorption of D-lactate was thought to function similarly.

D-Lactic Acid. Rats were fed a diet containing 5% calcium sodium DL-lactate for 1–2 days (Giesecke and Fabritius, 1974). Using a specific enzymatic assay (details of assay not provided) for detection of D-lactate, it was found that only 1–2% of the ingested D-lactate was recovered in the urine. Fasted rats were then given an IP injection of 247 mg/kg D-lactate containing D-[^{14}C]lactate. Within 6 h, 84.4% of the injected dose was recovered as expired carbon dioxide and 3% as both D-lactate and metabolites in the urine.

Sodium Lactate. Oral administration of sodium DL-lactate to dogs resulted in almost complete utilization (Craig, 1946). Increasing the plasma lactate concentration via IV infusion produced only slight urinary excretion until the plasma concentration approached 1 mg/mL. At concentrations of 1–4 mg/mL, the rate of excretion was proportional to the rate of glomerular filtration. The L-isomer was utilized more than the D-isomer at a ratio of three to two.

Fasted male rats were dosed via stomach tube with 2.2 mL Sodium Lactate in racemic, L-, and D- form (Cori and Cori, 1929). A small difference was observed in the amount of glycogen formed during absorption of racemic and L-lactate; the rats given L-Lactic Acid absorbed an average of 89.7 mg and the rats dosed with racemic Lactic Acid absorbed 115.1 mg. D-lactate did not form hepatic glycogen as rapidly as L-lactate. However, both L- and D-lactate were absorbed at similar rates. Also, the investigators noted that free Lactic Acid was absorbed more slowly than

Sodium Lactate. The investigators then fed the animals a dose of 170 mg of lactate/100 mg body wt. For an equal amount absorbed, racemic Lactic Acid formed less liver glycogen than L-Lactic Acid. Forty percent of the L-lactate absorbed was converted to glycogen, with less than 1% excreted, whereas 30% of the D-lactate absorbed was excreted in the urine and 18% was retained in the blood. With racemic Lactic Acid, 24% of the absorbed dose was converted to glycogen and approximately 1.5% was excreted. Male and female rats were given orally approximately 2150 mg/kg Sodium Lactate and the absorption from the intestine was determined after 1, 2, 3, and 4 h (Cori, 1930). After 1, 2, 3, and 4 h, approximately 26, 44, 61, and 75% of the amount fed was absorbed. The researcher stated that the "rate of absorption decreased with time and was roughly proportional to the amount of lactate present in the intestine."

Adult rats were intubated with 260–1800 mg/kg [^{11}C]Sodium Lactate, with ^{11}C in the carboxyl position (Conant et al., 1941). An average of 20% of the radioactivity was expired as carbon dioxide in a 2.5-h period following dosing.

TEA-Lactate. Published absorption, distribution, metabolism, and excretion data for TEA-Lactate were not found. Metabolism data for TEA were not given in the original CIR report on TEA (Elder, 1983), but data on TEA from a study found in published literature are included here to be used in assessing the safety of TEA-Lactate. A gas-chromatography assay to determine TEA in biological fluids was developed and the metabolism of TEA was studied using male and female rats (Kohri et al., 1982). Oral administration of TEA resulted in rapid absorption from the gastrointestinal tract and excretion in the urine of primarily unchanged TEA.

PENETRATION ENHANCEMENT

Glycolic Acid

The effect of Glycolic Acid on the penetration of other materials was examined (Hill Top Research, Inc., 1996). In phase I, 200 μL of either a formulation containing 10% Glycolic Acid in a thickened aq. solution, pH 3.5, or the vehicle, pH 3.5, was applied once daily to a 10 × 10-cm area of the volar aspect of one forearm of subjects with Fitzpatrick type I-III skin 6 days per week for 15 weeks, while the opposite forearm was untreated. The study was completed with 25 subjects, 16 (three males and 13 females) of which received the Glycolic Acid formulation and 9 (four males and five females) of which received vehicle only.

Following 15 weeks of dosing, in phase II, 20 μL of [^{14}C]hydrocortisone (lipophilic) and [^{14}C]glycerin (hydrophilic) in acetone were each applied

to two 1 × 0.5-in. portions of the treated and untreated area of each forearm of 20 of the subjects, 15 of which were dosed with the Glycolic Acid formulation and five of which were dosed with vehicle. A Telfa patch was placed over each section. After 1 and 4 h, one hydrocortisone- and one glycerin-treated area was wiped dry and tape stripped 21 times. The amount of radioactivity that penetrated the skin was determined. Total protein for all 21 strips per subject was determined by summation of the values for the initial tape strip and each subsequent set of five strips. Four of the subjects completing the study reported mild adverse reactions, consisting of mild, transient erythema, pruritus, rash, and product residue, which were possibly related to dosing. Significant differences were not observed in the amount of [^{14}C]hydrocortisone or [^{14}C]glycerin absorbed between the treated and untreated sites.

As described in the section on "Absorption, Distribution, Metabolism, Excretion" in the study by Hood et al. (1996), pretreatment of guinea pig skin with Glycolic Acid did not affect the absorption of hydroquinone or musk xylol.

Coleman and Futrell (1994) stated that some dermatologists use Glycolic Acid to prewound the skin prior to applying trichloroacetate (TCA) because it appears to allow the TCA to penetrate more deeply. Dial (1990) stated that Glycolic Acid was used with hydroquinone for treatment of melasma because it reportedly allowed better penetration of hydroquinone by altering the stratum corneum and epidermis.

Lactic Acid

Lactic Acid can facilitate the absorption of various active ingredients, functioning as a penetration enhancer, e.g., lidocaine (Zatz, 1994).

SKIN EFFECTS

AHAs have been reported to enhance extensibility of the solvent-damaged guinea pig footpad stratum corneum, which reached a maximum at a chain length of C_8, and AHAs resulted in a small increase in the water-binding capacity of solvent-damaged stratum corneum but decreased this capacity in undamaged stratum corneum (Alderson et al., 1984).

Takahashi et al. (1985) reported that AHAs were more effective than β-hydroxy acids for skin plasticization, and that plasticization increased with increasing chain length up to C_4.

Hill et al. (1988) reported that the relative humidity of the environment also has an effect upon the water content and extensibility of the stratum corneum.

Glycolic Acid

Fifty and 70% Glycolic Acid, 12% Lactic Acid, and other peeling agents were applied to an acetone-cleansed 2 × 2-cm area of the back of two minipigs for 15 min (Moy et al., 1996a). After 8 h and 7 and 21 days, 4-mm punch biopsies were taken. Epidermal necrosis and some inflammatory infiltrate and dermal necrosis were induced by 70% Glycolic Acid after 1 day. Some inflammatory infiltrate and dermal growth were observed with 50 and 70% Glycolic Acid and 12% Lactic Acid after 7 and 21 days. The depth of wounding of 10, 50, and 70% Glycolic Acid was 0.00, 0.202, and 0.464 mm, respectively. The researchers stated that Glycolic Acid "caused disproportionately more collagen staining and deposition at 7 and 21 days compared with the nonspecific reaction measure at 1 day."

Lactic Acid

In an *in vitro* assay examining the effect of Lactic Acid on the stratum corneum of guinea pig footpads, a modified tensile tester or extensometer was used (Hill et al., 1988). Six strips of guinea pig footpad epidermis were immersed in water for 3 h at 20°C, blotted dry, and allowed to equilibrate overnight at 20°C and 65% RH (relative humidity); the extensibility was measured. The strips were then immersed in an aq. Lactic Acid solution, 0.2 mol/L at natural pH, for 3 h at 20°C, blotted dry, and equilibrated following the same procedure. The efficacy of Lactic Acid, expressed as the mean ratio (±2 SE) of extensibility after test solution exposure to extensibility after water exposure, was 3.00 ± 0.65. (For comparison, 2-hydroxyoctanoic acid had the greatest efficacy, 5.9 ± 0.75.)

The effect of Lactic Acid and Sodium Lactate on water content and extensibility was examined using isolated stratum corneum obtained from the rear footpads of guinea pigs and then solvent-damaged (Middleton, 1974). All tests were performed at 81% RH. Immersion of the stratum corneum in 10% Lactic Acid for 30 min resulted in a statistically significant increase in water content and extensibility compared to immersion in water, using six replicates for both. When the stratum corneum was immersed in the 10% Lactic Acid solution for 30 min followed by immersion in water for 30 min, the amount of water held, using 10 replicates, increased slightly but not significantly and the extensibility, using 10 replicates, increased in a statistically significant manner as compared to control (water/water) values. The researcher demonstrated that Lactic Acid (0.01 M) was adsorbed by solvent-damaged stratum corneum, and adsorption was pH-dependent. However, Alderson et al. (1984) reported that no significant effects were observed with 0.1 or 0.15 M Lactic Acid.

Immersion of the stratum corneum in Sodium Lactate for 30 min statistically significantly increased water content and extensibility, using 9 and 20 replicates, respectively, with 5% lactate and 10 replicates for both with 10% lactate, as compared to immersion in water (Middleton, 1974). When the stratum corneum was immersed in the 10% Sodium Lactate solution for 30 min followed by immersion in water for 30 min, the amount of water held, using 10 replicates, did not change, and the extensibility, using 10 replicates, increased slightly. With immersion in 5% Sodium Lactate solution followed by immersion in water, the amount of water held, using 18 replicates, decreased slightly and the extensibility, using 30 replicates, increased slightly. The researcher reported that in earlier studies, 10% Sodium Lactate was not adsorbed. The addition of Lactic Acid and Sodium Lactate to a hand lotion and the effect of rubbing the lotion into damaged guinea pig footpad stratum corneum had on water content and extensibility was also examined. Since the pH of Lactic Acid was too low for incorporation into hand lotion, the Lactic Acid lotion was prepared by partially neutralizing Lactic Acid with sodium hydroxide to give a pH of 4 and incorporating this into the aqueous phase of a lotion to give a product containing 10% by weight of the Lactic Acid–Sodium Lactate mixture, calculated as Lactic Acid.

A lotion containing 10% Sodium Lactate was prepared similarly. At 81% RH, rubbing of the lotion into the stratum corneum for 90 s caused a statistically significant increase in water content and extensibility for both the Lactic Acid lotion, using 16 and 10 replicates, respectively, and for the Sodium Lactate lotion, using 10 replicates for both. The water content and extensibility were then determined after subsequent immersion in water for 30 min. The water content did not change with the Lactic Acid lotion, using 19 replicates, and increased slightly with the Sodium Lactate lotion, using 11 replicates. Extensibility increased in a statistically significant manner with the Lactic Acid lotion, using 11 replicates, and it decreased slightly with the Sodium Lactate lotion.

BIOCHEMISTRY

Glycolic Acid

Glycolic Acid is an intermediate in the photorespiratory carbon oxidation cycle (Lorimer, 1977). Much information is available on the formation pathways of glycolate, glyoxylate, and oxalate (Yanagawa et al., 1990; Fry and Richardson, 1979; Murthy et al., 1983) and the way in which substances affect the formation (Richardson, 1965, 1967, 1973; Liao and Richardson, 1972; Farinelli and Richardson, 1983; Varalakshmi and Richardson, 1983; Murthy et al., 1983; Talwar et al., 1985; Ogawa et al., 1986, 1990).

Also [^{14}C]glycolate was primarily converted directly to glycine and serine in both plants and animals (Richardson and Tolbert, 1961). Glycolate stimulation of ethanol oxidation (Harris et al., 1982) and the activating effect of Glycolic Acid on myosin ATPase have also been studied (Bolognani et al., 1992).

Lactic Acid

Lactic Acid is derived from glycogen breakdown, from amino acids, and from dicarboxylic acid (FAO/WHO, 1967). Sources of production within the body include muscular activity and liver and blood metabolism. Normal human blood contains 8–17 mg Lactic Acid/100 mL plasma (Life Sciences Research Office, 1978), and the concentration of lactate in normal human skin is three times or more of that in the blood due to glycolytic enzymes which actively convert glucose to Lactic Acid in the epidermis (Van Scott and Yu, 1977).

When glucose is present, Lactic Acid production via the Embden–Myerhoff pathway can be the primary metabolic pathway for glucose utilization (Monteiro-Riviere, 1991). Quantitative estimates of the interconversion of glucose and lactate, derived from precursor-product specific activity ratios and their respective turnover rates, indicated that 50% of lactate turnover in humans was derived from glucose, accounting for 45% of the glucose turnover rate (Kreisberg, 1972).

Ammonium Lactate. Lavker et al. (1992) reported that Ammonium Lactate increases the production of glycosaminoglycans.

IMMUNOLOGICAL EFFECTS

Glycolic Acid

Phagocytosis in the blood of rabbits was stimulated by IV injection of 500 mg/kg glycolate (Lamothe et al., 1971a).

Lactic Acid

Lactic Acid has been identified (along with interleukin-6) as the compound responsible for autocrine B cell stimulatory activity in serum-free supernatants of Epstein–Barr virus-immortalized B cells (Pike et al., 1991). Lactic Acid, 3.6–14.8 mM, accounted for approximately 90% of the autocrine B cell stimulatory activity in a 3-day lymphoblastoid cell lines proliferation assay. Frugoni et al. (1993) found that 1–4 mM synthetic Lactic Acid enhanced T-cell proliferation induced by either phytohemagglutinin-activated T cells of PWM (not defined).

L-Lactic Acid. Macrophages recovered from male F344 rats dosed intraperitoneally with thioglycolate were cultured in 1 mL of complete media, complete media and 5, 10, or 15 mM L-Lactic Acid, or complete media and endotoxin (LPS) (Jensen et al., 1990). The pH of each culture was measured, cell viability was determined at 24 h by trypan blue exclusion, and tumor necrosis factor (TNF) levels were determined by the L929 assay. The pH of complete media alone was 7.43, whereas the pH with the addition of 5, 10, and 15 mM L-Lactic Acid was 6.75, 6.34, and 5.91, respectively. At the end of 24 h, cell viability was 90% in all cultures. The addition of L-Lactic Acid to the cells resulted in a significant, non-dose-dependent, increase in TNF secretion. L-Lactic Acid did not demonstrate inherent activity in the L929 assay, and anti-TNF antibody completely eliminated the activity. Results of Northern blot analysis indicated that Lactic Acid exerted its effect on TNF secretion by enhancing gene transcription, supporting the idea that Lactic Acid concentration can regulate cytokine synthesis by macrophages. The investigators stated that "alterations of Lactic Acid concentration may participate more generally in the host response to inflammation and cancer by the local perturbation of cytokine homeostasis."

OTHER EFFECTS

Glycolic Acid

The effect of 0.35–0.8 mmol/kg Glycolic Acid and 1.0–4.4 mmol/kg Sodium Glycolate on cyclopropane–epinephrine-induced cardiac arrhythmias was examined using dogs (White and Stutzman, 1950). Doses of 0.35–0.5 mmol/kg Glycolic Acid increased the duration of arrhythmias in the 13 dogs tested, whereas doses > 0.5 mmol/kg decreased or totally eliminated the arrhythmias in each of 11 dogs. Depression was observed for many of the dogs at higher doses. Sodium Glycolate was much less effective in decreasing the arrhythmias, with 3 mmol/kg being required and its action being transient.

Glycolic Acid, 1000 mg/kg given intraperitoneally, was a potent inhibitor of respiration and glucose metabolism in the rat, but it did not have an effect on brain respiration (Lamothe et al., 1971b). A membrane site of action was postulated.

Sodium Glycolate. Groups of six male albino Wistar rats were given stock feed, feed with 3% Sodium Glycolate, or feed with 3% Sodium Glycolate along with oral doses by stomach tube of (+)-L-tartrate for 30 days (Selvam et al., 1992). In the group fed Sodium Glycolate without tartrate, statistically significant changes were seen for most of the examined biochemical parameters of the small intestine, including an increase in DNA, in the activities of the small intestine enzymes, and in

the activities of the intestinal homogenate and brush border membrane enzymes. (+)-L-Tartrate "normalized" many of these parameters.

Lactic Acid

Lactic Acid, 400 mM, was infused into New Zealand White rabbits through the ear vein for 4 h at a rate of 8 mL/h, along with polyethylene glycol (PEG) 400 through the opposite ear vein at a rate of 40 mL/h, to determine its effect on the passive permeability of the blood–brain barrier (McClung et al., 1990). The average mean molecular weight and quantity of PEG 400 entering the cerebrospinal fluid increased significantly, and the effective pore diameter of the blood–brain barrier increased from 7.3 to 8.5 Å.

The transport of L- and D-lactate into rat pancreatic islets and HIT-T15 insulinoma cells was studied (Best et al., 1992). The uptake of L-lactate into HIT-T15 cells was rapid, reaching equilibrium after 5 min; uptake of D-lactate by these cells did not occur as rapidly, and equilibrium was not reached within 10 min. The rates of transport for L- and D-lactate were greatly reduced with rat pancreatic islets.

ACUTE DERMAL TOXICITY

Glycolic Acid

No acute dermal toxicity data were available on Glycolic Acid.

Lactic Acid

TEA-Lactate. Published dermal acute toxicity data for TEA-Lactate were not found. Acute dermal irritation studies using rabbits included in the Safety Assessment on TEA (Elder, 1983) reported little potential for irritation.

Ethyl Lactate. There were no deaths during the 7-day observation period in 10 rabbits when 5 g/kg of Ethyl Lactate was applied to the skin; the dermal LD_{50} of Ethyl Lactate was >5000 mg/kg (Food and Drug Research Laboratories, Inc., 1976). The maximum tolerated dose applied to mouse skin was 250 mg/kg (Opdyke and Letizia, 1982).

Butyl Lactate. There were no deaths in 10 rabbits when 5 g/kg of Butyl Lactate was applied to the skin. The dermal LD_{50} of Butyl Lactate was >5000 mg/kg (MB Research Laboratories, Inc., 1977).

ACUTE ORAL TOXICITY

Glycolic Acid

The oral LD_{50} of a 5% aq. Glycolic Acid solution was 1950 and 1920 mg/kg for rats and guinea pigs, respectively (Smyth et al., 1941). The oral LD_{50} of a 20% aq. solution for the rat was 1600–3200 mg/kg (Patty et al., 1963).

Female white Holtzman rats were dosed orally with an approximately lethal dose of Glycolic Acid (reported to be of "high purity") and killed after 24 h (Bove, 1966). The kidneys, liver, and brain were examined microscopically. Of the six animals dosed with 5000 mg/kg, severe toxic effects were observed for all of the animals, three of the animals died 8–12 h after dosing, and all had severe renal tubular oxalosis; no crystals were found in the brain. None of the four animals dosed with 3000 mg/kg Glycolic Acid developed any signs of toxicity or oxalosis.

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In a range-finding study, 5000 mg/kg of 70% Glycolic Acid technical solution, equivalent to 3500 mg/kg Glycolic Acid, killed 8 to 10 male rats (Haskell Laboratory, 1990). A dose of 500 mg/kg 70% Glycolic Acid technical solution, equivalent to 350 mg/kg Glycolic Acid, produced no deaths. The oral LD_{50} of 70% Glycolic Acid technical solution was 4240 mg/kg, equivalent to 2968 mg/kg Glycolic Acid, for male rats (Haskell Laboratory, 1990). It was a severe gastrointestinal irritant. Surviving animals had increased kidney weights and, at microscopic examination, lesions were found in the stomach, liver, and kidneys, i.e., interstitial nephritis and calcium oxalate crystals in the tubules. For mice, the oral LD_{50} of Glycolic Acid was 2000 mg/kg (Perier et al., 1988). Death was "considerably delayed" and marked by neuromuscular inhibition. The researchers contributed the toxicity of glycolate to its consumption of reserves of $NADH_2$.

Sodium Glycolate. Cats were used to evaluate the toxicity of a 9.8% buffered solution, pH 7.3, of Sodium Glycolate and Glycolic Acid (Riker and Gold, 1942). A single dose of the solution was administered orally at concentrations ranging from 100 to 2500 mg/kg or intravenously at a concentration range of 1000–2400 mg/kg. Orally, a dose of 100 mg/kg was without effect, a dose of 250 mg/kg was toxic but not fatal, and doses of $\geq$500 mg/kg generally resulted in death. Two of the four animals receiving 1000 mg/kg intravenously died; all animals receiving higher concentrations died.

Lactic Acid

A skin cream containing 0.6% of 85% aq. Lactic Acid, pH 7.50, had an oral LD_{50} of >15,000 mg/kg and was classified as "practically nontoxic" when given undiluted to rats (Avon Products, Inc., 1995b). Standard operating procedures (Avon Products, Inc., 1986a) stated that five fasted female animals were to be used.

Groups of male Fischer 344 rats, five per group, were dosed with 0.5 mL of 130, 650, or 1300 mg/2000 kg body wt Lactic Acid via stomach tube; the control group received the same volume of water (Morotomi et al., 1981). Two rats of the 650-mg group and one rat of the 1300-mg group died within 24 h of dosing. The concentrations of Lactic Acid in the blood were 0.43 and 0.47 mg/mL for rats of the control and 1300-mg groups, respectively, one day after dosing. The rats were dosed with the same amounts of Lactic Acid after 8 days. Two rats of the 1300 mg readministration group died; dyspnea, snivel, vomiting, and abdominal inflation were observed in these animals immediately after dosing.

The oral LD_{50} for rats of a stone remover formulation containing 6.0% Lactic Acid dark (44%) was >4640 mg/kg (Stauffer Chemical Co., 1971).

The animals were necropsied 14 days after dosing, and no gross lesions were observed. The oral LD_{50} of Lactic Acid for mice was 4875 mg/kg (FAO/WHO, 1967).

L-Lactic Acid. The oral LD_{50} of L-Lactic Acid for rats was 3730 mg/kg (Smyth et al., 1941).

Ammonium Lactate. The oral LD_{50} of a 12% Ammonium Lactate lotion, pH 5.0–5.5, for both rats and mice was >15 mL/kg (FDA, 1988).

Sodium Lactate. The acute oral toxicity of a variety of cosmetic formulations containing 60% aq. Sodium Lactate was evaluated using five fasted female rats (Avon Products, Inc., 1986a, 1995c). The results of these studies are summarized in Table 18.

TEA-Lactate. Published oral toxicity data for TEA-Lactate were not found. Studies included in the Safety Assessment on TEA (Elder, 1983) reported that the oral LD_{50} of TEA for rats ranged from 4.19 g/kg to 11.26 g/kg; TEA was practically nontoxic to slightly toxic.

Ethyl Lactate. The oral LD_{50} for rats of a nail enamel corrector formulation that contained 50% Ethyl Lactate was determined in three studies in which the dose given to five fasted female rats in each study was 5000, 10,000, or 15,000 mg/kg, respectively (Avon Products, Inc., 1986a, 1995d). No deaths were observed when the animals were dosed with 5000 mg/kg, four deaths occurred among the five rats dosed with 10,000 mg/kg, and all five rats dosed with 15,000 mg/kg Ethyl Lactate died. The LD_{50} of Ethyl Lactate for rats was 8200 mg/kg.

Using 10 rats the oral LD_{50} of Ethyl Lactate was >5000 mg/kg; one animal died on day 7 of the 14-day observation period, all others survived (Food and Drug Research Laboratories, Inc., 1976). For mice, the oral LD_{50} was 2500 mg/kg (Opdyke and Letizia, 1982). The oral LD_{50} and LD_{100} of Ethyl Lactate for white mice (at least four mice per group) were 2.5 and 4.0 mL/kg, respectively (Latven and Molitor, 1939). The minimum toxic (producing hypnotic signs in one of four mice) and maximum nontoxic doses were 0.4 and 0.2 mL/kg, respectively.

Butyl Lactate. There were no deaths in 10 rabbits when 5 g/kg of Butyl Lactate was given orally. The oral LD_{50} of Butyl Lactate was >5000 mg/kg (MB Research Laboratories, Inc., 1977).

Lauryl Lactate. The acute oral toxicity of a number of body freshener formulations containing aq. Lauryl Lactate was evaluated using five fasted female rats (Avon Products, Inc., 1985a, 1995e). The results of these studies are summarized in Table 18.

Myristyl Lactate. The acute oral toxicity of lip pencil formulation containing 11.54% Lauryl Lactate was evaluated using five fasted female rats (Avon Products, Inc., 1986a, 1995f). The animals were dosed with

Table 18. Acute oral toxicity of Sodium, Lauryl, and Cetyl Lactate

Product type	Conc. (%)	pH	Dose	Deaths[a]	LD_{50}	Class
			60% Aq. Sodium Lactate			
Face cream	0.1	N/A	5,000 mg/kg	0	>5,000 mg/kg	Acceptable
Facial freshener	0.1	N/A	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Night cream	0.2	N/A	5,000 mg/kg	0	>5,000 mg/kg	Acceptable
Hair conditioner	0.2	3.45	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Face lotion	0.2	6.55	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Face cream	0.2	7.9	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
	100	N/A	5,000 mg/kg	0	>5,000 mg/kg	Acceptable
			Lauryl Lactate			
Body freshener	1	N/A	7,000 mg/kg	0	>7,000 mg/kg	Prac. nontoxic
Body freshener	2		10,000 mg/kg	1		Acceptable
Body freshener	2	N/A	15,000 mg/kg	5	11,600 g/kg	Acceptable
Body freshener	2		7,000 mg/kg	0		Acceptable
Body freshener	2	7.3	15,000 mg/kg	5	10,200 mg/kg	Acceptable
			Cetyl Lactate			
Body cream	0.5	N/A	10,000 mg/kg	0	>10,000 mg/kg	Acceptable
			33.3% in water			
Face lotion	0.75	N/A	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Face lotion	0.75	7.7	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Face lotion	0.75	7.85	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Face lotion	0.75	7.9	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
After shave	0.75	7.0–8.0	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Body freshener	1	N/A	7,000 mg/kg	0	>7,000 mg/kg	Prac. nontoxic
Body freshener	1	N/A	10,000 mg/kg	1	11,600 mg/kg	Acceptable
			15,000 mg/kg	5		

Moisturizing cream	1	N/A	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Night cream	1	6.2	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Moisturizing cream	1	7.2–8.0	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Cleansing cream	1	7.2–8.0	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Body freshener	1	7.3	7,000 mg/kg	0	10,200 mg/kg	Acceptable
			15,000 mg/kg	5		
Moisturizer cream	1	7.8	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Lipstick	3	N/A	15,000 mg/kg 50% in corn oil	0	>15,000 mg/kg	Prac. nontoxic
Lipstick	3	N/A	10,000 mg/kg 33.3% in corn oil	0	>10,000 mg/kg	Acceptable
Lipstick	3	N/A	10,000 mg/kg 33.3% in corn oil	0	>10,000 mg/kg	Acceptable
Lipstick	3	N/A	10,000 mg/kg 33.3% in corn oil	0	>10,000 mg/kg	Acceptable
Lipstick	3	N/A	10,000 mg/kg 33.3% in corn oil	0	>10,000 mg/kg	Acceptable
Lipstick	3	N/A	10,000 mg/kg 33.3% in corn oil	0	>10,000 mg/kg	Acceptable
Lipstick	3	N/A	10,000 mg/kg 33.3% in corn oil	0	>10,000 mg/kg	Acceptable
Lipstick	3	N/A	10,000 mg/kg 33.3% in corn oil	0	>10,000 mg/kg	Acceptable
Lip Pencil	3	N/A	10,000 mg/kg 33.3% in corn oil	0	>10,000 mg/kg	Acceptable

(Table continued on next page)

Table 18. Acute oral toxicity of Sodium, Lauryl, and Cetyl Lactate (*continued*)

Product type	Conc. (%)	pH	Dose	Deaths[a]	LD_{50}	Class
Foundation	3	7.05	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Lipstick	5	N/A	15,000 mg/kg 50% in corn oil	0	>15,000 mg/kg	Prac. nontoxic
Foundation	5	6.0	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Lipstick	7.5	N/A	15,000 mg/kg 33.3% in corn oil	0	>15,000 mg/kg	Prac. nontoxic
Lipstick	9	N/A	15,000 mg/kg 50% in corn oil	0	>15,000 mg/kg	Prac. nontoxic
Lipstick	9	N/A	15,000 mg/kg 50% in corn oil	0	>15,000 mg/kg	Prac. nontoxic
Lipstick	9	N/A	15,000 mg/kg 50% in corn oil	0	>15,000 mg/kg	Prac. nontoxic
Lipstick	9	N/A	15,000 mg/kg 50% in corn oil	0	>15,000 mg/kg	Prac. nontoxic
Lipstick	9	N/A	15,000 mg/kg 50% in corn oil	0	>15,000 mg/kg	Prac. nontoxic
Lipstick	9	N/A	15,000 mg/kg 50% in corn oil	0	>15,000 mg/kg	Prac. nontoxic

[a]Number of deaths out of 5 fasted female rats given oral doses.

10,000 mg/kg. No deaths were observed. The rat oral LD_{50} was estimated to be >10,000 mg/kg. Studies included in the original safety assessment of Myristyl Lactate (Elder, 1982) reported that no toxicity was seen with single 25,000-mg/kg doses of a lipstick formulation containing 13.8% Myristyl Lactate and that the rat oral LD_{50} was >20 mL/kg and >5000 mg/kg Myristyl Lactate.

Cetyl Lactate. The acute oral toxicity of a variety of cosmetic formulation containing aq. Cetyl Lactate was evaluated using five fasted female rats (Avon Products, Inc., 1986a, 1995g). The results of these studies are summarized in Table 18. A study included in the original safety assessment of Cetyl Lactate (Elder, 1982) reported that the female rat oral LD_{50} was >20 mL/kg.

ACUTE INHALATION TOXICITY

Glycolic Acid

The 4-h inhalation LC_{50} of Glycolic Acid for rats was 7.7–14 mg/L (Haskell Laboratory, 1990). Clinical signs increased in severity with increased concentration. During exposure, labored breathing, gasping, red ocular and nasal discharge, and salivation were observed. Postexposure, moderate to severe weight loss, gasping, lung noise, labored breathing, cloudy eyes, ocular discharge, red and clear nasal discharges, stained and ruffled haircoat, lacerations of the face and nose, a wet perineal area, and pallor were observed.

ACUTE PARENTERAL TOXICITY

Glycolic Acid

The IV LD_{50} of Glycolic Acid for the rat was 1000 mg/kg (Sax, 1979).

Calcium Glycolate. The IV LD_{50} of Calcium Glycolate for mice was 180 mg/kg (RTECS, 1995). The IV LD_{LO} of Calcium Glycolate for both the cat and rabbit was 100 mg/kg.

Sodium Glycolate. Cats were used to evaluate the toxicity of a 9.8% buffered solution, pH 7.3, of Sodium Glycolate and Glycolic Acid (Riker and Gold, 1942). Following IV administration, two of four animals dosed with 1000 mg/kg Sodium Glycolate and all animals dosed with ≥1270 mg/kg died. Signs of Sodium Glycolate toxicity included neuromuscular disturbances, weakness, ataxia, anorexia, and sometimes convulsions; the onset of these effects were usually delayed, generally occurring approximately 30 min after dosing, even following IV administration.

Ethyl Glycolate. The estimated average lethal dose for the female rat (either Wistar or Glaxo-Wistar) following IP injection of laboratory

grade Ethyl Glycolate was approximately 1500 mg/kg (Sanderson, 1959). Observations included narcosis, weakness, respiratory distress, peritoneal adhesions, and congestion, cyanosis, and a "rubbery" liver. The estimated "maximum symptomless dose" and estimated maximum dose without gross lesions at necropsy was 500 mg/kg.

Lactic Acid

Ammonium Lactate. The IP LD_{50} for mice of a 12% Ammonium Lactate lotion was approximately 4 mL/kg, with 80% mortality observed with 6 mL/kg (FDA, 1988). Hypoactivity, rough coat, and abdominal distention were dose related.

Calcium Lactate. The minimum lethal dose of Calcium Lactate via IV injection was 80–160 mg/kg for dogs, 180–380 mg/kg for rabbits (Life Sciences Research Office, 1978), and 140.5 mg/kg for white mice (Jenkins, 1938).

Sodium Lactate. The IP LD_{50} of Lactic Acid for the rat was 2000 mg/kg (FAO/WHO, 1967).

TEA-Lactate. Published acute parenteral toxicity data for TEA-Lactate were not found. A study included in the Safety Assessment on TEA (Elder, 1983) reported that the IP LD_{50} of TEA for mice was 1.450 g/kg.

Methyl Lactate. The estimated average lethal dose for the female rat (either albino, Wistar, or Glaxo-Wistar) following IP injection of laboratory grade Methyl Lactate was >2000 mg/kg (Sanderson, 1959). Observations included narcosis, respiratory distress, and peritoneal adhesions. The estimated maximum nontoxic dose and estimated maximum dose without gross lesions at necropsy was 500 mg/kg.

Ethyl Lactate. The estimated average lethal dose for the female rat (either Wistar or Glaxo-Wistar) following IP injection of laboratory grade Ethyl Lactate was approximately 1000 mg/kg (Sanderson, 1959). Observations included weakness, respiratory distress, peritoneal adhesions, and congestion, cyanosis, and a "rubbery" liver. The estimated maximum nontoxic dose and estimated maximum dose without lesions at necropsy were 750 and <500 mg/kg, respectively. The subcutaneous (SC) LD_{50} and LD_{100} of Ethyl Lactate for white mice (at least four mice per group) were 2.5 and 3.0 mL/kg, respectively (Latven and Molitor, 1939). The minimum toxic dose and maximum nontoxic doses were 1.0 and 0.8 mL/kg, respectively. The IV LD_{50} and LD_{100} of Ethyl Lactate for white mice (at least four mice per group) were 0.6 and 1.0 mL/kg, respectively (Latven and Molitor, 1939). The minimum toxic dose and maximum nontoxic doses were 0.3 and 0.2 mL/kg, respectively.

SHORT-TERM DERMAL TOXICITY

Lactic Acid

Ammonium Lactate. In a 21-day dermal study, a dose of 4 mL/kg of a 12% Ammonium Lactate lotion, pH 5.0–5.5, was applied to the backs of four rabbits, two per sex, and saline was applied to the backs of a control group of four rabbits, two per sex (FDA, 1988). (Whether restraints were used to prevent ingestion was not stated.) The backs of 50% of the animals were abraded. Additional details were not provided. Feed consumption, hematology, clinical chemistry, urinalysis, organ weights, and gross observations at necropsy were all normal, and no compound-related toxicity was noted. The application sites had local irritation with acanthosis, hyperkeratosis, and dermal inflammatory infiltration.

Sodium Lactate. Groups of six female New Zealand White rabbits were used to determine the short-term dermal toxicity of a facial freshener and a facial cleanser containing 0.15 and 0.10%, respectively, of 60% aq. Sodium Lactate (pH not applicable) (Avon Products, Inc., 1995c). The hair on the back of each animal was clipped and the animals were dosed dermally with 2.0 mL/kg of each test material 5 days/week for a total of 20 applications; the application site of three animals/group was abraded at weekly intervals. A collar was used to prevent ingestion of the test material. A third group served as an untreated control group. The animals were observed daily for dermal irritation and systemic toxicity. Both test formulations induced slight erythema, desquamation, and some drying of the skin. At microscopic examination, a slight intradermal inflammatory response was observed in three of the animals that received applications of the facial cleanser; no microscopic changes were observed in the animals dosed with the facial freshener. No other compound-related changes were observed during the study or at necropsy, and no significant differences were found in hematology or blood chemistry values between treated and control animals.

A group of nine female New Zealand White albino rabbits was used to determine the dermal toxicity of a tissue-off facial cleanser that contained 0.10% of 60% aq. Sodium Lactate following the same procedure described above (Avon Products, Inc., 1995c). A dose of 2000 mg/kg was used, and the application sites on three animals were abraded. Slight erythema was observed for the test animals by week 2 of dosing and slight erythema with slight scaling was then noted for the remainder of the study. This was not observed for the control group. No other dose-related observations were made during the study; animals of all test groups had mucoid enteritis. No compound-related deaths occurred. No significant changes were noted at necropsy or at microscopic examination.

SHORT-TERM ORAL TOXICITY

Glycolic Acid

Dogs (number and sex not specified) were given daily oral doses of 1000 mg Glycolic Acid for 35 days (Haskell Laboratory, 1990). No abnormal secretions of oxalic acid were found, and no damage to the gastroenteric tract or kidneys was reported.

Groups of 10 male Wistar rats were fed a basal diet or the basal diet with 3% Glycolic Acid for 3 weeks (Chow et al., 1975). Pooled 24-h urine samples were taken. At dose termination, the animals were necropsied, the kidneys and urinary tracts were examined grossly for calculi, and the kidneys were also analyzed for total oxalate and calcium. The feeding of Glycolic Acid resulted in a high incidence of oxalate urolithiasis; the uroliths were seen mostly in the kidneys, but some animals also had uroliths in the ureter and urinary bladder. Also, fine crystalline depositions were present throughout the cortex and medulla and clusters of concretions were on the surface or embedded in the renal papilla. The addition of alanine to the diet generally prevented calculi formation. Additionally, the feeding of diet containing alanine (without Glycolic Acid) to rats with concretions from previous feeding with Glycolic Acid dissolved the depositions.

Groups of 10 male Wistar rats were fed a basal diet or the basal diet with 3% Glycolic Acid for 4 weeks to examine Glycolic Acid's ability to induce calculi formation (Chow et al., 1978). Body weights were measured weekly and feed and water consumption were determined during weeks 2 and 4. At necropsy, the urinary tracts were examined grossly and the kidneys, heart, femur, and a section of skeletal muscle were analyzed for oxalate and/or glycolate. All rats appeared normal after 4 weeks. The addition of Glycolic Acid to basal diet resulted in decreased body weight gain and increased water intake, but it did not affect feed consumption. Glycolic Acid was a potent calculi producer, with deposits being observed in the ureters, urinary bladder, renal tubules, and/or renal pelvis and papilla of all 10 rats. The calculi recovered were composed of calcium oxalate and the calculi from the urinary bladder or renal pelvis were $\leq$4 mm in diameter. The addition of pyruvate to the diet had a preventive effect on oxalate urolith formation, and at microscopic examination no calcium deposits were found in the kidneys of rats fed pyruvate and pyruvate plus alanine. The kidneys of rats fed Glycolic Acid had an average of 2.4% oxalate on a dry weight basis; the addition of pyruvate and alanine reduced oxalate to approximately control values, i.e., 0.2%. No increase in oxalate content was found in the hearts, muscles, or femurs of the glycolate-fed rats.

In similar studies, Ogawa et al. (1986) found that sodium and potassium pyruvate, and to a lesser extent sodium and potassium bicarbonate

and pyruvic acid, did not produce stones in the urinary system. Ogawa et al. (1990) reported similar findings upon addition of magnesium hydroxide, magnesium citrate, and magnesium trisilicate. In both studies the researchers stated that urinary calculi formation was most likely reduced by an increase in urinary citrate concentration, not by decreased oxalate synthesis.

Krop and Gold (1944) dosed groups of six and eight cats via oral administration with 97 and 194 mg/kg Glycolic Acid, respectively, for 7–48 and 28–59 days, respectively. In the low-dose group, signs of toxicity appeared after 7–20 days of dosing, urinary and blood changes were observed, and four of the six animals had weight loss (7–24%). In the high-dose group, signs of toxicity appeared after 4–17 days of dosing and weight loss ranged from 9 to 30%. One of six animals of the low-dose group and all eight of the animals of the high-dose group died during the study.

Sodium Glycolate. Krop and Gold (1944) dosed groups of six cats orally with 125 or 250 mg/kg Sodium Glycolate for 44–54 or 12–50 days, respectively. In the low-dose group, signs of general toxicity were not seen; however, this dose was nephrotoxic and produced azotemia. In the high-dose group, signs of toxicity, including anorexia, weakness, depression, and vomiting, appeared after 5–18 days of dosing and progressed, terminating in coma and convulsions; all animals of this group died during the study. Weight loss for this group ranged from 9 to 30%.

LACTIC ACID

Two dogs were given 600–1600 mg/kg Lactic Acid orally 42 times over a 2.5-month period (Faust, 1910). No ill effects were observed.

Ten white rats were dosed by gavage with commercial fermenting 50% Lactic Acid to determine the lethal dose (Wysokinska, 1952). The dose volume on the first day was 0.25 mL, or approximately 625 mg pure acid/kg body wt. The dose was increased daily by 0.25-mL increments until a single administration of 4.5 mL 50% Lactic Acid, or 11,250 mg/kg, was given. Two rats died after dosing with 3 mL. The animals had a 15% reduction in body weight in 1 week. A single administration of large doses did not result in changes in the carbon dioxide content or the pH of the blood, but there was a considerable decrease in the pH of the urine. Necropsy findings included congestion of the liver and a "much-loosened" gastric and duodenal mucosae.

Cetyl Lactate. A group of 15 female CHR-CD rats was used to determine the toxicity of a lipstick formulation containing 7.5% Cetyl Lactate, pH not applicable (Avon Products, Inc., 1995g). The animals were dosed orally with 1000 mg/kg of the formulation suspended in corn oil

(25% w/w) once daily 5 days per week for 6 weeks. A control group of 15 female rats was dosed similarly with 1000 mg/kg corn oil. The animals were observed daily and body weights were determined weekly. All animals survived until study termination, except for one accidental death in the test group. The animals were killed at study termination. No significant differences in physical appearance, behavior, body weight, or body weight gain were observed between the test and control group. Hematology and clinical chemistry values were similar, with the exception of significantly increased serum alkaline phosphatase (SAP) values in the test group; this increase was not considered of toxicologic significance because the control values were considerably lower than historical control values. The kidney weights of the test animals were significantly greater than the kidney weights of the controls; again, this was not considered toxicologically significant. All other measured relative and absolute organ weights were similar. Microscopic lesions were not found.

SHORT-TERM INHALATION TOXICITY

Glycolic Acid

An inhalation study was performed in which rats, 10 per group, were exposed to 0.23, 0.72, or 2.0 mg/L of a 70% Glycolic Acid solution for 6 h/day, 5 days/week, for 2 weeks; the animals of the 2.0-mg/L group received only eight exposures due to their deteriorating condition (Haskell Laboratory, 1990). The animals were observed for 2 weeks after dosing. One animal of the 0.72-mg/L dose group died during the recovery period from dose-related effects. Rats dosed with 2.0 mg/L had increased serum glutamate pyruvate transaminase (SGPT) and serum glutamic-oxaloacetic transaminase (SGOT) values and decreased urine volume and pH. Rats dosed with 0.72 mg/L had increased SGOT values, decreased urine volume, and reversible hepatic effects. No signs of toxicity were observed in rats dosed with 0.23 mg/L. At microscopic examination, hepatic changes were observed in one rat of the 0.23-mg/L group, nine rats of the 0.72-mg/L group, and seven rats of the 2.0-mg/L group. Gross observations included small spleen, liver, and thymus and a distended gastrointestinal tract.

SHORT-TERM PARENTERAL TOXICITY

Glycolic Acid

Sodium Glycolate. Five rabbits were used to determine the nephrotoxicity of Sodium Glycolate (Silbergeld, 1960). Two groups of rabbits,

one male and one female per group, were dosed with 0.5 or 1.0 g Sodium Glycolate by SC injection on day 4 of the 7-day study period; a fifth rabbit served as a control. The rabbits were given water *ad libitum* but no feed during the study. NPN and blood creatinine were determined prior to and 16 and 87 h after dosing, and renal function was further evaluated by the PSP test of Geraghty and Rowntree (1911). PSP elimination and blood NPN and creatinine values remained within normal limits for all the rabbits. A single SC dose of 0.5–1.0 g Sodium Glycolate did not appear to alter renal function.

SUBCHRONIC DERMAL TOXICITY

Lactic Acid

The dermal toxicity of a face cream containing 0.25% of 85% aq. Lactic Acid was evaluated using two groups of 15 female Sprague–Dawley rats (Avon Products, Inc., 1995b). The test group received daily applications of 886 mg/kg applied 5 days/week for 13 weeks to a shaved dorsal area of the back; the control group was untreated. (The dose was determined by applying a factor of 100× to the average daily human use determined using 1 g/day.) Animals were observed daily, and blood and urine samples were collected during weeks 7 and 13 from randomly selected animals. All animals survived to study termination. No significant gross observations, with the exception of minimal skin irritation throughout the study, could be attributed to dosing. During week 7, the blood urea nitrogen value was significantly increased for test animals as compared to controls; no other hematological effects were seen, and urinary parameters were normal. Absolute brain weight and kidney-to-body weight ratios were statistically significantly increased for the test animals. No lesions were observed at necropsy or at microscopic examination. The investigators concluded this formulation is "safe in terms of cumulative toxicity" and that "based upon the exaggerated dose level used in this study for skin care products, dermal application is not likely to produce adverse effects under conditions of consumer use."

Ammonium Lactate. In a 90-day dermal study, 1 mL/kg day^{-1} of a 12% Ammonium Lactate lotion, pH 5.0–5.5, was applied to the backs of six rabbits, three per sex, and 4 mL/kg day^{-1} of a 12% Ammonium Lactate lotion, pH 5.0–5.5, was applied to the backs of eight rabbits, four per sex; saline was applied to the backs of a control group of 10 rabbits, five per sex (FDA, 1988). Use of restraints was not specified. The backs of half of the animals were abraded. Three control, one low-dose, and two high-dose animals, which died on study due to acute pneumonia and/or mucoid enteritis, were replaced. Feed consumption, body weights, hematology, clinical chemistry, and urinalysis were normal for all test

groups. Absolute kidney weights of the low-dose group were significantly increased compared to controls, while the relative kidney weights were comparable. Both dose groups had mild irritation, described as a minimal to slight acanthosis, inflammatory cellular infiltration, and hyperkeratosis. Three of the high-dose animals developed minimal focal ulceration of the application areas.

Sodium Lactate. A group of 15 female ChR-CD albino rats was used to evaluate the dermal toxicity of a face cream containing 0.10% of 60% aq. Sodium Lactate (Avon Products, Inc., 1995c). The cream was applied as supplied to shaved dorsal skin 5 days/week for a total of 63 applications at a dose of 2000 mg/kg and a dose volume of 2 mL/kg. The test area was not rinsed prior to subsequent applications, and no attempt to prevent ingestion was made. A second group of 15 rats was dosed with distilled water and served as a control group.

Observations were made daily, and body weights were determined weekly. No significant differences in body weight, physical appearance, or behavior were observed between test and control animals. Both test and control animals had slight erythema and drying of the skin. The mean value of serum glucose was statistically significantly increased for test animals as compared to controls, but this was deemed unrelated to dosing. No significant findings were reported at necropsy or at microscopic examination.

TEA-Lactate. Published subchronic dermal toxicity data for TEA-Lactate were not found. Subchronic dermal irritation studies using rabbits included in the Safety Assessment on TEA (Elder, 1983) reported that hair dyes containing 0.10–0.15% or 1.5% TEA did not result in toxicity. However, application of 8000 mg/kg to guinea pigs for 17 applications produced evidence of adrenal, hepatic and renal damage.

Cetyl Lactate. A group of 15 male Sprague–Dawley N(DS)FBR albino rats was used to determine the dermal toxicity of an aftershave moisturizer containing 0.75% Cetyl Lactate, pH 7.0–8.0 (Avon Products, Inc., 1995g). The formulation, at a dose of 1870 mg/kg or 1.9 mL/kg, was applied by gentle inunction to a shaved dorsal site once daily 5 days/week for 13 weeks, for a total of 68 doses. Fifteen male rats were used as an untreated control group. Observations were made daily, body weights were determined weekly, and blood samples were taken at weeks 7 and 13. All animals survived until study termination. The animals were killed at study termination. Transient and sporadic minimal skin irritation was observed for 6 weeks for animals of the test group after four doses. One animal of the test group was hyperactive upon dosing beginning at week 5 and continuing through the end of the study. No significant differences in body weight gain were observed between animals of the test and control groups. No statistically, toxicologically significant

differences in urinalysis values were observed. No dose-related observations were made at necropsy or upon microscopic examination of tissues, and no statistically, toxicologically significant differences in organ weights were observed.

A group of 15 female Crl:Cobs CD(SD)Br albino rats was used to determine the dermal toxicity of a moisturizing cream formulation containing 1% Cetyl Lactate, pH 7.3 (Avon Products, Inc., 1995g). The formulation, at a dose of 920 mg/kg, was applied to a shaved anterior dorsal site once daily 5 days/week for 13 weeks, for a total of 67 applications. A group of 15 control rats was also used. Observations were made daily, body weights were determined weekly, and blood samples were taken at weeks 7 and 13. All animals survived to study termination. The animals were killed at the termination of dosing. Sporadic, minimal irritation was observed until week 7 at the application site of the test animals. Body weight gains were similar for animals of the test and control groups. Hemoglobin, mean cell volume, and white blood cell count total/differential were statistically significantly increased at week 7; these increases were considered toxicologically insignificant because they were not seen at week 13. The neutrophil/lymphocyte ratio was statistically significantly decreased at weeks 7 and 13, and SGPT values were statistically significantly decreased at week 13; these decreases were considered toxicologically insignificant because the mean values were within historical limits. All urinalysis values were within the normal range. No compound-related lesions were found at necropsy. The relative and absolute lung weights were statistically significantly increased for animals of the test group compared to the controls. At microscopic examination, no compound-related lesions were found.

SUBCHRONIC ORAL TOXICITY

Glycolic Acid

Available subchronic oral toxicity studies by Krop and Gold (1944) on Glycolic Acid were not considered useful.

Lactic Acid

A group of white rats was fed 10% Lactic Acid at a dose of 4 mL/20 g of meal and a control group was given untreated feed (Wysokinska, 1952). No differences in appearance, gross observations at necropsy, or organ weights were observed between the test and control animals. Changes in blood carbon dioxide were slight. No overt toxic effects were observed in pigs given approximately 3.6–18 g/kg Lactic Acid in feed or water for up to 5 months (Lamb and Evvard, 1919; Kershaw et al., 1966).

Groups of 15 Syrian hamsters, 8 males and 7 females per group, were dosed with Lactic Acid by adding 0.057 mL Lactic Acid (80%) to 100 g of feed or by adding 0.050 mL Lactic Acid (80%) to 100 mL distilled water for 100 days; the amount of Lactic Acid added to the feed and water provided the same daily ingested dose for the two groups (Granados et al., 1949). A third group was given untreated feed and water. All animals were killed for necropsy at study termination. No differences in appearance or growth rate were noted between the groups, and no gross changes were observed at necropsy. Various degrees of alveolar resorption were reported for several animals, but no significant difference was observed between the groups.

Calcium Lactate. Five groups of 10 F344 rats, five per sex, were dosed with 0.3–5.0% Calcium Lactate in the drinking water for 13 weeks and fed basic diet ad libitum; a control group was given untreated drinking water (Matsushima et al., 1989). All animals survived until study termination. A <10% decrease in body weight gains were observed for all treated groups. Some hematological and biochemical parameters changed in the treated groups, but no severe lesions were found at microscopic examination.

Four groups of 10 F344 rats, five per sex, were fed 0.3–5.0% Calcium Lactate (duration of dosing not stated); a control group was given untreated feed (Matsushima et al., 1989). The body weight gains of males and females of the high-dose group and males of the 20%-dose group were significantly decreased as compared to control values after 20 weeks. The amount of calcium in the urine was significantly increased for males of all dose groups and females of the 10–30%-dose groups. At microscopic examination, nephrocalcinosis and degeneration of the epithelium of the proximal and collecting tubules of the kidneys were observed in all groups, including the control group, and an inverse dose–effect relationship was seen in regard to the degree of development. These lesions were less severe in females than in males. Two groups of rats were then fed basal diet or Calcium Lactate-containing feed (dose not stated) for 8 weeks. Nephrocalcinosis was observed only in the group fed the lactate-containing diet, indicating that nephrocalcinosis was dependent on the low calcium/phosphorus ratio (<1) of the lactate-containing diet.

Myristyl Lactate. Groups of 20 Sprague–Dawley rats, 10 males and 10 females per group, were dosed orally with 0.5, 2.5, and 5.0 mg/kg (0.55, 2.75, 5.5 mL/kg, respectively) Myristyl Lactate 5 days/week for 13 weeks (Avon Products Inc., 1995f). All animals survived until study termination, and their appearance and behavior were relatively unaffected by treatment. Body weight gain was significantly decreased for males of the 5.0-mg/kg-dose group. Body weight gains of males of

the 0.5 and 2.5-mg/kg-dose groups and for all females were similar to control values. No dose-related changes in hematologic parameters were observed, but statistically significant changes were observed in some clinical chemistry values. SGPT values were significantly increased for males and females of the mid- and high-dose groups and SGOT and SAP were significantly increased for males of the high-dose group. In the urinalysis results, ketones were significantly increased for males and females of the high-dose group and males of the mid-dose group at week 7, but this was not considered dose related and, therefore, not toxicologically significant; values were normal at week 13. At necropsy, three males of the high-dose group and one of the mid-dose group had slightly enlarged livers with a prominent lobular pattern, three females of the high-dose group had slightly enlarged livers with paleness of all lobes, and liver weight was significantly increased for males and females of the mid- and high-dose groups. Dose-related effects were also seen in the gastrointestinal tract, including enlargement or thickening of the walls of the stomach and duodenum. At microscopic examination of selected tissues, alterations found included a dose-related diffuse mucosal hyperplasia in the duodenum of treated animals, inflammatory and/or proliferative lesions in the non-glandular stomach of several mid- and high-dose rats, and hepatic changes, primarily Kupffer cell hypertrophy and a slight disorganization of hepatic cords in some areas, in four males and three females of the high-dose group. The researchers thought the doses used in this study were exaggerated when compared to normal use in the oral area, with a 463× safety factor for the low dose. They concluded that "because of the exaggerated conditions used in this study, (Myristyl Lactate) is considered safe for use in oral area cosmetic products."

CHRONIC DERMAL TOXICITY

Lactic Acid

TEA-Lactate. Published chronic dermal toxicity data for TEA-Lactate were not found. Studies included in the Safety Assessment on TEA (Elder, 1983) reported that chronic cutaneous administration of 13% TEA for 6 months to rats produced evidence of hepatic and renal damage.

CHRONIC ORAL TOXICITY

Glycolic Acid

Male and female albino rats were fed 1 and 2% Glycolic Acid for 218–248 days in a 1943 General Foods Corporation study (Haskell Laboratory, 1990). Decreased growth weight, an increase in renal oxalate,

and nephrotoxic effects were observed in the male rats. No effects were observed in female rats or in male rats fed 0.5% Glycolic Acid. Mortality was 60 and 70% for the 1 and 2% dose groups, respectively, with deaths beginning at day 89. Four groups of male and female albino rats were fed a 1% yeast-fortified diet, and Glycolic Acid was added to the diet of three of the four groups (Silbergeld and Carter, 1959). The dose groups, which were fed 0.5, 1.0, and 2.0% Glycolic Acid, consisted of 4 males and 4 females, 7 males and 11 females, and 7 males and 5 females, respectively. The control group, which was fed untreated feed, consisted of 9 males and 11 females. Feed consumption, body weight gains, and signs of toxicity were observed during the study; the kidneys were examined at necropsy and final kidney oxalate content was determined. For the male animals of the 1.0 and 2.0%-dose groups, average body weight gains were significantly decreased; the decreased growth rate was consistently noted during the first 91 days of the study. No effect on weight gain was observed for the females. Four of the seven males fed 1.0% and five of the seven males fed 2.0% Glycolic Acid died on study, with death being preceded by a marked weight loss over a 2- or 3-week period. No females died on study. The animals that died had granulated, mottled, yellowish brown kidneys and were smaller than those of controls. Microscopic changes were reported for all of the examined kidneys of male rats of the 2.0%-dose group and three of the four males of the 1.0%-dose group. The kidneys of the males of the 2%-dose group and one of the four males of the 1% dose group had masses of mainly calcium oxalate crystals. No microscopic lesions were reported for male animals of the 0.5%-dose group or any of the female animals.

Sodium Glycolate. Five rabbits were used in an approximately 7-month oral study examining the effects of glycolate (Silbergeld, 1960). Two female rabbits were given a daily dose of 0.25 or 0.5 g/kg Sodium Glycolate and a male rabbit was given 0.5 g/kg Glycolic Acid in 100 mL of drinking water; a male and a female rabbit given water only were controls. Phenolsulfonphthalein (PSP) and blood nonprotein nitrogen (NPN) determinations were made 3 days prior to dosing and determined throughout the study. After approximately 7 months, the animals were necropsied and the kidneys were analyzed for oxalic acid. Long-term oral administration of Sodium Glycolate and Glycolic Acid resulted in a greater than 10-fold increase in the oxalate content of the kidneys as compared to control values. However, PSP and blood NPN values were normal throughout the study. No clinical signs of toxicity and no gross renal lesions were observed. The rabbit dosed with 0.5 g/mg Sodium Glycolate died unexpectedly after approximately 4 months of the study.

In a 1943 General Foods Corporation study, rats (number and sex not specified) were fed 2.5% Sodium Glycolate (equivalent to 2000 mg/kg)

for 1 year (Haskell Laboratory, 1990). Growth rate was significantly less than that of the controls. More than half of the animals died during the study, and mortality was greater for males than females. Death was attributed to renal and urinary bladder damage produced by calcium oxalate crystals.

Lactic Acid

TEA-Lactate. Published chronic oral toxicity data for TEA-Lactate were not found. Studies included in the Safety Assessment on TEA (Elder, 1983) reported that the effects of chronic oral TEA administered to rats and guinea pigs were limited primarily to hepatic and renal lesions.

DERMAL IRRITATION

Glycolic Acid

Dermal irritation tests using male white rabbits were performed according to the methods of the *Journal Officiel de la République Française* on one face cream product containing 15% Glycolic Acid and two peeling products containing 25 and 50% Glycolic Acid; the pH of the products was 4.5 (Natura Bissé, 1996). The test dose, 100% of net product, was applied to whole and flaky skin of six rabbits.

All test compounds produced some erythema but no edema. The dermic irritation indices were 0.50, 0.33, and 0.38 for the 15, 25, and 50% Glycolic Acid products, respectively, and it was concluded they were "not irritable." It should be noted that FDA analyzed Natura Bissé Glycoline, a product reported to contain 50% Glycolic Acid (FDA, 1996b); analysis of three random samples determined Glycolic Acid was present at 30%, and the pHs of the samples were 3.56, 3.55, and 3.53.

Glycolic Acid was classified as a primary skin irritant when 70% technical Glycolic Acid, 0.5 mL, applied undiluted to abraded and intact skin of one rabbit resulted in primary skin irritation bordering on corrosive (Haskell Laboratory, 1990). Strong erythema and mild edema were seen on the intact skin and strong erythema and necrosis were seen along the lines of abrasion; these observations were not visible at 72 h. However, in another study in which the same dose was applied to the intact skin of six rabbits under an occlusive patch for 4 h and then washed, skin corrosion was not observed at 24 or 48 h.

Lactic Acid

The primary skin irritation potential of a formulation containing 85% Lactic Acid was assayed in single-insult occlusive patch tests using

rabbits; the cream was applied undiluted (Avon Products, Inc., 1995b). Standard operating procedures (Avon Products, Inc., 1987) stated that six shaved animals/study with intact skin were to be dosed with 0.1 g of solid test material under an occlusive patch for 24 h; the test sites were to be scored 2 and 24 h after patch removal for erythema and edema on a scale of 0–8. The results of these studies are summarized in Table 19.

A 5% aq. solution of Lactic Acid, 0.2 mL, was "very slightly irritant" after repeated application to shaved rat skin (number of animals not stated) (ESLUR, 1994a). One-half milliliter of 5 and 10% aq. Lactic Acid was applied for 4 h to the clipped dorsum of rabbits (number and sex not stated) using occlusive patches; the treatment sites had been prehydrated for 60 min immediately prior to dosing (ESLUR, 1994a). The 5% solution was "virtually nonirritant," and the 10% solution was "only slightly irritant, causing similar effects to those of marketed skin care creams." The primary cutaneous irritation potential of Lactic Acid was determined using rabbits following a modification of the procedure described in the *Journal Officiel de la République Française* (Guillot et al., 1982a). Pure Lactic Acid and an aq. 20% solution applied under occlusive patches were moderately and slightly irritating. Irritation was expressed as the primary irritation index (PII). PIIs of 2.50 and 0.54 were reported for the pure Lactic Acid and the 20% solution, respectively. Cumulative cutaneous irritation was then determined for Lactic Acid, also following a modification of the procedure described in the *Journal Officiel de la République Française* (Guillot et al., 1982a). Two milliliters/animal of the test substance as supplied (100%) and in dilution (10 and 20%) were applied to the right and left flanks of each of three rabbits. Daily readings were expressed as a weekly average. Qualitative evaluation was made for thickening and dryness of the skin, and microscopic examinations were made after 6 weeks of dosing. Recovery from cutaneous injury was determined by examining the skin 7 days after the last application. Undiluted Lactic Acid produced severe orthoergic intolerance and dosing was discontinued after 1 week of treatment. Both 10 and 20% Lactic Acid were well tolerated, with mean maximum irritation indices (MMII) of 0.50 and 1.00, respectively.

A stone remover formulation containing 6.0% Lactic Acid dark (44%) was evaluated in a Draize test for dermal irritation potential (Stauffer Chemical Co., 1971). The PII of the material, applied undiluted, was 7.46 and it was classified as corrosive. After application of the material diluted to the maximum use concentration (0.4% in water), the PII was 0.46, and it was classified as a mild irritant.

Ammonium Lactate. Two studies were performed in which 0.5 mL 12% Ammonium Lactate lotion, pH 5.0–5.5, was applied to one intact and one abraded site on the back of six rabbits. In one study, 0.5 mL

Table 19. Primary skin irritation potential of Lactic Acid and Sodium, Ethyl, Lauryl, Myristyl, and Cetyl Lactate

Product type	Conc. (%)	pH	Irritation scores (2 h/24 h)	PII[a]	Conclusion
		85% Lactic Acid			
Skin cream	0.6	7.5	1.67/1.67	1.78	Mild irritation
Skin cream	0.6	7.5	1.33/2.89	2.89	Mild irritation
Skin cream	0.6	7.5	2.00/3.22	3.22	Moderate irritation
		60% Aq. Sodium Lactate			
Facial freshener	0.1	N/A	—	0	No irritation
Face cream	0.1	N/A	—	0.5	Negligible irritation
Face cream	0.2	N/A	0.11/0.06	0.11	Negligible irritation
Night cream	0.2	N/A	—	0.89	Minimal irritation
Hair conditioner	0.2	3.4	0.67/0.78	0.94	Minimal irritation
Hair conditioner	0.2	3.45	0.39/0.22	0.39	Negligible irritation
Hair conditioner	0.2	4.9	—	1.39	Minimal irritation
Hair conditioner	0.2	5.0	—	1.39	Minimal irritation
Night cream	0.2	5.78	0.33/0.33	0.56	Minimal irritation
Face lotion	0.2	6.55	0.67/0.33	0.67	Minimal irritation
Face lotion	0.2	7.0	0.33/0.22	0.44	Negligible irritation
Face cream	0.2	7.9	0.78/0.83	0.83	Minimal irritation
Night cream	0.2	8.6	1.44/1.11	1.56	Mild irritation
Night cream	0.4	5.25	0.22/0.11	0.22	Negligible irritation
	100	N/A	—	0.11	Negligible irritation

(*Table continued on next page*)

Table 19. Primary skin irritation potential of Lactic Acid and Sodium, Ethyl, Lauryl, Myristyl, and Cetyl Lactate (*continued*)

Product type	Conc. (%)	pH	Irritation scores (2 h/24 h)	PII[a]	Conclusion
Nail Enamel Corrector	0.5	N/A	0.00/0.00	0.00	No irritation
		Lauryl Lactate			
Body freshener	2	N/A	1.00/0.67	1.00	Minimal irritation
Face cream	5	4.65	2.33/1.67	2.33	Mild irritation
		Myristyl Lactate			
Foundation	7.65	N/A	0.67/0.11	0.67	Mild irritation
Lip pencil	11.54	N/A	0.78/0.00	0.78	Minimal irritation
		Cetyl Lactate			
Body cream	0.5	N/A	0.67/0.00	0.67	Minimal irritation
Face lotion	0.75	N/A	0.11/0.33	0.33	Negligible irritation
Aftershave moisturizer	0.75	7.0–8.0	0.44/0.00	0.44	Negligible irritation
Face lotion	0.75	7.7	0.67/0.78	0.89	Minimal irritation
Face lotion	0.75	7.85	1.11/1.22	1.22	Minimal irritation
Face lotion	0.75	7.90	0.67/0.67	0.78	Minimal irritation
Body lotion	1	N/A	0.33/0.22	0.44	Negligible irritation
Body refresher	1	N/A	1.00/0.67	1.00	Minimal irritation
Moisturizing cream	1	N/A	1.00/0.89	1.22	Minimal irritation
Night cream	1	6.2	0.00/0.00	0.00	No irritation
Moisture cream	1	6.5	0.56/0.11	0.56	Minimal irritation
Moisture lotion	1	7.0	0.33/0.22	0.44	Negligible irritation
Cleansing cream	1	7.15	1.78/1.44	1.89	Mild irritation
Moisturizing cream	1	7.2–8.0	0.28/0.28	0.44	Negligible irritation
Cleansing cream	1	7.2–8.0	—	0.61	Minimal irritation

Moisturizing cream	1	7.8	0.39/0.28	0.44	Negligible irritation
Body lotion	1.1	7.0	2.00/1.67	2.00	Mild irritation
Moisturizing cream	1.5	6.1	0.56/0.44	0.56	Minimal irritation
Lipstick	3	N/A	0.00/0.00	0.00	No irritation
Lipstick	3	N/A	0.00/0.00	0.00	No irritation
Lipstick	3	N/A	0.00/0.00	0.00	No irritation
Lipstick	3	N/A	0.00/0.00	0.00	No irritation
Lipstick	3	N/A	0.00/0.00	0.00	No irritation
Lipstick	3	N/A	0.00/0.00	0.00	No irritation
Lipstick	3	N/A	0.06/0.06	0.06	Negligible irritation
Lipstick	3	N/A	—	0.39	Negligible
Lip Pencil	3	N/A	0.44/0.11	0.56	Minimal irritation
Foundation	3	7.05	0.89/0.56	1.00	Minimal irritation
Lipstick	4.5	N/A	0.67/0.56	0.67	Minimal irritation
Foundation	5	6.0	1.33/1.22	1.44	Minimal irritation
Foundation	5	6.0	2.33/1.83	2.50	Mild irritation
Lipstick	7.5	N/A	—	0.00	No irritation
Lipstick	9	N/A	0.00/0.00	0.00	No irritation
Lipstick	9	N/A	0.00/0.00	0.00	No irritation
Lipstick	9	N/A	—	0.00	No irritation
Lipstick	9	N/A	—	0.00	No irritation
Lipstick	9	N/A	—	0.00	No irritation
Lipstick	9	N/A	—	0.00	No irritation

[a]PII = Primary Irritation Index.

distilled water was applied similarly to treated areas while in the second study a control was not used (FDA, 1988). The sites were covered by occlusive patches for 24 h and evaluated 24 and 72 h after dosing. Mild irritation was observed after 24 and 72 h.

Sodium Lactate. The primary irritation potential of a variety of cosmetic formulations containing 60% aq. Sodium Lactate was evaluated in single-insult occlusive patch tests using rabbits (Avon Products, Inc., 1995c). Standard operating procedures (Avon Products, Inc., 1987) were described previously. No pattern of effect as a function of pH or concentration was discernable. The results of these studies are summarized in Table 19.

Two guinea pig immersion tests were performed to evaluate the irritation potential of two shampoo formulations, one which contained 0.25% of 60% aq. Sodium Lactate, pH 5.60, and the other which contained 0.20% of 60% aq. Sodium Lactate, pH 5.50 (Avon Products, Inc., 1995c). Standard operating procedures (Avon Products, Inc., 1986b) state that six shaved outbred Dunkin–Hartley guinea pigs are to be placed in wire mesh restrainers that are then immersed in test solution at 37°C for 4 h/day for three successive days. Forty-eight hours after the last immersion, the animals are to be evaluated for dermal irritancy reactions and signs of toxicity graded on a scale of 1–10 (with a score of 10 signifying no irritation). For these tests, the concentration in water was 0.5%. For the formulation containing 0.25% Sodium Lactate, three animals had scores of 9 and three had scores of 10, resulting in an immersion score of 9.5. For the formulation containing 0.20% Sodium Lactate, two animals had scores of 9 and four had scores of 10, resulting in an immersion score of 9.7. Both scores indicated that the formulations are "practically nonirritating."

Sodium Lactate was evaluated when applied under occlusive patches as supplied, i.e., 50 and 70%, for primary cutaneous irritation potential using rabbits following the same procedure as described previously for Lactic Acid (Guillot et al., 1982a). The solutions were nonirritating, with PII scores of 0.00 and 0.17 for the 50 and 70% solutions, respectively.

Cumulative cutaneous irritation was determined for Sodium Lactate again following the same procedure as described previously for Lactic Acid (Guillot et al., 1982a). Sodium Lactate was supplied as 50 and 70% solutions. With 50% Sodium Lactate, the undiluted solution was relatively well tolerated and the diluted solution (10%) was well tolerated, with MMIIs of 0.73 and 0.33, respectively. With 70% Sodium Lactate, both the undiluted and diluted (14%) solutions were relatively well tolerated, with MMIIs of 1.33 and 1.00, respectively.

TEA Lactate. Published dermal irritation data for TEA-Lactate were not found. Studies included in the Safety Assessment on TEA (Elder,

1983) reported that both 10 open applications and three to 10 semi-occluded applications of TEA to abraded and intact skin, respectively, were slightly to moderately irritating, and that prolonged or repeated exposure can be irritating.

Ethyl Lactate. The primary irritation potential of a nail enamel corrector formulation containing 50% Ethyl Lactate, pH N/A, was evaluated in single insult occlusive patch test using rabbits (Avon Products, Inc., 1995d). Standard operating procedures (Avon Products, Inc., 1987) were described previously. The results of this study are summarized in Table 19.

Ethyl Lactate (volume not specified) was applied under occlusive gauze pads, 2 sq cm, to the shaved abdominal skin of rabbits (number not specified) for 24 h (Latven and Molitor, 1939). No irritation was reported. The application of 5–20% Ethyl Lactate to a guinea pig did not produce irritation or an allergic reaction (details not provided) (Opdyke and Letizia, 1982). Intradermal injection of 0.1 mL Ethyl Lactate into the shaved abdominal skin of guinea pigs produced severe irritation (Latven and Molitor, 1939).

Butyl Lactate. Application of Butyl Lactate (assumed to be applied undiluted under occlusive patches to intact and abraded skin for 24 h) to 10 rabbits produced moderate and marked erythema in eight and two animals, respectively, and slight and moderate edema in one and nine animals, respectively (MB Research Laboratories, Inc., 1977).

Lauryl Lactate. The primary irritation potential of two cosmetic formulations containing Lauryl Lactate was evaluated in single insult occlusive patch tests using rabbits (Avon Products, Inc., 1995e). Standard operating procedures (Avon Products, Inc., 1987) were described previously. The results of these studies are summarized in Table 19.

Myristyl Lactate. The primary irritation potential of two cosmetic formulations containing Myristyl Lactate was evaluated in single-insult occlusive patch tests using rabbits (Avon Products, Inc., 1995f). Standard operating procedures (Avon Products, Inc., 1987) were described previously. The results of these studies are summarized in Table 19. Studies included in the original safety assessment of Myristyl Lactate (Elder, 1982) reported that Myristyl Lactate had little to moderate potential for skin irritation and that a lipstick formulation containing 13.8% Myristyl Lactate tested in an open patch test produced mild irritation.

Cetyl Lactate. The primary irritation potential of a number of cosmetic foundation formulations containing Cetyl Lactate was evaluated in single-insult occlusive patch tests using rabbits (Avon Products, Inc., 1995g). Standard operating procedures (Avon Products, Inc., 1987) were described previously. No pattern of effect as a function of pH or

concentration was discernable. The results of these studies are summarized in Table 19. Studies included in the original safety assessment of Cetyl Lactate (Elder, 1982) reported that 5–25% solutions were not primary irritants.

DERMAL SENSITIZATION

Glycolic Acid

In a modified Draize test (species and number of animals not stated) in which the intradermal injection challenge was 3% and the topical application challenge was 60%, Glycolic Acid was not a sensitizer (ESLUR, 1994b).

Sodium Glycolate. A maximization study using guinea pigs (number of animals not stated) was performed in which induction consisted of intradermal injection of 10% and topical application of 25% Sodium Glycolate; the challenge application was 25% (ESLUR, 1994b). Sodium Glycolate was not a sensitizer.

Lactic Acid

A maximization study was performed using guinea pigs (number of animals not stated) in which induction consisted of intradermal injection of 0.2% and topical application of 50% Lactic Acid; challenge consisted of intradermal injection of 0.2% and application of 10% (ESLUR, 1994a). Lactic Acid was not a sensitizer.

Ammonium Lactate. The sensitization potential of a 12% Ammonium Lactate lotion, pH 5.0–5.5, was examined using 10 guinea pigs (FDA, 1988). The first induction application consisted of 0.5 mL applications of undiluted material as well as 25 and 50% dilutions. The remaining two induction applications (one per week), as well as the two subsequent challenge applications (applied 2 and 3 weeks after the last induction dose), of 0.5 mL were undiluted lotion. The first induction dose and the two challenge doses were placed under occlusive patches for 24 h; the remaining two induction doses were placed under occlusive patches for 6 h. One animal was found dead on day 18 (reason not stated). No erythema was observed after induction or challenge applications, and 12% Ammonium Lactate lotion was not a sensitizer using guinea pigs. A second sensitization study using 10 guinea pigs, following the same procedure as above, using a scented vehicle. One guinea pig was found dead on day 6 (reason not specified). Very slight erythema was noted for one animal after the first induction application and for two animals after the third induction application. No erythema was observed

following either challenge application, and the scented 12% Ammonium Lactate lotion was not a sensitizer.

TEA-Lactate. Published animal sensitization data for TEA-Lactate were not found. Studies included in the Safety Assessment on TEA (Elder, 1983) reported that TEA was not a sensitizer.

Lauryl Lactate. The allergic contact sensitization potential of Lauryl Lactate was evaluated in a modified Magnusson–Kligman maximization test using 10 female guinea pigs (Avon Products, Inc., 1995e). The induction phase consisted of intradermal injections of 0.05 mL of 5% Lauryl Lactate in propylene glycol, 50% aq. Freund's complete adjuvant (FCA), and 5% Lauryl Lactate and 50% aq. FCA. One week after induction, a topical booster of 50% Lauryl Lactate in petrolatum was applied to the induction site. Two weeks after the booster, occlusive patches of 5 and 25% Lauryl Lactate in petrolatum were used for the challenge; the sites were scored 48 and 72 h after patch application. At 72 h after challenge, none of the animals had reacted to the 5% concentration and the irritation index was 0; with the 25% challenge, 30% of the animals reacted (had scores ≥ 1), and the irritation index was 1.3.

Cetyl Lactate. The allergic contact sensitization potential of an aftershave moisturizer containing 0.75% Cetyl Lactate, pH 7.0–8.0, was evaluated in a modified Magnusson–Kligman maximization test using 10 female guinea pigs (Avon Products, Inc., 1995g). The induction phase consisted of intradermal injections of 50% of the test formulation in propylene glycol, 50% aq. FCA, and 50% of the test formulation in 50% aq. FCA. A control group of 10 female guinea pigs received intradermal injections of 50% aq. FCA, propylene glycol, and 1:1 propylene glycol and 50% aq. FCA. One week after induction, a topical booster of 100% of the test formulation in petrolatum was applied to the induction site. Two weeks after the booster, occlusive patches of 50 and 100% of the test material in petrolatum were used for the challenge; the sites were scored 48 and 72 h after patch application. None of the animals reacted and the aftershave moisturizer formulation containing 0.75% Cetyl Lactate, pH 7.0–8.0, was not a sensitizer.

A study included in the original safety assessment of Cetyl Lactate (Elder, 1982) reported that Cetyl Lactate was a nonsensitizer.

PHOTOTOXICITY

Lactic Acid

Five phototoxicity assays were performed on a face cream containing 0.25% of 85% aq. Lactic Acid using six New Zealand White rabbits per test (Avon Products, Inc., 1995b). The undiluted test materials and the

positive control, 8-methoxypsoralen (1/128% in ethanol), were applied to the shaved left side of the back and allowed to penetrate for 30 min; one application/animal was made in all tests except one (test 3) in which two applications/animal were made.

The backs of the animals were irradiated with a UV light source (FL40-BL, >320 nm) placed 8 in. above the midline. In tests 1 and 4, there was one 1-h irradiation period; in test 2, there was one 1-h and one 2-h irradiation period; and in tests 3 and 5, there was one 2-h irradiation period. Following irradiation, the test materials were applied to the shaved right side of the back in the same manner. Test sites were scored using the Draize scale for erythema and edema at 24, 48, 72, and 96 h after application. Upon examination of all results, it was concluded that the face cream containing 0.25% of 85% aq. Lactic Acid was a"weak phototoxin."

Two phototoxicity assays were performed on a face cream containing 0.25% of 85% aq. Lactic Acid (Avon Products, Inc., 1995b). The following standard operating procedures were used (Avon Products, Inc., 1986c). Six New Zealand White albino rabbits received 0.1-mL applications of the test material and a positive control, 0.008% 8-methoxypsoralen in ethanol, on the shaved left side of the back. After 15 min of drying, the site was exposed to nonerythemogenic (i.e., UVA >320 nm) UV light (FL-40) for 60 min at a distance of 10 in.; the shaved right side was irradiated simultaneously without the test materials. After removal of the UV light source, the same materials were applied to the right side of the back. The application sites were scored for erythema and edema at 24, 48, 72, and 96 h after treatment. The face cream product, which was applied undiluted, was a "weak phototoxin" in both assays.

Ammonium Lactate. Two studies were performed using four and three restrained guinea pigs, respectively, with four dipped sites per animal, in which the animals received topical applications of 0.1 mL of 12% Ammonium Lactate lotion, pH 5.0–5.5, and 0.05 mL of Oxsoralen (as a positive control) on two contralateral sites (FDA, 1988). The right side of each animal was shielded with cardboard and the left side was uncovered. The animals were exposed to UVA light (light source details not provided) 15–20 min after dosing; the animals were examined after 24 h. In both studies, Ammonium Lactate lotion did not produce erythema at either the irradiated or nonirradiated sites. The positive control produced severe erythema at the irradiated site, but no reactions were observed at the non-irradiated sites.

TEA-Lactate. Published phototoxicity data for TEA-Lactate were not found. Studies included in the Safety Assessment on TEA (Elder, 1983) reported that a lotion containing 1% TEA was not phototoxic to guinea pigs.

OCULAR IRRITATION

Glycolic Acid

The ocular irritation potential of a number of cosmetic formulations containing Glycolic Acid was determined in primary eye irritation studies, and the formulations were generally found to be non- or mildly irritating. These ocular irritation studies are summarized in Table 20.

The ocular irritation potential of a number of cosmetic formulations containing Glycolic Acid was determined in vitro using the Eytex assay, the basis for which is a specialized protein reagent whose conformation and hydration are altered when exposed to a chemical irritant (Avon Products, Inc., 1995a,h). A direct comparison to the Draize scale was made to determine Ocular Safety Classifications and was expressed as an Eytex/Draize Equivalent (EDE) score. All formulations were tested undiluted unless stated otherwise. The Eytex assay protocols used were MPA (not defined), UMA (upright membrane assay), and RMA (rapid membrane assay). The UMA protocol was used for samples that had a pH of <8.5; samples that did not qualify in the UMA could be retested in the RMA (Avon Products, Inc., 1994). The results of these assays (Avon Products, Inc., 1995a) are summarized in Table 21.

Potassium Glycolate. Potassium Glycolate was mildly irritating to rabbit eyes (RTECS, 1995). See Table 20.

Ethyl Glycolate. Ethyl Glycolate irritated guinea pig eyes (Sanderson, 1959) (see Table 20).

Lactic Acid

The ocular irritation potential of Lactic Acid was determined in many studies in vivo. Results ranged from no significant irritation to severe irritation. These assays and the results are described in Table 22.

The ocular irritation potential of a number of cosmetic formulations containing 85% aq. Lactic Acid was determined *in vitro* using the Eytex assay (Avon Products, Inc., 1995b). In addition to the protocols described earlier in this report, the HSA (high-sensitivity assay) protocol, which can be used to retest samples with an EDE of <15.0, was also run. All formulations were tested undiluted unless otherwise stated. The results of these assays are summarized in Table 23. In a chorioallantoic membrane vascular assay (CAMVA), two eye cream formulations containing 1.18% of 85% aq. Lactic Acid, pHs 5.64 and 4.00, tested undiluted had RC_{50} values >100% (Avon Products, Inc., 1995b). These test samples were considered "nonirritating to the eyes."

Ammonium Lactate. Ammonium Lactate was an irritant to rabbit eyes (FDA, 1988). See Table 22.

Table 20. Ocular irritation potential of Glycolic Acid, Potassium Glycolate, and Ethyl Glycolate *in vivo*

Product type	Conc. (%)	pH	Animals	Protocol	Mean score	Conclusion	Reference
				Glycolic Acid			
Lotion	4	3.8–4.0	3 New Zealand White (NZW) rabbits	0.1 mL of test article was placed on the cornea of the eye and the eyes were held shut for 2 s; the eyes were rinsed after 15 s. The contralateral eye served as a control. The eyes were examined 24, 48, and 72 h after dosing, or up to a max. of 21 days if all scores are not 0. Sodium fluorescein and UV were used.	0.0/110 at 24 h	Nonirritating	TML, 1994a
Lotion	4	3.8–4.0			0.0/110 at 24 h	Nonirritating	TML, 1994b
Cream	4	3.8–4.0			0.7/110 at 24 h	Practically nonirritating	TML, 1994c
Cream	4	3.8–4.0			0.7/110 at 24 h	Practically nonirritating	TML, 1994d
Lotion	8	3.8–4.0			2.0/110 at 24 h	Practically nonirritating	TML, 1994e
Lotion	8	3.8–4.0			2.0/110 at 24 h	Practically nonirritating	TML, 1994f
Cream	8	3.8–4.0			2.0/110 at 24 h	Practically nonirritating	TML, 1994g
Cream	8	3.8–4.0			4.0/110 at 24 h	Minimally irritating	TML, 1994h

Lotion	8	3.8–4.0		Same as above, except that the eyes were not rinsed.	3.3/110 at 24 h	Minimally irritating	TML, 1994i
Lotion	8	3.8–4.0		Same as above, except that an additional examination was made at 168 h.	6.0/110 at 24 h; 72 h scores were not all 0	Mildly irritating	TML, 1994j
Cream	8	3.8–4.0			4.0/110 at 24 h; 72 h scores were not all 0	Mildly irritating	TML, 1994k
Cream	8	3.8–4.0			4.0/110 at 24 h; 72 h scores were not all 0	Mildly irritating	TML, 1994l
Lotion	8 w/1 salicylic acid	3.8–4.0		Same as above, except the eyes were rinsed.	5.3/110 and 24 h; 72 h scores were not all 0	Mildly irritating	TML, 1995
—	Undiluted	—	1 rabbit	0.1 mL was placed in the eye.	—	Corrosive, causing irreversible effects	Haskell Lab., 1990
—	1–18%, 24%	—	Rabbit	0.1 mL was placed in the eye, which may or may not have been rinsed.	—	*1–18%:* mild irritation *24% unrinsed:* severe irritation *24% rinsed:* similar but milder effect	Haskell Lab., 1990
—	40	—	1 rabbit	0.1 mL was placed in the eye and the eye was not rinsed.	—	The eye was normal after 39 days	Haskell Lab., 1990

(*Table continued on next page*)

Table 20. Ocular irritation potential of Glycolic Acid, Potassium Glycolate, and Ethyl Glycolate (*continued*)

Product type	Conc. (%)	pH	Animals	Protocol	Mean score	Conclusion	Reference
—	—	—	Rabbits	Applied to the center of the cornea for 1 min and the eye was not rinsed.	—	Grade 7 injury (0.005 mL and 40% soln yield score of >5.0 and a 15% soln yields a score of ≤5.0)	Carpenter and Smyth, 1946
Mixed fruit acid	38–39% sugar cane extract	—	—	Applied neat and at 10% in a primary eye irritation study.	—	*Neat:* mildly irritating *10%:* nonirritating	Dermatech of Conn., Inc., 1993
				Potassium Glycolate			
—	100 mg	—	Rabbit	Not available	—	Mild irritant	RTECS, 1995
				Ethyl Glycolate			
—	10 μl	—	Guinea pig	Ethyl Glycolate was applied to the corneal surface of one eye; the contralateral eye served as a control.	—	Irritation produced (degree not specified)	Sanderson, 1959

Table 21. Ocular irritation potential of Glycolic Acid using the Eytex assay

Product type	Conc. (%)	pH	Protocol	Eytex class	EDE	Conclusion
			70% Aq.			
Body lotion	2.86	3.80	UMA	Mild moderate	26.5	Mild–moderate irritant
Face cream	5.71	5.35	RMA	Minimal	10.6	Minima irritant
Lipline gel	7.04	3.90	UMA	Mild moderate	31.0	Mild–moderate irritant
Hand and body lotion	8.57	3.89	UMA	Mild moderate	31.5	Mild–moderate irritant
Body lotion	11.42	3.50	MPA	Moderate	24.0	Moderate-severe irritant
Body lotion			RMA	Severe	50.2	Moderate-severe irritant
Body lotion	11.42	3.50	MPA	Moderate	49.5	Moderate-severe irritant
Body lotion			RMA	Severe	54.1	Moderate-severe irritant
Body lotion	11.42	3.50	MPA	Moderate	51.9	Moderate-severe irritant
Body lotion			RMA	Severe	Not	Moderate-severe irritant
Face cream	11.42	3.75	RMA	Moderate severe	43.3	Moderate-severe irritant
Body lotion	11.42	3.78	MPA	Moderate	54.0	Moderate-severe irritant
Body lotion			RMA	Severe	47.3	Moderate-severe irritant
Face cream	11.42	5.50	RMA	Minimal mild	13.1	Minimal-mild irritant
Lipline gel	14.08	3.89	UMA	Moderate severe	46.0	Moderate-severe irritant
Body lotion	14.29	N/A (@50% EtOH)	UMA	Moderate severe	49.6	Moderate-severe irritant
Body lotion	14.29	3.60	MPA	Moderate	51.2	Moderate-severe irritant
Body lotion			RMA	Severe	54.0	Moderate-severe irritant
Body lotion	14.29	3.65	MPA	Moderate	51.6	Moderate-severe irritant
Body lotion			RMA	Severe	54.0	Moderate-severe irritant

(*Table continued on next page*)

Table 21. Ocular irritation potential of Glycolic Acid using the Eytex assay (*continued*)

Product type	Conc. (%)	pH	Protocol	Eytex class.	EDE	Conclusion
Body lotion	14.29	3.65	MPA	Moderate	54.0	Moderate-severe irritant
Body lotion			RMA	Severe	Not	Moderate-severe irritant
Lipline gel	14.29	3.77	MPA	Severe	51.0	Severe irritant
Lipline gel			RMA	Severe	Not	Severe irritant
Hand and body lotion	14.29	3.82	UMA	Moderate severe	51.0	Moderate-severe irritant
Lipline gel	14.29	4.01	MPA	Moderate	37.4	Moderate irritant
Lipline gel			RMA	Moderate	Not	Moderate irritant
			99% Pure			
Face lotion	8.08	3.70–3.90	UMA	Moderate severe	48.5	Moderate–severe irritant
			Glycolic Acid/copolymer powder 50% tested at 10%			
—	—	—	UMA	Moderate severe	46.9	Moderate-severe irritant
			Glycolic Acid powder-99% tested at 0.10%			
—	—	—	UMA	Mild moderate	26.5	Mild-moderate irritant

Potassium Lactate. Potassium Lactate was slightly irritating to rabbit eyes (Guillot et al., 1982b) (Table 22).

Sodium Lactate. See Table 22 for in vivo ocular irritation studies. No pattern of effect as a function of pH or concentration was discernable.

Corneas from male and female New Zealand white rabbits were used to examine the corneal toxicity of 5 and 20 M Sodium Lactate (Huff, 1990). Sodium Lactate was similar to equimolar excesses of sodium chloride. Lactate had no acute toxic effect on the epithelium, endothelium, or stroma to influence corneal thickness. However, corneas loaded with Sodium Lactate swell osmotically. See Table 23 for in vitro (Eytex assay) results, which reported minimal irritation.

TEA-Lactate. Published ocular irritation data for TEA-Lactate were not found. Studies included in the Safety Assessment on TEA (Elder, 1983) reported that, with long contact time, 100% TEA was an ocular irritant to rabbits.

Methyl Lactate. Methyl Lactate was not irritating to guinea pig eyes (Sanderson, 1959) (Table 22).

Table 22. Ocular irritation potential of Lactic Acid and Ammonium, Potassium, Sodium, TEA-, Methyl, Ethyl, Lauryl, Myristyl, and Cetyl Lactate

Product type	Conc.	pH	Animals	Protocol	Results	Conclusion	Reference
				Lactic Acid			
Skin cream	0.6% of 85% Lactic Acid	7.5	3 albino rabbits	Standard operating procedures: 0.1 mL of test article was placed on the cornea of the eye (Avon Products, Inc., 1988); the eyes were not rinsed.	*Positives*: 4/day 1–2; 0/day 3–4, and 7 *Opacities*: 2/day 1–2; 0/day 3–4, and 7	Minimal irritation	Avon Products Inc., 1995b
—	—	—	Rabbits	Applied to the center of the cornea for 1 min and the eye was not rinsed.		Grade 8 injury (0.005 mL and 15% soln yield score of >5.0 and a 5% soln yields a score of ≤5.0)	Carpenter and Smyth, 1946
—	10% 20%	—	Rabbits	*Journal Officiel de la République Française* procedure. Eyes were examined after 1 and 24 h and after 2, 3, 4, and 7 days w/fluorescein staining.	*10%*: acute ocular irritation index (AOII)-31.17; lesions were reversible after 7 days *20%*: AOII-39.50	Produced significant ocular irritation	Guillot et al., 1982a
Stone remover—6.0% Lactic Acid dark (44%)	Diluted to 0.4%	—	6 NZW rabbits	Followed Code of Federal Regulations (Part 191.12, Ch. 1, Title 21) procedures. 10 mg was placed in one eye and the eye was held shut for 1 s; the contralateral eye served as a control.	*Undiluted*: total destruction of the entire eye structure and surrounding membrane was evident. *Diluted*: no irritation		Stauffer chemical Co., 1971
				Ammonium Lactate			
Lotion	12%	—	9 rabbits	0.1 mL was applied to the left eye, with the eyes of 3 rabbits being rinsed after 2 s; 0.1 mL distilled water was placed in the right eye as a control. The eyes were examined 24 h–7 days after dosing.	Caused transient conjunctival irritation	Irritant	FDA, 1988

(*Table continued on next page*)

Table 22. Ocular irritation potential of Lactic Acid and Ammonium, Potassium, Sodium, TEA-, Methyl, Ethyl, Lauryl, Myristyl, and Cetyl Lactate (*continued*)

Product type	Conc.	pH	Animals	Protocol	Results	Conclusion	Reference
				Potassium Lactate			
—	60% aq.	8.1	6 male NZW rabbits	0.1 mL was instilled into the conjunctival sac of one eye and the eye was not rinsed; the other eye served as a control. Observations were made after 1 h and 1, 2, 3, 4, and 7 days, with reactions scored according to the Association Française de Normalisation (1982) and lesions scored according to Kay and Calandra (1962).	*AOII*: 15.00/110 *Mean ocular irritation index*: 0 after 4 days Slight corneal opacity was seen after 1 h	Slightly irritating	Guillot et al., 1982b
				Sodium Lactate			
—	50% 70%	—	Rabbits	*Journal Officiel de la République Française* procedure. Eyes were examined after 1 and 24 h and after 2, 3, 4, and 7 days w/fluorescein staining	*50%*: AOI-11.67/110 *70%*: AOI-13.00/110	No significant irritation	Guillot et al., 1982a
				60% Aq. Sodium Lactate			
Facial freshener	0.1%	N/A	Rabbits	Protocol described in Avon Products, Inc., 1988. One instillation of undiluted material was made, and the eyes were not rinsed.	*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products, Inc., 1995c
Face cream	0.1%	N/A			*Positives*: 0/day 2 *Opacities*: 0/day 2	Minimal irritation	Avon Products, Inc., 1995c
Night cream	0.2%	N/A			*Positives*: 0/day 2 *Opacities*: 0/day 2	Minimal irritation	Avon Products, Inc., 1995c
Hair conditioner	0.2%	3.4			*Positives*: 3/day 1; 1/day 2–4; 0/day 7 *Opacities*: 0/days 1–4, 7	Mild irritation	Avon Products, Inc., 1995c
Hair conditioner	0.2%	3.45 5			*Positives*: 1/day 1–2; 0/day 3 *Opacities*: 0/day 1–3	Minimal irritation	Avon Products, Inc., 1995c

Hair conditioner	0.2%	4.9			*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products, Inc., 1995c
Hair conditioner	0.2%	5.0			*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products, Inc., 1995c
Shampoo	0.2%	5.5	Rabbits	Protocol described in Avon Products, Inc. (1988) dosed as 25% in water.	*Positives*: 1/day 1; 0/day 2 *Opacities*: 0/day 1–2	Minimal irritation	Avon Products, Inc., 1995c
Shampoo	0.2%	5.5			*Positives*: 1/day 1; 0/day 2 *Opacities*: 1/day 1 0/day 2	Minimal irritation	Avon Products, Inc., 1995c
Night cream	0.2%	5.78		Protocol described in Avon Products, Inc. (1988). One instillation of undiluted material was made, and the eyes were not rinsed.	*Positives*: 2/day 1; 0/day 2–4; 1/day 7 *Opacities*: 0/day 1–4, 7	Mild irritation	Avon Products, Inc., 1995c
Face lotion	0.2%	6.55			*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products, Inc., 1995c
Face lotion	0.2%	7.0			*Positives*: 1/day 1, 3, 7; 0/day 2, 4 *Opacities*: 0/day 1–4, 7	Mild irritation	Avon Products, Inc., 1995c
Face cream	0.2%	7.9			*Positives*: 3/day 1; 0/day 2 *Opacities*: 0/day 1, 2	Minimal irritation	Avon Products, Inc., 1995c
Night cream	0.2%	8.6			*Positives*: 1/day 1 0/day 2, 3 *Opacities*: 0/day 1–3	Minimal irritation	Avon Products, Inc., 1995c
Shampoo	0.25%	5.6		Protocol described in Avon Products, Inc. (1988) dosed as 25% in water.	*Positives*: 6/day 1, 3/day 2; 1/day 3; 0/day 4 *Opacities*: 4/day 1; 2/day 2; 0/day 3, 4	Mild irritation	Avon Products, Inc., 1995c
Night cream	0.4%	5.25		Protocol described in Avon Products, Inc. (1988). One instillation of undiluted material was made, and the eyes were not rinsed.	*Positives*: 0/day 1–4, 7 *Opacities*: 0/day 1–4, 7	No irritation	Avon Products, Inc., 1995c

(Table continued on next page)

Table 22. Ocular irritation potential of Lactic Acid and Ammonium, Potassium, Sodium, TEA-, Methyl, Ethyl, Lauryl, Myristyl, and Cetyl Lactate (*continued*)

Product type	Conc.	pH	Animals	Protocol	Results	Conclusion	Reference
—	100%	N/A	3 albino rabbits		*Positives*: 0/day 3 *Opacities*: 0/day 3	Minimal irritation	Avon Products, Inc., 1995c
—	—	8.0	6 male NZW rabbits	0.1 mL was instilled into the conjunctival sac of one eye and the eye was not rinsed; the other eye served as a control. Observations were made after 1 h and 1, 2, 3, 4, and 7 days, with reactions scored according to the Association Française de Normalisation (1982) and lesions scored according to Kay and Calandra (1962).	*AOI*: 12.00/110 *MOI*: 2.50 after 2 days No corneal opacity	Slight irritant	Guillot et al., 1982b
				Methyl Lactate			
—	—	—	Guinea pig	10 μL was applied to the corneal surface of one eye and the other eye served as a control		No irritation	Sanderson, 1959
				Ethyl Lactate			
Nail enamel corrector pen	50%	N/A	3 albino rabbits	Standard operating procedures as described earlier (Avon Products, Inc., 1988). One instillation of undiluted material was made, and the eyes were not rinsed.	*Positives*: 6/day 1–2; 1/day 3–4; 2/day 7 *Opacities*: 6/day 1; 5/day 2	Moderate irritation	Avon Products Inc., 1995d
Nail enamel corrector pen	50%	N/A			*Positives*: 6/day 1–2; 4/day 3; 2/day 4; 0/day 7 *Opacities*: 6/day 1–3; 1/day 4; 0/day 7	Moderate irritation	Avon Products Inc., 1995d
—	—	—	5 rabbits	0.5 mL was instilled into the eye for 1 min; the other eye served as a control.	Edema hyperemia, and permanent damage	Severely irritating	Latven and Molitor, 1939
				Lauryl Lactate			
Face cream	5%	4.65	5 rabbits	0.5 mL was instilled into the eye for 1 min; the other eye served as a control.	*Positives*: 5/day 1; 2/day 2; 0/day 4–7 *Opacities*: 1/day 1; 0/day 2–4, 7	Minimal irritation	Latven and Molitor, 1939

Face cream	5%	4.65		Standard operating procedures as described earlier (Avon Products, Inc., 1988). 0.05 mL was instilled; it was not stated whether the eyes were rinsed.	*Positives*: 4/day 1; 1/day 2–3; 0/day 7 *Opacities*: 0/day 1–3, 7	Mild irritation	Latven and Molitor, 1939
Face cream	5%	4.65		Standard operating procedures as described earlier (Avon Products, Inc., 1988). 0.1 mL was instilled; it was not stated whether the eyes were rinsed.	*Positives*: 5/day 1; 3/day 2; 1/day 3; 0/day 7 *Opacities*: 0/day 1–3, 7	Mild irritation	Latven and Molitor, 1939
	15.0% in propylene glycol	N/A	3 albino rabbits	Standard operating procedures as described earlier (Avon Products, Inc., 1988). One instillation was made, and the eyes were not rinsed.	*Positives*: 2/day 1; 0/Day 2–4, 7 *Opacities*: 0/day 1–4, 7	Minimal irritation	Avon Products Inc., 1995e
				Myristyl Lactate			
Foundation	7.65%	N/A	3 albino rabbits	Standard operating procedures as described earlier (Avon Products, Inc., 1988). One instillation was made, and the eyes were not rinsed.	*Positives*: 1/day 1–2; 0/day 3–7 *Opacities*: 0/day 1–4, 7	Mild irritation	Avon Products Inc., 1995f
Lip pencil	11.54%	N/A			*Positives*: 0/day 1–4, 7 *Opacities*: 0/day 1–4, 7	No irritation	Avon Products Inc., 1995f
				Cetyl Lactate			
Body cream	0.5%	N/A	3 albino rabbits	Standard operating procedures as described earlier (Avon Products, Inc., 1988). One instillation was made, and the eyes were not rinsed.	*Positives*: 0/day 1–2; 1/day 3; 0 day 4, 7 *Opacities*: 0/day 1–4, 7	Mild irritation	Avon Products Inc., 1995g
Face lotion	0.75%	N/A			*Positives*: 0/day 1; 1/day 2–4, 7 *Opacities*: 0/day 1–4; 1/day 7	Mild irritation	Avon Products Inc., 1995g
Aftershave moisturizer	0.75%	7.0–8.0			*Positives*: 0/day 1–4, 7 *Opacities*: 0/day 1–4, 7	No irritation	Avon Products Inc., 1995g

(*Table continued on next page*)

Table 22. Ocular irritation potential of Lactic Acid and Ammonium, Potassium, Sodium, TEA-, Methyl, Ethyl, Lauryl, Myristyl, and Cetyl Lactate (*continued*)

Product type	Conc.	pH	Animals	Protocol	Results	Conclusion	Reference
Face lotion	0.75%	7.7	3 albino rabbits	Standard operating procedures as described earlier (Avon Products, Inc., 1988). One instillation was made, and the eyes were not rinsed.	*Positives*: 4/day 1; 2/day 2; 0/day 3 *Opacities*: 0/day 1–3	Minimal irritation	Avon Products Inc., 1995g
Face lotion	0.75%	7.85			*Positives*: 2/day 1–2; 1/day 3; 0/day 4, 7 *Opacities*: 0/day 1–4, 7	Mild irritation	Avon Products Inc., 1995g
Face lotion	0.75%	7.9			*Positives*: 0/day 1–4, 7 *Opacities*: 0/day 1–4,7	No irritation	Avon Products Inc., 1995g
Moisturizing cream	1%	N/A			*Positives*: 2/day 1–2; 1/day 3–4; 0/day 7 *Opacities*: 0/day 1–4, 7	Mild irritation	Avon Products Inc., 1995g
Body lotion	1%	N/A			*Positives*: 6/day 1–4; 4/day 4 *Opacities*: 6/day 1–4; 5/day 7	Severe irritation	Avon Products Inc., 1995g
Night cream	1%	6.2			*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products Inc., 1995g
Moisture cream	1%	6.5			*Positives*: 2/day 1, 2, 7; 1/day 3; 0/day 4 *Opacities*: 0/day 1–4, 7	Mild irritation	Avon Products Inc., 1995g
Moisture lotion	1%	7.0			*Positives*: 1/day 1, 3, 7; 0/day 2, 4 *Opacities*: 0/day 1–4, 7	Mild irritation	Avon Products Inc., 1995g
Cleansing cream	1%	7.15			*Positives*: 3/day 1; 1/day 2; 0/day 3–4, 7 *Opacities*: 0/day 1–4, 7	Mild irritation	Avon Products Inc., 1995g
Cleansing cream	1%	7.2–8.0			*Positives*: 1/day 1; 0/day 2; *Opacities*: 0/day 1–2	Minimal irritation	Avon Products Inc., 1995g

Moisturizing cream	1%	7.2–8.0			*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products Inc., 1995g
Moisturizing cream	1%	7.8			*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products Inc., 1995g
Body lotion	1.1%	7.0			*Positives*: 2/day 1, 3 ; 3/day 2; 1/day 4, 7 *Opacities*: 0/day 1–4, 7	Mild irritation	Avon Products Inc., 1995g
Moisturizing cream	1.5%	6.1			*Positives*: 0/day 1–4, 7 *Opacities*: 0/day 1–4, 7		Avon Products Inc., 1995g
Lip pencil	3%	N/A			*Positives*: 0/day 1–4, 7 *Opacities*: 0/day 1–4, 7	No irritation	Avon Products Inc., 1995g
Lipstick	3%	N/A			*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products Inc., 1995g
Lipstick	3%	N/A			*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products Inc., 1995g
Lipstick	3%	N/A			*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products Inc., 1995g
Lipstick	3%	N/A			*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products Inc., 1995g
Lipstick	3%	N/A	3 albino rabbits	Standard operating procedures as described earlier (Avon Products, Inc., 1988). One instillation was made, and the eyes were not rinsed.	*Positives*: 1/day 1; 0/day 2 *Opacities*: 0/day 1–2	No irritation	Avon Products Inc., 1995g
Lipstick	3%	N/A			*Positives*: 1/day 1; 0/day 2 *Opacities* 0/day 1–2	No irritation	Avon Products Inc., 1995g
Lipstick	3%	N/A			*Positives*: -/day 1; 0/day 2 *Opacities* -/day 1; 0/day 2	Minimal irritation	Avon Products Inc., 1995g

(*Table continued on next page*)

Table 22. Ocular irritation potential of Lactic Acid and Ammonium, Potassium, Sodium, TEA-, Methyl, Ethyl, Lauryl, Myristyl, and Cetyl Lactate (*continued*)

Product type	Conc.	pH	Animals	Protocol	Results	Conclusion	Reference
Lipstick	3%	N/A			*Positives*: 2/day 1; 5/day 2; 0/day 3–4, 7 *Opacities* 0/day 1–4, 7	Minimal irritation	Avon Products Inc., 1995g
Foundation	3%	7.05			*Positives*: 0/day 1–4, 7 *Opacities*: 0/day 1–4, 7	No irritation	Avon Products Inc., 1995g
Lipstick	4.5%	N/A			*Positives*: 0/day 1–4, 7 *Opacities*: 0/day 1–4, 7	No irritation	Avon Products Inc., 1995g
Lipstick	5%	N/A			*Positives*: 1/day 1; 0/day 2–4, 7 *Opacities*: 0/day 1–4, 7	Minimal irritation	Avon Products Inc., 1995g
Foundation	5%	6.0			*Positives*: 1/day 1; 0/day 2–4, 7 *Opacities*: 0/day 1–4, 7	Minimal irritation	Avon Products Inc., 1995g
Foundation	5%	6.0			*Positives*: 2/day 1; 1/day 2; 0/day 3–4 *Opacities*: 0/day 1–4	Minimal irritation	Avon Products Inc., 1995g

Lipstick	7.5%	N/A	*Positives*: 3/day 1; 0/day 2 *Opacities*: 0/day 1–2	Minimal irritation	Avon Products Inc., 1995g
Lipstick	9%	N/A	*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products Inc., 1995g
Lipstick	9%	N/A	*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products Inc., 1995g
Lipstick	9%	N/A	*Positives*: 0/day 1 *Opacities*: 0/day 1	No irritation	Avon Products Inc., 1995g
Lipstick	9%	N/A	*Positives*: -/day 1; 0/day 2 *Opacities*: -/day 1; 0/day 2	Minimal irritation	Avon Products Inc., 1995g
Lipstick	9%	N/A	*Positives*: -/day 1; 0/day 2 *Opacities*: -/day 1; 0/day 2;	Minimal irritation	Avon Products Inc., 1995g
Lipstick	9%	N/A	*Positives*: 5/day 1; 1/day 2; 0/day 3–4, 7 *Opacities*: 0/day 1–4, 7	Minimal irritation	Avon Products Inc., 1995g

Table 23. Ocular irritation potential of Lactic Acid and Sodium, Lauryl, Myristyl, and Cetyl Lactate using the Eytex assay

Product type	Conc. (%)	pH	Protocol	Eytex class	EDE	Conclusion	Reference
				85% Aq. Lactic Acid			
Eye cream	0.12	6.33	UMA	Minimal	5.5	Minimal irritant	Avon Products Inc., 1995b
Nail strengthener	0.4	7.36	UMA	Minimal	6.2	Minimal irritant	Avon Products Inc., 1995b
Nail strengthener	0.4	7.52	UMA	Minimal	5.6	Minimal irritant	Avon Products Inc., 1995b
Eye cream	1.18	4.84	UMA	Minimal	5.9	Minimal irritant	Avon Products Inc., 1995b
Eye cream	1.18	5.45	UMA	Minimal	6.1	Minimal irritant	Avon Products Inc., 1995b
Eye cream	1.77	5.79	RMA	Minimal mild	13.1	Minimal–mild irritant	Avon Products Inc., 1995b
Eye cream	2.35	5.66	RMA	Minimal	12.6	Minimal irritant	Avon Products Inc., 1995b
Eye cream	3.53	5.3	UMA	Minimal	7.4	Minimal irritant	Avon Products Inc., 1995b
Face cream	5.88	3.0–3.2	UMA	Mild moderate	31.5	Mild–moderate irritant	Avon Products Inc., 1995b
Face lotion	7.06	3.75	UMA	Mild moderate	31.6	Mild–moderate irritant	Avon Products Inc., 1995b
Face cream	7.06	4.26	UMA	Mild moderate	31.2	Mild–moderate irritant	Avon Products Inc., 1995b
Face cream	8	3.9	UMA	Moderate	32.2	Moderate irritant	Avon Products Inc., 1995b

Face cream	9.41	3.87	UMA	Moderate	37.6	Moderate irritant	Avon Products Inc., 1995b
Cuticle cream	11.77	3.79	RMA	Moderate	37.1	Moderate irritant	Avon Products Inc., 1995b
Face cream	11.8	2.02	UMA	Moderate severe	50.9	Moderate-severe irritant	Avon Products Inc., 1995b
				85% Aq. Lactic Acid tested at 25%			
Shampoo	0.7	5.3–5.7	HSA	Non-irritating	0.1	Nonirritating	Avon Products Inc., 1995b
Shampoo	0.7	5.3–5.7	UMA	Minimal	12.6	Minimal irritant	Avon Products Inc., 1995b
Shampoo	0.8	5.6–6.2	UMA	Minimal mild	13.3	Minimal–mild irritant	Avon Products Inc., 1995b
				60% Aq. Sodium Lactate			
Foundation	0.15	N/A	UMA	Minimal	4.4	Minimal irritant	Avon Products Inc., 1995c
Hair conditioner	0.20	3.2–3.8	UMA	Minimal	9.1	Minimal irritant	Avon Products Inc., 1995c
Hair conditioner	0.20	3.45	MPA	Minimal-MPA Minimal-RMA	8.7 5.0	Minimal irritant	Avon Products Inc., 1995c
				Lauryl Lactate			
Eye cream	0.1	5.3	UMA	Minimal	5.3	Minimal irritant	Avon Products Inc., 1995e
Eye cream	0.1	5.45	UMA	Minimal	6.1	Minimal irritant	Avon Products Inc., 1995e

(Table continued on next page)

Table 23. Ocular irritation Potential of Lactic Acid and Sodium, Lauryl, Myristyl, and Cetyl Lactate using the Eytex assay (*continued*)

Product type	Conc. (%)	pH	Protocol	Eytex class	EDE	Conclusion	Reference
Eye cream	0.1	6.33	UMA	Minimal	5.5	Minimal irritant	Avon Products Inc., 1995e
Face cream	3.2	3.87	UMA	Moderate	37.6	Moderate irritant	Avon Products Inc., 1995e
				Myristyl Lactate			
Eye shadow	5	N/A	UMA	Minimal	8.6	Minimal irritant	Avon Products Inc., 1995f
Eye shadow	5	N/A	MPA	Minimal-MPA Minimal-RMA	12.8 Not	Minimal irritant	Avon Products Inc., 1995f
				Cetyl Lactate			
Face lotion	0.75	7.85	MPA	Minimal-MPA Mild-RMA	6.2 13.9	Minimal–mild irritant	Avon Products Inc., 1995g
Cleansing cream	1	7.2–8.0	MPA	Minimal-MPA Mild-RMA	5.9 22.4	Minimal–mild irritant	Avon Products Inc., 1995g
Eye cream	2	5.3	UMA	Minimal	7.4	Minimal irritant	Avon Products Inc., 1995g
Body cream	2	5.4	UMA	Minimal	11.4	Minimal irritant	Avon Products Inc., 1995g
Eye cream	2	5.45	UMA	Minimal	6.1	Minimal irritant	Avon Products Inc., 1995g
Eye cream	2	6.33	UMA	Minimal	5.5	Minimal irritant	Avon Products Inc., 1995g

Ethyl Lactate. See Table 22 for *in vivo* ocular irritation studies reporting moderate to severe irritation.

Lauryl Lactate. See Table 22 for *in vivo* ocular irritation studies reporting minimal to mild irritation and see Table 23 for *in vitro* (Eytex assay) results reporting minimal to moderate irritation.

Myristyl Lactate. See Table 22 for *in vivo* ocular irritation studies reporting no to mild irritation and Table 23 for *in vitro* (Eyetex assay) results reporting minimal to mild irritation. Studies included in the original safety assessment of Myristyl Lactate (Elder, 1982) reported that it was not an ocular irritant.

Cetyl Lactate. See Table 22 for *in vivo* ocular irritation studies reporting no to severe irritation and Table 23 for *in vitro* (Eyetex assay) results reporting minimal to mild irritation. Studies included in the original safety assessment of Cetyl Lactate (Elder, 1982) reported that it was not an ocular irritant.

Glycolic Acid

A developmental toxicity study was conducted using Glypure 99% high-purity Glycolic Acid crystalline in which groups of 25 rats were dosed with 75–600 mg/kg of the test material in deionized water by gavage on days 7–21 of gestation (Haskell Laboratory, 1996). A control group was dosed with vehicle only. Surviving dams were killed on day 22, and their fetuses were examined. Developmental toxicity was observed at doses of 300 and 600 mg/kg of 99% Glycolic Acid. In fetuses of the 300-mg/kg-dose group, a slight, but non-statistically significant, increase was observed in the incidence of fused ribs and fused vertebrae. In fetuses of the 600-mg/kg-dose group, the incidence of fused ribs and fused vertebrae, as well as of absent ribs, abnormally fused and cleft sternebrae, hemi-vertebrae, misaligned and incompletely ossified sternebrae, and incompletely ossified vertebrae was significantly increased. Mean fetal weight was significantly reduced at this dose. Maternal toxicity was also observed at doses of 300 and 600 mg/kg of 99% Glycolic Acid. In dams of the 300-mg/kg group, lung noise was slightly increased. In dams of the 600-mg/kg group, lung noise was markedly increased, and abnormal gait, lethargy, and irregular respiration were observed and mean maternal body weight, weight change, and feed consumption were significantly reduced. No evidence of developmental or maternal toxicity was observed in animals of the 75- and 150-mg/kg-dose groups; therefore, the no-observed-effect-level was 150 mg/kg. It was the opinion of the researchers that collateral stress on the dam resulted in fetal damage and that Glycolic Acid itself was not a developmental toxin.

A pilot developmental toxicity study was conducted using 70% Glycolic Acid technical solution (a grade that DuPont Specialty Chemicals (1995, 1996) states that they prohibit for use in personal care applications) in which groups of eight Crl:CD®BR gravid rats were dosed by gavage with 125, 250, 500, or 1000 mg/kg of the test material in distilled water at a volume of 10 mL/kg on days 7–21 of gestation (Haskell Laboratory, 1995). A control group was dosed with vehicle only. Clinical signs were recorded once or twice daily, and observations for morbidity and mortality were also made daily. The dams were weighed on days 1 and 7–22 of gestation. Surviving dams were killed on day 22 of gestation, and the fetuses were examined. Maternal toxicity was observed at doses of 500

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and 1000 mg/kg. Females of the 500-mg/kg-dose group had significant increases in the clinical observations of "wet chin" and "lung noise." For this dose group, body weight changes were significantly reduced between days 21 and 22, but no other significant effects on body weight were observed; feed consumption was not affected at this dose. Abnormal gait and mobility, lung noise, salivation, and stained and wet haircoats were observed for dams of the 1000-mg/kg-dose group. Body weight gains were significantly decreased at several intervals; maternal body weights for animals of this dose group were statistically significantly reduced (88% of control) on day 22. Feed consumption was also significantly reduced. One moribund female of the 1000-mg/kg-dose group was killed. Ulcerations of the gastric mucosa, distended intestines, and mottled kidneys were observed at necropsy.

No evidence of toxicity was observed for females of the 125- or 250-mg/kg-dose groups. Fetuses of the 500-mg/kg-dose group had statistically significantly decreased mean fetal weight, and the incidence of retarded sternebral ossification was statistically significantly increased. Fetuses of the 1000-mg/kg-dose group had statistically significantly decreased mean fetal body weight, and the incidence of early resorptions, specific malformations (gastroschisis, hydrocephaly, fused ribs, fused vertebra(e), and hemivertebra(e)), and specific variations (misaligned sternebra(e) and retarded vertebral and sternebral ossification) were statistically significantly increased. No evidence of toxicity was noted for fetuses of the 125- or 250-mg/kg-dose groups. No dose-related effects were observed on reproductive parameters. The maternal and developmental no-observed-adverse-effect level was 250 mg/kg day^{-1}.

An *in vitro* embryo culture study was performed in which rat embryos were removed from the uterus and allowed to develop in culture medium. On day 10.5 of gestation, groups of 10 embryos were cultured for 46 h in medium containing 0.5, 2.5, 12.5, 25.0, or 50.0 mM Glycolic Acid. A control group was also cultured (Carney et al., 1996). No effects on embryo development were observed with 0.5 or 2.5 mM Glycolic Acid. At a concentration of 12.5 mM, crown–rump length, head length, embryo and visceral yolk sac protein content, somite number, and morphology score were significantly decreased. Structural abnormalities, mainly in the craniofacial region, were observed. Doses greater than 12.5 mM caused embryolethality. Sodium Glycolate, 12.5 mM at pH 7.42, caused effects similar to those seen with 12.5 mM Glycolic Acid, pH 6.74, but were of a lesser degree.

Sodium Glycolate. In a 1943 General Foods Corporation embryotoxicity study, male and female rats (number not specified) were fed 2.5% Sodium Glycolate (duration of dosing not specified) and mated (Haskell Laboratory, 1990). The average age of test group dams at birth of the

first young was 50% greater than that of the control dams. The number of young born was 65% less in the test group than in the control group, and the number of test group pups weaned was 4.4% as compared to 19.3% in the control group.

Lactic Acid

Twelve gravid Swiss albino CD-1 mice were dosed daily with 570 mg/kg Lactic Acid by gavage on days 6–15 of gestation; a control group of 13 mice received distilled water (Colomina et al., 1992). All dams were killed on day 18 of gestation. No significant difference was observed in gestational body weight gain between test and control animals, but feed consumption was significantly decreased during days 6–9, 6–12, and 15–18 of gestation as compared to control values. Also, relative maternal liver weight was significantly decreased as compared to controls. The only observed effect on the fetus was a statistically significant increase in delayed ossification of the parietal bones.

Rats were fed stock diet supplemented with 2.5 or 5% Lactic Acid or untreated stock diet to determine the effect of Lactic Acid on the sex ratio in rats (D'Amour, 1934). The sex ratio of rats was not affected by oral administration of Lactic Acid.

Sodium Lactate. Sodium Lactate, 5 mM, was added to $B_6C_3F_1$ mice pre-embryo cultures to examine its effect on the development of these cells over a 72-h period; a control group was cultured in medium alone (Moley et al., 1994). No significant difference was observed in the overall rate of development between embryos cultured in the presence of Sodium Lactate as compared to those cultured in medium alone. No difference was found in the distribution of pre-embryo growth stages.

TEA-Lactate. Published teratogenicity data for TEA-Lactate were not found. A study included in the Safety Assessment on TEA (Elder, 1983) reported that topical application of TEA to pregnant rats did not produce teratogenic effects.

MUTAGENICITY

Glycolic Acid

An Ames test was performed to determine the mutagenic potential of Glycolic Acid, 20% active ingredient, using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 with and without metabolic activation (Microbiological Associates, Inc., 1994a). A dose-range-finding study was first performed using TA100 with and without metabolic activation; the doses were not adjusted for the amount of active ingredient. No precipitate or appreciable toxicity was observed with a concentration range of 6.5–5000 μg Glycolic Acid per plate (1.3–1000 μg active ingredient). The dose concentrations were adjusted for the amount of active ingredient in the Ames assay; doses of 10–5000 μg active ingredient were plated in triplicate. The pH of the test article was 4.0. Positive controls were sodium azide, 2-nitrofluorene, and 9-aminoacridine in the absence of and 2-aminoanthracene in the presence of S9 activation; the vehicle, distilled water, served as a negative control. No positive responses were observed with or without metabolic activation in any of the tester strains, and no precipitate or appreciable toxicity was observed. Glycolic Acid was not mutagenic in this Ames test.

In a modified Ames test using *S. typhimurium* strain TA100, 500 μg/plate Glycolic Acid (of "guaranteed grade") resulted in 53 revertants; with metabolic activation and catalase, the number or revertants was 50 and 52, respectively (Yamaguchi and Nakagawa, 1983). When reactivity in autoxidation was investigated, Glycolic Acid had no activity on nitro blue tetrazolium chloride. Glycolic Acid was not mutagenic to *S. typhimurium* strains TA1535, TA1537, TA98, or TA100 with or without metabolic activation (Haskell Laboratory, 1990).

A chromosome aberration assay using Chinese hamster ovary ($CHO\text{-}K_1$) cells was performed to evaluate the clastogenic potential of Glycolic Acid, 20% active ingredient, with and without metabolic activation (Microbiological Associates, Inc., 1994b). Based on the results of a preliminary toxicity test using a dose range of 0.5–5000 μg/mL active ingredient, the concentration range used for the assay was 625–5000 μg/mL active ingredient. Test article pH was adjusted from approximately 4 to approximately 6.5 with 1 N sodium hydroxide. Positive controls were mitomycin C in the absence of and cyclophosphamide in the presence of S9; solvent vehicle, phosphate buffered saline, treated

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cultures, and untreated cultures served as negative control groups. At the highest dose concentration, 5000 μg/mL, toxicity (mitotic inhibition) was approximately <10% and 43% with and without metabolic activation, respectively. The percentage of cells with structural aberrations in the test groups, both with and without metabolic activation, were not statistically increased as compared to the solvent control. Glycolic Acid was not clastogenic in this chromosome aberration assay.

Lactic Acid

The mutagenicity studies on Lactic Acid and its salts discussed in this section are summarized in Table 24. In a modified Ames test using *S. typhimurium* strain TA100, Lactic Acid (of "guaranteed grade"; doses not specified) was not a mutagen (Yamaguchi and Nakagawa, 1983).

Lactic Acid induced chromosomal damage at a dose of 2 mg/mL in cultured mammalian cells without metabolic activation (ESLUR, 1994a). However, negative results were obtained when the mutagenic potential of Lactic Acid, 90.5% pure, in phosphate buffer was assayed in an Ames test using *S. typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98 with metabolic activation (Ishidate et al., 1984). Duplicate plates of six concentrations ≤ 10.0 mg/plate were examined. The positive results obtained in the first study could be attributable to pH alone rather than genotoxic potential of Lactic Acid (ESLUR, 1994a) since rendering the test medium slightly acidic can cause chromosomal damage.

Negative results were also obtained in an Ames test for 1000 μg/mL 11 mM Lactic Acid using a clonal subline of Chinese hamster fibroblasts derived from lung tissue in the absence of metabolic activation (Ishidate et al., 1984).

An Ames test was performed to determine the mutagenic potential of Lactic Acid using *S. typhimurium* strains TA97, TA98, TA100, and TA104 (Al-Ani and Al-Lami, 1988). Triplicate plates of 0.5, 1.0, and 2.0 μL/plate Lactic Acid were tested with and without metabolic activation, and negative (medium only) and positive (2-aminoanthracene) controls were used. Lactic Acid was not mutagenic with or without metabolic activation.

Lactic Acid, 0.045, 0.09, and 0.18% (USP grade), was mutagenic neither in plate tests using *S. typhimurium* strains TA1535, TA1537, and TA1538 with or without metabolic activation nor in nonactivation and activation suspension tests using *S. typhimurium* and *Saccharomyces cerevisiae* (Litton Bionetics, Inc., 1976). Negative and positive controls were also assayed.

The "streptomycin" method (Bertani, 1951) was performed using *E. coli* strains B/Sd-4/1, 3, 4, 5 and B/Sd-4/3, 4 to determine the mutagenic potential of 0.010–0.021% Lactic Acid and 2.0–3.0% Sodium

Table 24. Lactic Acid and Ammonium, Calcium, and Sodium Lactate mutagenicity studies

Test	Organism and strain	Dose and methods	Results and comments	Reference
		Lactic Acid		
Ames test	*S. typhimurium* TA100		Negative	Yamaguchi and Nakagawa, 1983
		2 mg/mL	Chromosomal damage in the absence of metabolic activation	ESLUR, 1994a
Ames test	*S. typhimurium* TA92, TA1535, TA100, TA98, TA1537, TA94	≤10.0 mg/plate of 90.5% pure Lactic Acid	Negative	Ishidate et al., 1984
Ames test	Clonal subline of Chinese hamster lung fibroblasts	1000 μg/plate of 11 mM Lactic Acid	Negative	Ishidate et al., 1988
Ames test	*S. typhimurium* TA97, TA98, TA100, TA104	0.5–2.0 μL/plate Lactic Acid	Negative with and without metabolic activation	Al-Ani and Al-Lami, 1988
Plate tests	*S. typhimurium* TA1535, TA1537, TA1538	0.045–0.18% USP grade Lactic Acid	Negative with and without metabolic activation	Litton Bionetics, Inc., 1976
Suspension tests	*S. typhimurium*; *Saccharomyces cerevisiae*		Negative in nonactivation and activation tests	Litton Bionetics, Inc., 1976
"Streptomycin" method	*E. coli* B/Sd-4/1, 3, 4, 5, B/Sd-4/3, 4	0.01–0.021% Lactic Scid 2.0–3.0% Sodium Lactate	Lactic Acid: weak mutagenic effect seen at some doses Sodium Lactate: negative	Demerec et al., 1951
Chromosomal aberration test	Chinese hamster fibroblast cells	≤1.0 mg/mL of 90.5% pure Lactic Acid for 48 h	Negative without metabolic activation	Ishidate et al., 1984
Chromosomal aberration test	CHO K1 cells	10–16 mM without metabolic activation; pH range of 6.3–5.8 8–14 mM with metabolic activation; pH range of 6.4–5.7	Nonclastogenic with "pseudo-positive" results attributable to nonphysiological pH	Morita et al., 1990

(*Table continued on next page.*)

Table 24. Lactic Acid and Ammonium, Calcium, and Sodium Lactate mutagenicity studies (*continued*)

Test	Organism and strain	Dose and methods	Results and comments	Reference
DNA–cell binding assay	Ehrlich ascites cells	100 μM Lactic Acid	Negative in the presence and absence of lysozyme, liver extract, and lysozyme and liver extract	Kubinski et al., 1981
Reversion test	*S. typhimurium hisC3076*	Treated in growth and nongrowth media with 9-aminoacridine	"Intermediate" mutant yields in the presence of Lactic Acid	Kopsidas and MacPhee, 1994
		Ammonium Lactate		
Ames test	*S. typhimurium* TA1515, TA1517, TA1538, TA98; *Saccharomyces* D4	1–1000 μg/plate of a 12% lotion	Negative with and without metabolic activation	FDA, 1988
		Sodium Lactate		
Ames test	*S. typhimurium* TA92, TA1535, TA1537, TA100, TA94, TA98	≤100.0 mg/plate 50.8% pure Sodium Lactate	Negative with metabolic activation	Ishidate et al., 1984
Chromosomal aberration test	Chinese hamster fibroblast cells	≤2.0 mg/mL of 10 mM Sodium Lactate solution, 50.8% pure for 48 h	Negative without metabolic activation	Ishidate et al., 1984
Forward mutation induction	Chinese hamster V79 A cells	Stationary-phase cells were exposed to 10 Gy of X-rays and ≤20 mM Sodium Lactate	No change in mutation frequency was observed in cells incubated with 20 mM subjected to 6 h postirradiation recovery. A slight increase was seen after a 24-h recovery period compared to mutation frequency at immediate plating.	Kumar et al., 1985

Lactate (Demerec et al., 1951). Some of the concentrations tested indicated a weak mutagenic effect for Lactic Acid. Sodium Lactate did not have mutagenic potential.

A chromosomal aberration test was performed using a Chinese hamster fibroblast cell line in which the cells were exposed to three doses $\leq$1.0 mg/mL of Lactic Acid, 90.5% pure, in physiological saline for 48 h without metabolic activation (Ishidate et al., 1984). Lactic Acid was negative for chromosomal aberrations.

Lactic Acid was evaluated for its ability to induce clastogenic effects using Chinese hamster ovary (CHO) K1 cells in a chromosomal aberration test (Morita et al., 1990). Doses of 10–16 and 8–14 mM were used without and with metabolic activation, respectively, with initial pH ranging from 6.3 to 5.8 and 6.4 to 5.7, respectively. At a dose of 14 mM Lactic Acid without metabolic activation, initial pH 6.0, 22.5% of the cells had aberrations. At a dose of 12 mM with metabolic activation, initial pH 6.0, 35.5% of the cells had aberrations. Initial pHs of 5.8 and 5.7 were toxic without and with metabolic activation, respectively. Neutralization of the media decreased the number of aberrations both without and with metabolic activation. No clastogenic activity was observed when the cultures were first exposed to Lactic Acid and then neutralized to pH 6.4 or 7.2 with sodium hydroxide. With F12 medium supplemented with 34 mM sodium bicarbonate, no clastogenic activity was seen at concentrations <25 mM Lactic Acid, but approximately 10% of the cells had aberrations at pH $\leq$ 5.7. The investigators concluded that Lactic Acid was nonclastogenic and that the "pseudo-positive" results were attributable to nonphysiological pH.

In a DNA-cell binding assay using Ehrlich ascites cells, negative results were obtained with 100 μM Lactic Acid with and without lysozyme, liver extract, and lysozyme and liver extract (Kubinski et al., 1981).

Reversion of the *hisC3076* frameshift marker of *S. typhimurium* was measured following treatment of cells in growth and nongrowth media with 9-aminoacridine (Kopsidas and MacPhee, 1994). In the presence of Lactic Acid, "intermediate" mutant yields were observed.

Ammonium Lactate. A 12% Ammonium Lactate lotion, pH 5.0–5.5, was evaluated for mutagenic activity in an Ames assay using *S. typhimurium* strains TA1515, TA1517, TA1538, and TA98 and *Saccharomyces* strain D4 with and without metabolic activation (FDA, 1988). Standard positive controls were used. A 12% Ammonium Lactate lotion, 1–1000 μg/plate, was not mutagenic.

Sodium Lactate. The mutagenic potential of a Sodium Lactate solution, 50.8% pure, in phosphate buffer was evaluated in an Ames test using *S. typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98 with metabolic activation (Ishidate et al., 1984). Duplicate

plates of six concentrations $\leq$ 100.0 mg/plate were examined. Negative results were obtained.

A chromosomal aberration test was performed using a Chinese hamster fibroblast cell line in which the cells were exposed to three doses $\leq$ 2.0 mg/mL of a 10 mM Sodium Lactate solution, 50.8% pure, in physiological saline for 48 h without metabolic activation (Ishidate et al., 1984). The results were negative.

Induction of forward mutation leading to 6-thioguanine resistance was also studied in stationary-phase Chinese hamster V79 A cells exposed to 10 Gy of X-rays, with survival and mutation frequency being determined immediately after irradiation or after 6 and 24 h of postirradiation recovery with and without Sodium Lactate (Kumar et al., 1985). No change in mutation frequency was observed in cells incubated with 20 mM Sodium Lactate subjected to 6 h postirradiation recovery, but there was a slight increase after a 24-h recovery period, compared to mutation frequency at immediate plating.

TEA-Lactate. Published mutagenicity data for TEA-Lactate were not found. Studies included in the Safety Assessment on TEA (Elder, 1983) reported that TEA was neither mutagenic in the Ames test, nor was it mutagenic toward cultures of *Bacillus subtilus*. In an unscheduled DNA synthesis assay, TEA did not cause DNA-damage-inducible repair.

CARCINOGENICITY

DERMAL

Lactic Acid

TEA-Lactate. Published dermal carcinogenicity data for TEA-Lactate were not found. Studies included in the Safety Assessment on TEA (Elder, 1983) reported that dermal application of TEA to mice for 18 months did not produce carcinogenic or cocarcinogenic activity.

ORAL

Lactic Acid

Female rabbits (number not specified) were dosed orally with 0.1–0.2 g/kg Lactic Acid in 100–150 mL water twice daily for 5 months, and five female rabbits were dosed orally with 0.1–0.7 g/kg Lactic Acid in 50–100 mL water twice daily for 16 months (13 months actual treatment) (Shubik and Hartwell, 1957). No tumors were reported after 5 or 16 months, respectively. Details not provided.

Calcium Lactate. Groups of 100 SPF F344 rats, 50 per sex, were used to examine the carcinogenic potential of Calcium Lactate (purity > 97%) (Maekawa et al., 1991). Two groups of rats were given 2.5 or 5% Calcium Lactate in distilled water *ad libitum* for 104 weeks; a third group was given untreated water and served as a control group. These doses were based on the results of a subchronic study summarized previously in this report (Matsushima et al., 1989). All animals were then given untreated water for a recovery period of 9 weeks. Males were housed three or four animals per cage, and females were housed five per cage. Observations were made daily and body weights were determined weekly for the first 13 weeks; determinations were then made every 4 weeks. All animals that died on study, or were killed, were necropsied, and gross and microscopic examinations were made for the presence of nonneoplastic and neoplastic lesions. A dose-dependent decrease in body weight gains was observed for dosed male and female animals, with a 13% decrease in body weight gain being reported for all high-dose-group animals. Daily water consumption was similar for all groups. The mortality rate was slightly increased (51 vs. 73%, approximately) and the mean survival

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time slightly, but insignificantly, decreased for females of the high-dose group as compared to controls. The kidney weights of females of the high-dose group were slightly but significantly increased compared to control values, and there was a slight increase in calcium deposition in the papilla. However, no difference in the severity of chronic nephropathy was observed between females of the high-dose and control groups, and no toxic lesions, such as cortico-medullary nephrocalcinosis, were observed. A significant, dose-dependent increase was observed in the relative brain weights of male and female rats, but no microscopic lesions were found. No specific dose-related changes were found in any hematological or biochemical parameters. No significant differences were observed in the incidences of total neoplasms between test and control male and female animals; the incidences of total neoplasms were 100% and 80–86% for all males and females, respectively. The test animals did not have a significant increase in the incidence of any specific neoplasm, and no positive trend was noted in the occurrence of any neoplasm. Male rats of the high-dose group did have a slightly greater incidence of pheochromocytomas as compared to current and historical controls and the incidence of adrenal medullary hyperplasias (24%) was greater than in the low-dose (12%) or control (10%) groups. A positive trend was observed in the occurrence of the two types of lesions (combined hyperplasias and pheochromocytomas); however, the investigators considered the increases due to "experimental variability."

TEA-Lactate. Published oral carcinogenicity data for TEA-Lactate were not found. Studies included in the Safety Assessment on TEA (Elder, 1983) reported that there was a greater incidence of malignant lymphoid tumors in female mice fed diets containing 0.03 and 0.3% TEA for their entire lifespan than in control mice or male mice fed the diet without TEA.

COSMETIC SKIN EFFECTS

AHAs are skin plasticizers in that they make the skin more flexible (Hall and Hill, 1986). The plasticization has been attributed to a reduction in the interaction between polar groups of keratin chains in skin due to reductions in hydrogen bonding (Takahashi et al., 1985; Alderson et al., 1984). It has also been proposed that hydroxyacids can occupy sites in the stratum corneum that are normally occupied by water molecules, thereby increasing skin extensibility.

Glycolic Acid

A double-blind, randomized, complete block design study was performed using 11 subjects to determine the effect of Glycolic and Lactic Acid on the skin (Berardesca et al., 1997). Glycolic and Lactic Acid were each applied as 8% creams, pH 4.4, to an 8 × 5-cm area of the volar arm or forearm twice daily for 4 weeks (ca. 2 mg/cm^2). Vehicle (not defined) and untreated control sites were also used. At week 4, a challenge was performed by applying 5% sodium lauryl sulfate (SLS) under an occlusive patch for 6 h. Clinical evaluations were made prior to and 1–4 weeks after AHA application and 0, 24, and 48 h following challenge with SLS. Transepidermal water loss (TEWL) was measured, and chromometry was used. Significant differences in TEWL were not observed between the Glycolic and Lactic Acid-treated sites during the 4 weeks of the study. TEWL was statistically significantly greater at the vehicle-treated site than at the Glycolic or Lactic Acid-treated sites. A statistically significant difference in erythema was not observed between sites. Following the challenge with SLS, TEWL values generally increased, with the greatest effects observed at the vehicle-treated site; TEWL at the Glycolic and Lactic Acid-treated sites was not statistically significantly different from that at the untreated control site. TEWL values are summarized in Table 25. Statistically significantly less erythema was observed at the Glycolic and Lactic Acid-treated sites as compared to the vehicle-treated site following SLS application; a statistically significant difference was not observed between the AHA-treated sites and the untreated control site. "Skin brightness" was reduced at all sites following SLS application, but AHA-treated sites had less reduced brightness as compared to the vehicle and untreated control sites. The researchers

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Table 25. TEWL ($G/m^2/h$) values before and after challenge with SLS

Site	0 wk	4 wk	+30 min SLS	+24 h SLS	+48 h SLS
Glycolic Acid	5.0 ± 1.3	5.4 ± 1.2	10.7 ± 8.2	11.0 ± 5.8	9.6 ± 4.5
Lactic Acid	4.7 ± 1.7	5.4 ± 1.1	8.6 ± 3.9	10.3 ± 5.7	9.6 ± 3.2
Vehicle	5.4 ± 2	6.4 ± 0.8	12.5 ± 11.3	14.3 ± 9.2	11.9 ± 8.6
Untreated	4.9 ± 1.2	5.4 ± 1.2	8.6 ± 5.0	12.0 ± 10.9	9.0 ± 7.6

stated that the larger reduction in brightness at the vehicle and untreated control sites was "indicative of greater damage by SLS causing disruption to the stratum corneum in non-AHA treated sites."

The effect of 0.5–1 M Glycolic Acid on cell renewal, skin hydration, firmness, thickness, and condition, and wrinkle reduction was assessed (Smith, 1996). The test solutions were formulated in a simple liquid vehicle (15% ethanol [SD 40], 5% ethoxydiglycol, and 5% butylene glycol). The dansyl chloride method was used to assess skin renewal by applying 2 mg/cm^2 of the test solution to the volar forearm stained with dansyl chloride twice daily until all the stain was removed. At pH 3, a 24.1–31.3% increase was observed, at pH 5 a 17–28.3% increase was observed, and at pH 7 a 9.1–10.8% increase was observed in cell renewal with 0.5–1.5 M Glycolic Acid, respectively. Skin hydration was measured using an impedance meter. At least 10 subjects were used to determine immediate skin hydration by applying 2 mg/cm^2 of the test material and measuring skin impedance every 15 min until the readings returned to within 5% of the preapplication values. Glycolic Acid, 0.75 M, had a duration of skin moisturization of <1, 2, and 3.5 h at pH 3, 5, and 7, respectively. The increase in skin moisturization after long-term use was determined using at least six subjects. Skin impedance was determined on the cheek area prior to and after 3 and 6 weeks of twice daily application of 2 mg/cm^2 0.75 M Glycolic Acid. Skin impedance increased 11.2 and 14.1% after 3 and 6 weeks, respectively. Skin firmness, thickness, and wrinkles were assessed for at least six subjects prior to and after 6 weeks of application of 2 mg/cm^2 0.75 M Glycolic Acid. Skin firmness was measured using ballistometry, skin thickness using ultrasound analysis, and wrinkles using image analysis. The improvements in skin firmness, thickness, and wrinkles were 17.4, 6.7, and 19%, respectively; these changes from baseline values were statistically significant.

A double-blind, vehicle-controlled, randomized study was performed using ≥10 white female subjects per group to determine the effects of Glycolic and Lactic Acid on moderately photo-damaged skin of the face (average global score 5.2) and on skin of the forearms (Unilever Research U.S., Inc., 1995). (Portions of this study have been published by Stiller et al. [1996].) After a 14-day preconditioning period, the applications shown in Table 26 were made. The creams were applied at a dose of

Table 26. Glycolic Acid, Lactic Acid, and vehicle applications in Unilever study

Group	Face	Left arm	Right arm
1	8% Glycolic Acid (pH 3.8)	8% Glycolic Acid (pH 3.8)	Vehicle (pH 7.55)
2	8% Glycolic Acid (pH 3.8)	Vehicle (pH 7.55)	8% Glycolic Acid (pH 3.8)
3	8% Lactic Acid (pH 3.89)	8% Glycolic Acid (pH 3.8)	8% Lactic Acid (pH 3.89)
4	8% Lactic Acid (pH 3.89)	8% Lactic Acid (pH 3.89)	8% Glycolic Acid (pH 3.8)
5	Vehicle (pH 7.55)	Vehicle (pH 7.55)	8% Lactic Acid (pH 3.89)
6	Vehicle (pH 7.55)	8% Lactic Acid (pH 3.89)	Vehicle (pH 7.55)

approximately 1 g per application twice daily for 22 weeks. At study completion, groups 1 and 2 consisted of 21 subjects, groups 3 and 4 consisted of 24 subjects, and groups 5 and 6 consisted of 22 subjects; of the 74 initial subjects, six subjects withdrew for personal reasons and one subject withdrew due to skin irritation. Clinical evaluations were made at weeks 0, 2, 6, 10, 14, 18, and 22, clinical chemistry and hematologic parameters were determined at weeks 0, 10, and 22, and 4-mm punch biopsies were obtained from both forearms of half of the subjects at weeks 0 and 22. Twenty-two subjects (30% incidence) in both the AHA and vehicle groups had some irritation. Irritation occurred more often on the face than on the arms, but the severity of irritation was greater on the arms than on the face. On the face, the creams containing Glycolic and Lactic Acid produced lower erythema scores than the vehicle as measured by change from the baseline. However, significant increases in erythema on the forearm produced by both Glycolic and Lactic Acid were observed after 2 weeks of dosing; average erythema scores were <1 above the baseline. The severity of erythema generally subsided with continued application. No adverse systemic changes were reported, and no indications of adverse effects on hepatic or renal functions were observed. No remarkable changes in clinical chemistry or hematologic parameters were reported; a statistically significant increase in electrolyte balance was considered an artifact because the absolute values of the major anions and cations were mostly normal and numerically, the electrolyte balance was only slightly elevated. Microscopic examination did not provide any evidence of adverse reactions to or adverse skin thickening by Glycolic or Lactic Acid. Glycosaminoglycans were marginally elevated.

A double-blind study was performed using groups of 20 female subjects with "smoker's face" to evaluate the effects of formulations containing

Glycolic and Lactic Acid (Morganti et al., 1994a). Two formulations, one that contained vehicle and 8% AHAs (Glycolic Acid, Lactic Acid, and ammonium lactilate) and one that contained the vehicle, 8% AHAs, and 6% gelatin-glycine were used. Each group received creams to apply after using a "soothing lotion" (which contained Glycolic Acid and Lactic Acid, concentration not given, and other ingredients), to the right and left side of the face twice daily for 16 weeks. Surface sebum and skin hydration were measured and fine wrinkling was assessed weekly. Both test creams increased skin hydration and surface lipids and reduced fine wrinkling as compared to controls. The cream containing gelatin-glycine had greater effects than the cream that contained only the AHAs.

Dermal effects of Glycolic Acid application in conjunction with pH were investigated (Smith, 1994). First, the dansyl chloride method was used to monitor changes in rates of normal skin cell renewal as a result of twice daily application of Glycolic Acid. As pH increased, the stimulation of cell renewal decreased; at a pH of 6, very little stimulation was observed. The relationship between irritation, renewal, and pH was then examined using 4% Glycolic Acid, with skin irritation being evaluated clinically by subjective assessment of stinging in the nasal fold area on a scale of 1–5 and with the Minolta Chroma Meter, which measured changes in skin redness. A strong correlation between irritation and stimulation was observed. At pH 3, irritation and cell renewal were scored as 2.9 and 34%, respectively. At pHs of 5 and 7, irritation/cell renewal were scored as 2.1/23% and 1.1/10%, respectively. The stimulation of skin renewal by 3% Glycolic Acid, pH 3, in subjects never exposed to AHAs or exfoliant treatment over an extended period of time was also investigated. After 10 weeks of applications, cell renewal diminished by approximately 43%. After 20 weeks of applications, cell renewal diminished by approximately 60%. Similar results were obtained upon measurement of the rate of cell shedding. A baseline of 1 was used for test and control subjects. After 1, 2, 4, 8, and 12 weeks, the percent change in cell sloughing due to continued application of 3% Glycolic Acid, pH 3, was 2.21, 2.08, 1.73, 1.36, and 1.15, respectively, as compared to control values of 1.08, 0.95, 1.17, 1.06, and 1.11, respectively. The difference between treated and control values at week 12 was not significantly different. Skin pH after 3% Glycolic Acid application, pH 3.0, was measured by pressing a flat-head temperature-normalized pH probe to the skin. The baseline skin surface pH was 5.41 and 5.37 for test and control subjects, respectively. At 30 min, 1, 2, 4, and 6 h after Glycolic Acid application, the skin surface pH was 4.35, 4.97, 5.21, 5.42, and 5.47, respectively. For the same time periods, the skin surface pH of the controls was 5.39, 5.35, 5.34, 5.41, and 5.61, respectively. The pH of different layers of the skin was also determined. The baseline skin surface pH was 5.41 for the groups dosed with 3 and 10% Glycolic Acid and 5.37 for controls; the test

readings were taken 30 min after application. After 1, 3, 5, 10, and 20 tape strippings, the skin to which 3% Glycolic Acid was applied had a pH of 4.47, 4.82, 5.04, 5.65, and 5.93, respectively; the pH after one and three strippings was significantly different compared to the initial pH. After the same number of strippings upon application of 10% Glycolic Acid, the pH values were 4.42, 4.67, 4.88, 4.93, and 5.55, respectively, all of which were significantly different than the control values, with the exception of the pH value after 20 tape strippings. The control values upon tape stripping were 5.26, 5.21, 5.07, 5.68, and 6.04, respectively.

Twelve female subjects were used to study the effect of 30% Glycolic Acid chemical washes on the barrier function of the skin (DiNardo et al., 1996a). The washes were partially neutralized with ammonium hydroxide to a pH of 2.5, 3.0, or 3.5, creating three formulations. The three formulations were applied to eight sites on the left or right upper thigh for 20 min on days 0, 3, and 6. (This represented a threefold exaggeration of the generally recommended duration and a six-fold exaggeration of the recommended frequency of application.) TEWL was measured at baseline, 15 min and 3 h after each application, and 1 week after the last application on day 13 of the study. Superficial shave biopsies were taken prior to application on day 0, 15 min after the last chemical wash on day 6, and on day 13. No clinical irritation was observed during the study. All TEWL values were within the normal range (3–8 $g/m^2\ h^{-1}$). The results are shown in Table 27. The researchers stated that the values obtained for the three formulations "represents little to no change in the fluctuation of the amounts of water loss expressed in $g/m^2\ h^{-1}$ and for the purpose of comparison reflect ranges that have been reported for conventional soap-based and synthetic-detergent-based cleansers." TEWL measurements obtained 1 week after the last application implied a nonstatistically significant trend of improved barrier function capabilities, with higher pH having a greater increase in barrier function (13, 17, and

Table 27. TEWL ($g/m^2/h$) for female subjects treated with 30% Glycolic Acid

	Baseline	Wash 1/day 0	Wash 2/day 3	Wash 3/day 6	Day 13
pH 2.5	4.8 ± 0.9				4.2 ± 1.4
15 min		5.0 ± 1.4	5.9 ± 1.6	6.6 ± 1.9	
3 h		5.0 ± 1.3	5.7 ± 1.1	5.6 ± 1.4	
pH 3.0	4.7 ± 0.8				3.9 ± 1.2
15 min		5.7 ± 1.3	4.8 ± 1.3	5.8 ± 1.3	
3 h		4.4 ± 1.4	5.3 ± 1.3	5.2 ± 1.0	
pH 3.5	5.3 ± 1.2				4.3 ± 1.2
15 min		5.1 ± 1.5	5.2 ± 1.7	6.1 ± 1.8	
3 h		4.9 ± 1.3	6.2 ± 2.1	6.2 ± 1.6	

19% improvement at pH 2.5, 3.0, and 3.5, respectively). Adverse microscopic effects were not found. Tissues had the typical "basketweave" pattern. A trend toward increased overall thickness was observed on day 13; baseline values were 19.0, 21.6, and 21.8 μ and day 13 values were 24.8, 31.0, and 26.7 μ for pH 2.5, 3.0, and 3.5, respectively.

One male and three female subjects were used in attempts to analyze the mode of action of Glycolic Acid on the stratum corneum and to examine whether desquamation compromises barrier lipid structures of the stratum corneum (CTFA, 1995d). A lotion containing 4% Glycolic Acid, pH 3.88, and the vehicle formulation, pH 3.74, were applied to opposite volar forearms twice daily for 3 weeks. The number of stratum corneum layers, glycosaminoglycan material in intercellular spaces, existence of epidermal component abnormalities, lamellar bodies and lipid bilayer organization, and "corneosome" degradation were examined. Two punch biopsies were done on both ventral forearms of the four subjects at study termination, and tissues were processed for electron microscopy. The effect on barrier function was studied by measuring TEWL using three of the four subjects; mean values were obtained from three successive recordings for every test site. Using light microscopy, no structural differences were found between Glycolic Acid-treated and vehicle-treated skin, but the stratum corneum appeared more compact at the Glycolic Acid-treated site. Cell layers of the stratum corneum and the stratum granulosum were not increased. Glycosaminoglycan material was not seen in intercellular spaces between spinous and granular cells; one of the probands indicated the occurrence of a transitional cell, but this was considered a normal finding. No abnormalities of epidermal components were found and no loss of cohesion was found between the corneocytes of the stratum compactum. Lamellar body morphology in the cytoplasm of the stratum granulosum cells was normal; at the stratum granulosum/stratum corneum interface, the lamellar body–lipids were extruded and transformed into regular lipid bilayers (lamellar body secretory system). The intercellular lipids were similar between Glycolic Acid- and vehicle-treated sites and were comparable to normal stratum corneum profile. Corneosome degradation was more advanced at the site treated with Glycolic Acid in the superficial layers (stratum disjunctum) of the stratum corneum; desmosomes in the lower layers (stratum compactum) appeared normal. No marked increase in TEWL was observed after 3 weeks of Glycolic Acid application; this indicated that there was no barrier disruption. Also in this study, the effect on stratum corneum hydration was also determined. Using skin capacitance as an indicator, it was reported that a lotion containing 4% Glycolic Acid, pH 3.88, and the control vehicle formulation, pH 3.74, did not increase or decrease water content of the stratum corneum.

A study using 10 female subjects was performed to determine whether twice daily application of a cream containing 8% Glycolic Acid, pH 3.89,

for 28 days altered the structure or thickness of the stratum corneum or viable epidermis (CTFA, 1994a). Following a preconditioning period, 100 mg of the Glycolic Acid cream (2 mg/cm^2) and a control cream not containing Glycolic Acid, pH 3.98, were applied to a 50-cm^2 area on opposite sides of the back twice daily, with applications at least 8 h apart. At 12–16 h after the last application, shave biopsies were taken from the test site, the control site, and an untreated site. Light microscopy was used to evaluate changes in viable epidermal thickness (VET), stratum corneum thickness, acanthosis and spongiosis, thickened granular layer, stratum corneum alterations, and dermal alterations; viable epidermis and stratum corneum thickness were also quantified by image analysis. VET and stratum corneum thickness were not significantly altered by application of either the Glycolic Acid or the control cream. The epidermis appeared normal with relatively homogeneous, tightly associated, round to cuboidal basal cells in all but two subjects; it was slightly thickened with no inflammation at the Glycolic Acid-treated site of one subject and was thickened with signs of inflammation at the untreated site of the second subject. After examination of the stratum corneum, the following were reported: a compact, irregular stratum corneum for one subject; a slightly thinned stratum corneum with a basketweave pattern and some discontinuity for one subject; and a slightly thinned stratum corneum with a basketweave pattern at the Glycolic Acid site in two subjects. In the remaining subjects, the stratum corneum had the normal basketweave pattern at the Glycolic Acid-treated sites; retention of nuclei and lipid droplets were not observed within the individual horny cells. Dermal changes indicative of cellular injury or toxicity were not observed; any changes that were observed in dermal cellularity were attributed as normal variability by the investigator. It was concluded that application of a cream containing 8% Glycolic Acid, pH 3.89, twice daily for 28 days "did not elicit any major changes in epidermal histology, viable epidermal thickness, or stratum corneum thickness compared to untreated sites."

In two studies using five and eight subjects, respectively, 0.5 g of a formulation containing 4% Glycolic Acid, adjusted with TEA to pH 4.0 and 3.7, respectively, was applied twice daily to one forearm of each subject for 4 weeks and the vehicle was applied to the contralateral arm and served as a control (CTFA, 1995e). After 4 weeks of application, TEWL was measured. An occlusive patch containing 0.2 mL of 0.25% SLS solution was then applied to each forearm at the site of the TEWL measurement for 24 h; 3 h after the patches were removed, TEWL was again measured. The results of these studies are summarized in Table 28.

Nineteen female subjects with normal skin were used in a 24-week study to determine whether chronic application of a formulation containing 4% Glycolic Acid, pH 3.89, altered the "normal barrier properties" of the skin (KGL, Inc., 1995). Semi-supervised applications of 2 mg/cm^2 of

Table 28. Effect of 4% Glycolic Acid on TEWL ($g/m^2\ h^{-1}$)

	Pre-SLS	Post-SLS	Difference
Study 1			
	4.0% Glycolic Acid, pH 4.0		
Mean	4.38	12.00	7.62
SD	1.48	4.64	3.78
	Vehicle		
Mean	5.90	15.92	10.02
SD	2.31	3.67	1.64
P value	0.090	0.073	0.20
Study 2			
	4.0% Glycolic Acid, pH 3.7		
Mean	3.45	9.90	6.45
SD	0.95	3.24	2.62
	Vehicle		
Mean	4.15	12.12	7.97
SD	1.53	3.91	2.99
P value	0.081	0.006	0.008

the test material were made twice daily to a 112.5-cm^2 area on one side of the lower back of each subject. At the treated site and an adjacent untreated site, TEWL was measured at study initiation and after 6, 12, 18, and 24 weeks, water content was assessed after 12, 18, and 24 weeks, and the skin surface cells were sampled using tape stripping at 12 and 24 weeks.

Average TEWL values were slightly but statistically significantly increased for the treated site at all measurements; the change in TEWL was within the range of normal TEWL values for this body site. Water content was statistically significantly increased and the amount of surface dryness was statistically significantly decreased at all measurements for the treated site as compared to control values. The researchers postulated that "the TEWL change was caused by an increase in water hydration and/or an improvement in skin surface smoothness" and concluded that "chronic use of a 4% Glycolic Acid cream does not adversely alter skin barrier function."

Eight normal subjects, six males and two females, were used in a study assessing the ability of topical applications of 4% Glycolic Acid, pH 3.90, for 6 months to induce clinical or subclinical cutaneous alterations indicative of cellular toxicity or injury (CTFA, 1994b). Following a preconditioning period in which the subjects did not apply any skin care products to their volar forearms, the subjects were instructed to

apply Glycolic Acid to a site on the volar forearm once daily for 2 weeks and then twice daily for $5\frac{1}{2}$ months, with at least 8 h between applications. An adjacent site on the same forearm was untreated and served as a control. Clinical evaluations were made every 2 weeks, and a 3-mm punch biopsy was taken from each site, which was injected with xylocaine, at dose termination. The biopsies were evaluated using light microscopy for VET, acanthosis and spongiosis, thickened granular layer, stratum corneum alterations, dermal alterations, and ground substance determined as glycosaminoglycan deposition. No irritation, scaling, or other reactions were observed at the test site, and no adverse effects were reported. The viable epidermis was normal in all subjects, and its thickness was not significantly increased after 6 months of Glycolic Acid application. For two subjects, the stratum corneum was compact or thin and compact as compared to the normal basketweave pattern at the site to which Glycolic Acid was applied; however, this was not accompanied by other alterations and was attributed to individual variability. Basal, spinous and granular cells were not separated by excessively wide intercellular spaces suggestive of acanthosis and/or spongiosis, and the granular layer was normal at the test site in all but one subject, in which it was slightly thickened. No significant change in glycosaminoglycan deposition or cellular infiltrate was observed as compared to controls. It was concluded that Glycolic Acid "did not elicit any subclinical cutaneous alterations that would suggest cellular toxicity or injury."

A portion of each of the biopsies from the study described above (CTFA, 1994b) was preserved for electron microscopy (CTFA, 1995f). The following parameters were evaluated for evidence of injury: dermal/epidermal junction for evidence of basal lamina reduplication; basal, spinous, and granular keratinocytes; dermal vasculature; mast cells. No changes were detected in the basement region; specifically, no reduplication of lamina densa or anchoring fibrils was noted. Also, no breaks or discontinuities were found in the basement membrane. No atypical keratinocytes or abnormally widened intercellular spaces between adjacent cells were observed. Lipid droplets were not observed within the individual basal, spinous, or granular cells. No vascular abnormalities were observed. Mast cells appeared inactive with no degranulation. It was concluded that Glycolic Acid "did not elicit any ultrastructural cutaneous alterations that would suggest cellular toxicity or injury."

Six women participated in a study to determine whether the treatment of human skin with Glycolic Acid-enhanced epidermal proliferation (CTFA, 1995g). After a "preconditioning" period in which no skincare products were applied, open applications of a 4% Glycolic Acid emulsion, pH 3.89, and a conventional moisturizer, pH 6.57, were made twice daily for 24 weeks to the back of each subject with each application at least 8 h apart; the weekday morning applications were made by

laboratory personnel and the evening and weekend applications were made by the subjects. An adjacent site on the back served as an untreated control. Approximately 14 h after the last application, superficial shave biopsies were taken from the two treated sites and the untreated site. The effects on epidermal proliferation was measured directly by labeling index and indirectly by VET and microscopic assessment. The labeling index, which represents the percentage of cells in S phase, for the Glycolic Acid-and moisturizer-treated skin, 5.3 ± 0.7 and 6.2 ± 0.8, respectively, was not significantly different from that of untreated skin, 4.1 ± 0.7; these values were within the normal range for human skin. The epidermis from all subjects contained basal and some suprabasal cells with labeled nuclei. Quantitative image analysis of VET provided data that neither the Glycolic Acid emulsion nor the moisturizer altered VET, indicating that the cells were not in a hyperproliferative state. No evidence of abnormalities, i.e., cellular toxicity or injury in the epidermis, was seen at light microscopic examinations.

The effect on skin firmness of creams containing 10% Glycolic Acid was evaluated using 30 female subjects (Morganti et al., 1996a). Creams containing Glycolic Acid, gelatin, glycine, and arginine or lysine, pH 5.5, were applied twice daily to one arm of each subject; vehicle only was applied to the other arm, which served as the control. Skin firmness was evaluated using a "Twistometer." Elastic recovery was significantly increased after 60 days of treatment with the Glycolic Acid-containing creams.

Lactic Acid

The effect of D- and L-Lactic Acid on cell renewal, skin hydration, firmness, thickness, and condition, and wrinkle reduction was assessed (Smith, 1996). The test solutions were formulated in a simple liquid vehicle (15% ethanol [SD 40], 5% ethoxydiglycol, and 5% butylene glycol). The dansyl chloride method was used to assess skin renewal by applying 2 mg/cm^2 of the test solution to the volar forearm stained with dansyl chloride twice daily until all the stain was removed. At pH 3, a 23–30.1% and a 25.4–31.2% increase was observed, at pH 5 a 21.9–27.4% and a 17.8–26.8% increase was observed, and at pH 7 a 5–10.3% and a 4–11.2% increase was observed in cell renewal with 0.5–1.5 M D- and L-Lactic Acid, respectively. Skin hydration was measured using an impedance meter. At least 10 subjects were used to determine immediate skin hydration by applying 2 mg/cm^2 of the test material and measuring skin impedance every 15 min until the readings returned to within 5% of the preapplication values. Both D- and L-Lactic Acid, 0.75 M, had a duration of skin moisturization of 1, 6, and >6 h at pH 3, 5, and 7, respectively. The increase in skin moisturization after long-term use was determined using at least six subjects. Skin impedance

was determined on the cheek area prior to and after 3 and 6 weeks of twice daily application of 2 mg/cm^2 0.75 M acid. After 3 and 6 weeks of application, skin impedance increased 16 and 27.8% with D-Lactic Acid, respectively, and 15 and 24.8% with L-Lactic Acid, respectively. Skin firmness, thickness, and wrinkles were assessed for at least six subjects prior to and after 6 weeks of application of 2 mg/cm^2 0.75 M Lactic Acid. Skin firmness was measured using ballistometry, skin thickness using ultrasound analysis, and wrinkles using image analysis. The improvements in skin firmness, thickness, and wrinkles were 21, 6.8, and 24%, respectively, with D-Lactic Acid and 24, 5.6, and 27%, respectively with L-Lactic Acid. These changes from baseline values were statistically significant.

Smith (1994) investigated the dermal effects of Lactic Acid application in conjunction with pH in the same manner they were examined for Glycolic Acid (described previously). First, the dansyl chloride method was used to monitor changes in rates of normal skin cell renewal due to twice daily application of Lactic Acid. As observed with administration of Glycolic Acid, an increase in pH decreased the stimulation of cell renewal; again, at a pH of 6, very little stimulation was observed. The relationship between irritation, renewal, and pH was then examined using 4% Lactic Acid; skin irritation was evaluated clinically by subjective assessment of stinging on a scale of 1–5 in the nasal fold area and with the Minolta Chroma Meter. A strong correlation between irritation and stimulation was observed. At pH 3, irritation and cell renewal were scored as 2.8 and 35%, respectively. At pHs of 5 and 7, irritation/cell renewal were scored as 2.1/24% and 1.2/13%, respectively. The ability of 3% Lactic Acid (pH not stated, but assumed to be 3) to stimulate skin renewal on subjects never exposed to AHAs or exfoliant treatment over an extended period of time was also investigated. After 10 weeks of applications, cell renewal had diminished by approximately 40%. After 20 weeks of applications, cell renewal had diminished by approximately 64%. Similar results were obtained upon measurement of the rate of cell shedding. A baseline of 1 was used for test and control subjects. After 1, 2, 4, 8, and 12 weeks, the percent change in cell sloughing due to continued application of 3% Lactic Acid, pH 3, was 1.98, 2.08, 1.65, 1.32, and 1.21, respectively, as compared to control values of 1.08, 0.95, 1.17, 1.06, and 1.11, respectively. The change at week 12 was not significantly different from control values.

As with Glycolic Acid, the skin pH after application of 3% Lactic Acid, pH 3.0, was measured. The baseline skin surface pH was 5.36 and 5.37 for test and control subjects, respectively. At 30 min and 1, 2, 4, and 6 h after Lactic Acid application, the skin surface pH was 4.47, 4.67, 5.11, 5.42, and 5.44, respectively. For the same time periods, the skin surface pH of the controls was 5.39, 5.35, 5.34, 5.41, and 5.61, respectively. The pH of different layers of the skin was determined. The baseline skin

surface pH was 5.41 for the group dosed with 3% Lactic Acid and 5.37 for controls; the test readings were taken 30 min after application. After 1, 3, 5, 10, and 20 tape strips, the skin to which 3% Lactic Acid was applied had a pH of 4.35, 4.67, 5.01, 5.63, and 6.03, respectively; the pH after one and three strippings was significantly different than the initial skin pH. The control values upon tape stripping were 5.26, 5.21, 5.07, 5.68, and 6.04, respectively.

The ability of Lactic Acid to induce hyperkeratosis was also evaluated. Lactic Acid, 3 and 8%, pH 3, was applied to the outer aspect of the calf to induce scaling. When visible scaling and irritation occurred, the skin desquamation profile was altered. Control values were 5.7% for cell renewal and 1 for irritation, clinical scaling, desquamation amount, and desquame size. After 3 weeks of application of 3% Lactic Acid, the values increased to 27.8% for cell renewal, 1.9 for irritation, 1.5 for scaling and the desquamation amount, and 1.6 for desquame size. With 8% Lactic Acid, these values increased to 44.2% for cell renewal, 4.2 for irritation, 3.5 for scaling, 1.8 for desquamation amount, and 3.8 for desquame size.

Smith (1994) then determined the effect of 5% Lactic Acid, pH 3, on skin thickness, which was measured by a 20-MHz ultrasound sweep. (Different skin layers could not be differentiated, so full skin thickness was measured.) The changes in skin thickness after 2, 4, 8, 12, and 26 weeks was 2, −1, 3, 5, and 8%, respectively. The difference was significant from baseline after 12 and 26 weeks.

As described earlier for Glycolic Acid, two studies were also performed examining the effect of Lactic Acid on TEWL before and after application of SLS (CTFA, 1995e). A 0.5-g dose of the formulation was applied twice daily to the volar forearm of each subject for 4 weeks, and the vehicle was applied to the contralateral arm, which served as a control. After 4 weeks of application, TEWL was measured. An occlusive patch containing 0.2 mL of 0.25% SLS solution was then applied for 24 h to each forearm at the site of the TEWL measurement; 3 h after the patches were removed, TEWL was again measured. In the first study, the test formulation contained 4% D,L-Lactic Acid, adjusted with TEA to pH 4.0, and in the second study the test formulations contained 4% DL-Lactic Acid or 4% L-Lactic Acid, adjusted with TEA to pH 3.7. The results of these studies are summarized in Table 29.

A double-blind study was performed in which 13 healthy female subjects applied two products to the right and left ventral forearm twice a day for 6 months; one product, pH 4.2, contained three AHAs (Lactic Acid, alpha-hydroxy octanoic acid, and alpha-hydroxy decanoic acid) at a total concentration of 1.4% w/w and one was an oil-in-water emulsion (Estee Lauder Research and Development, no date). At study termination, 4-mm punch biopsies were taken from each arm and processed for microscopic examination. After 6 months of AHA application, no changes

Table 29. Effect of 4% D, L-Lactic Acid and 4% L-Lactic Acid on TEWL

	Pre-SLS	Post-SLS	Difference
Study 1			
	4.0% D, L-Lactic Acid, pH 4.0		
Mean	4.38	12.00	7.62
SD	1.48	4.64	3.78
	Vehicle		
Mean	5.90	15.92	10.02
SD	2.31	3.67	1.64
P Value	0.090	0.073	0.20
Study 2			
	4.0% D, L-Lactic Acid, pH 3.7		
Mean	3.45	9.90	6.45
SD	0.95	3.24	2.62
	Vehicle		
Mean	4.15	12.12	7.97
SD	1.53	3.91	2.99
P Value	0.081	0.006	0.008
	4.0% L-Lactic Acid, pH 3.7		
Mean	4.15	12.12	7.97
SD	1.53	3.91	2.99
	Vehicle		
Mean	4.15	12.12	7.97
SD	1.53	3.91	2.99
P Value	0.081	0.006	0.008

in epidermal or dermal morphology were observed, and the test and control sites were often indistinguishable. This same AHA formulation was evaluated for its effect on barrier condition of the skin using female subjects; the same material without the AHAs served as a control (number not specified) (Estee Lauder Research and Development, no date). The AHA formulation was applied to the face and the forearm and the control material was applied to the opposite forearm twice a day for 8 weeks. Stratum corneum barrier quality was determined by the number of Scotch tape strippings required to damage the skin barrier, i.e., TEWL measurements reach 18 $g/cm^2\ h^{-1}$ as measured with a Servomed Evaporimeter. The sites were monitored at study initiation and after 4 and 8 weeks. No significant change in barrier condition of facial skin was observed after 4 and 8 weeks of AHA application as compared to baseline values. No significant change was observed in barrier condition of the arm to which vehicle was applied, but there was "significant

improvement in barrier condition" on the arm treated with the AHA formulation as compared to baseline values.

Middleton (1974) examined the effect of Lactic Acid and Sodium Lactate on water content and extensibility of the skin of women's hands using a qualitative scoring method. It was reported that 10% Lactic Acid and Sodium Lactate solutions and a 5% Lactic Acid solution decreased skin dryness and flaking, as compared to a control lotion that did not contain either of these ingredients, and that Lactic Acid produced greater effects.

The effect of 5% Lactic Acid, pH 3, on skin hydration was studied using a group of subjects over a 26-week period and the Nova Impedance meter to measure skin hydration (Smith, 1994). After 2, 4, 8, 12, and 26 weeks, the change in hydration from baseline determination was 3, 32, 41, 29, and 33%, respectively.

The effects of Lactic Acid and Sodium Lactate on the rheological properties of the stratum corneum were examined (Takahashi et al., 1985). A sample of stratum corneum removed from human abdominal skin was immersed in a 1 mmol/L solution of 10 mL/mg Lactic Acid or Sodium Lactate for 1 h and then dried at 25°C and 50% relative humidity (RH) for 24 h. Hygroscopicities, i.e., the water uptake in milligrams by 100-mg dry samples, were measured by the Karl-Fisher method. The sorptions by the stratum corneum were determined using [^{14}C] Lactic Acid. The pH of the Lactic Acid was adjusted using sodium hydroxide, and 10 × 10-mm samples of the stratum corneum were immersed in 1 mol/L solutions at 25°C. The radioactivity was determined using a liquid scintillating system. Water uptake increased exponentially with increasing relative humidity; however, Sodium Lactate-treated stratum corneum took up more water than samples treated with Lactic Acid. At 84% RH, Sodium Lactate-treated stratum corneum adsorbed 170% of its weight in water, as compared to the 80% by stratum corneum treated with Lactic Acid. Lactic Acid treatment appeared to have little effect on the hygroscopity of stratum corneum. However, Lactic Acid plasticized the stratum corneum more than Sodium Lactate at every relative humidity, even though it did not increase the water content in the stratum corneum.

Hill et al. (1988) has reported plasticization to be a linear function of free acid penetration. The amount of Lactic Acid sorbed by the stratum corneum increased with increasing immersion time and did not reach a saturation value during the 60 min test period. The pliability of the stratum corneum was closely related to the sorption of Lactic Acid, with greater pliability observed with more Lactic Acid sorbed. The sorption of Lactic Acid decreased as the pH of the solution increased, so Lactic Acid was sorbed more easily than Sodium Lactate, again demonstrating that the stratum corneum was plasticized more by Lactic Acid than Sodium Lactate. Also, the investigators reported that AHAs were more effective in plasticizing stratum corneum than β-hydroxy acids.

Takahashi et al. (1985) concluded that "water is not necessarily the only material capable of softening the stratum corneum. Alpha-hydroxy acids can be incorporated in stratum corneum and break hydrogen bonds in keratin to lower elasticity as with water." In regard to the greater plasticizing ability of AHAs compared to β-hydroxy acids, the researchers assumed "that the α-type penetrates more readily into the interkeratin chains to reduce the interaction between them and has a favorable molecular structure to interact with the keratin chains."

Ammonium Lactate. The effect of Ammonium Lactate on skin changes attributed to aging and photodamage was examined (Ridge et al., 1990). Twenty-one subjects, ages 29–61, applied a 12% lotion to one side of their face and continued their pretest skin care regimen on the other side. After 4 and 8 weeks, both the researchers and the subjects evaluated improvement in a side-by-side comparison in a blind manner. Equivocal results were reported after 4 weeks, with a mild smoothing of fine wrinkles being observed. Some subjects had no improvement, while dramatic changes were seen in others. After 8 weeks, more improvement was recognizable, with mild to moderate reduction in fine and periorbital wrinkling observed in 15 subjects. For 18 subjects, a positive change in skin texture was noted, with treated skin described as "consistently smoother and softer." Coarse wrinkles and pigment variabilities were minimally improved.

Six male subjects received open applications of 0.02 mL 12% buffered Ammonium Lactate on the ventral forearm daily for 4 weeks and six male subjects received 0.02 mL 12% buffered Ammonium Lactate under occlusive patches on the ventral forearm three times weekly for 3 weeks (Lavker et al., 1992). At the end of the treatment periods, a 3-mm pouch biopsy specimen was taken from the test area and from untreated and vehicle control areas. Biopsy specimens of the skin of subjects treated with either open or occlusive patches had an increase in VET; epidermal thickness increased from 67 ± 11 to 79 ± 14 μm after open application and from 62 ± 10 to 74 ± 17 μm after application of occlusive patches. However, despite an average 19% increase in VET, individual differences were observed when some subjects had minimal change and others had increases of 50%. The undulating nature of the dermoepidermal interface and the "basketweave" architecture of the stratum corneum were generally maintained. The granular layer was prominent compared to controls. In several subjects Hale's stainable (glycosaminoglycan-like) material was present in the intercellular spaces between spinous and granular cells and ground substance was increased; microspectrophotometry data indicated a 49 and 51% increase in Hale's stainable material after open and occlusive application, respectively. Vascular profiles were more prominent after Ammonium Lactate treatment. No increases in cellularity were observed. Neither

inflammatory infiltrate nor any evidence of cell injury in the epidermis was observed.

Sodium Lactate. Sodium Lactate, along with the sodium salt of pyrrolidone carboxylic acid (sodium PCA), constitutes the most hygroscopic fraction of the stratum corneum (Middleton, 1978). The researcher stated that experiments using isolated stratum corneum and consumer trials demonstrated that the inclusion of Sodium Lactate in a product can result in skin moisturizing and that the extra water can result in reduced skin dryness and flakiness.

A 2^2 factorial design was used to examine the effect of Sodium Lactate and urea on TEWL (McCallion and Li Wan Po, 1995). A 5 and a 10% w/w Sodium Lactate solution in propylene glycol was used. TEWL was measured three times at five sites on four Caucasian female subjects. The effect of propylene glycol on TEWL was used as a control. Baseline values were also established. Increasing the Sodium Lactate concentration from 5 to 10% w/w in the presence of both 10 and 20% urea resulted in a statistically significant decrease in TEWL, as did increasing the urea concentration from 10 to 20% w/w in the presence of 5 and 10% w/w Sodium Lactate. Sodium Lactate and urea did not demonstrate any interactions.

The forearms of three subjects used in determining the hydration effects of Sodium Lactate via impedance measurements were placed in a glovebox at 66% RH and 25°C for an equilibration period of 20 min (Clar et al., 1975). The modulus of the impedance vector (Z) at 25 Hz was measured in symmetrical sites on the distal face of the forearm. After α-relaxation parameters were determined at these conditions, a 10% aq. Sodium Lactate solution was applied to the test sites and allowed to dry for 30 min before rinsing. The parameters were then again measured. Both the relaxation time and Z were decreased, indicating that the skin was hydrated.

Fox et al. (1962) reported that lactate is a major constituent of the water-soluble fraction of back scrapings, callus, skin strippings, and scalp flakes. In examining the water sorption of this and the other constituents in a callus, it was found that Sodium Lactate absorbed much greater quantities of water than any of the other major water-soluble components of the stratum corneum, and it absorbed more water than glycerol and propylene glycol under the same conditions. The researchers concluded that "Sodium Lactate at low concentration enhances the water uptake of callus considerably."

MEDICAL/THERAPEUTIC SKIN EFFECTS

The data from clinical testings of AHAs included here are to provide a record of reported dermal effects. As stated earlier in this report,

portions of such information included in this section represent the opinions of researchers. Such information is included only to provide the full scope of information available on the ingredients in this report. The inclusion of these references is not an endorsement of their validity.

Fourteen patients, 11 males and 3 females, with various forms of ichthyosiform dermatoses were used to evaluate the therapeutic potential of more than 60 chemicals, including a number of AHAs (Van Scott and Yu, 1974). The test materials were dissolved in either water or ethanol, incorporated into a hydrophilic ointment of plain petrolatum, and applied twice daily to the appropriate test site for 2 weeks; all acids were at 5% concentration in hydrophilic ointment, pH not stated. Daily to weekly observations were made. Of the various classes of compounds tested, AHAs and closely related compounds were the most effective, providing 3+ (disappearance of scales from lesions) or 4+ (restoration to normal looking skin) improvement in all patients except one with epidermolytic hyperkeratosis. Ten percent ethyl and Methyl Glycolate provided 1+ improvement (slight improvement over that provided by vehicle alone). The comparative efficacy of the acids in therapy for lamellar ichthyosis was then tested in one patient by determining the time required for test sites that were treated three times daily with 5% concentrations of the acids in hydrophilic ointment to improve or be restored to normal appearing skin. Glycolic and Lactic Acid provided 2+ (substantial improvement of the lesions) improvement after 2 and 1 days, respectively, and 4+ improvement after 3 days of treatment. Larger body areas were then treated, providing information on potential irritancy. Whereas concentrations of 5–10% had been used on the test sites, 2–5% was used on larger areas or the whole body. However, the investigators found that degrees of irritancy encountered with 10% concentrations were mild, quickly detected, and readily reversed. Except for personal patient preference, the vehicle has not been a major determinant of final effectiveness. Van Scott and Yu (1977) later reported that oil-in-water vehicles, such as hydrophilic ointment USP, are preferred to water-in-oil vehicles because desquamation of the thickened stratum corneum occurs more rapidly. Biopsy specimens taken from treated and adjacent untreated skin of patients with lamellar ichthyosis had "distinct changes that suggest that these compounds (AHAs) may affect the epidermis primarily, and that this effect mediates a prompt influence of the keratinization process." Instead of a gradual dissolution of successive outer layers of the stratum corneum, an abrupt loss of the entire abnormal stratum corneum was observed. Also, epidermal thickness was greatly diminished. The investigators reported that AHAs altered keratinization in other pathologic conditions.

Some AHAs can cause epidermolysis and dermolysis (Yu and Van Scott, 1994). However, variable results have been obtained when using

70+% solutions of Glycolic and Lactic Acid as desquamative reagents, in part due to the presence of sebum or other liquid materials on the skin. Neutralization with ammonium or sodium hydroxide can cause even more variability because the bioavailability of the AHA is further compromised. Also, a potential for postinflammatory hyperpigmentation exists when AHAs are used as desquamative agents on dark skin.

Glycolic Acid

Thirty-four subjects completed a double-blind vehicle-controlled study that examined the effect of 50% Glycolic Acid on photoaged skin of the face, dorsal forearms, and hands (Newman et al., 1996). A 50% Glycolic Acid gel was applied to the face, forearm, and hands on the right side of each subject, and the vehicle was applied to the left side. The test gel was made with unneutralized, pharmaceutical-grade Glycolic Acid, pH 1.2. One milliliter of each gel was applied once every 7 days for 4 weeks by a dermatologist for 5 min, after which the areas were washed. Punch biopsies, 3.5 mm, were taken prior to dosing and at 5 weeks from both treated and control sites; clinical evaluations were also performed at these times. Statistically significant improvements were observed in rough texture, the number of solar keratoses, and the amount of fine wrinkling as compared to controls. Solar lentigines were slightly lighter in color at the Glycolic Acid-treated areas. Erythema, scaling, and irritant dermatitis were observed, and the subjects reported a mild stinging sensation upon application of Glycolic Acid. Postpeel erythema or scaling was not observed at 5 weeks, and scaling, hyper-, or hypopigmentation, or persistent erythema were also not observed. At light microscopy, a 53% decrease was observed in the stratum corneum layer treated with Glycolic Acid, reflecting the compaction of the basket-weaved stratum corneum, a 19% increase in epidermal thickness, and a 50% increase in the layer thickness and in the number of granules of the stratum granulosum. These changes were not observed for the control sites.

Seventeen subjects, 3 males and 14 females, were used in a study that examined the effects of AHAs on moderate to severe photoaged skin (Ditre et al., 1996). Groups of five, five, and seven subjects applied a lotion containing 25% Glycolic, Lactic, or Citric Acid, respectively, pH 3.5, to one forearm and a control lotion to the opposite forearm twice daily. (Citric Acid is included here because the results are not separated by acid but are given as an acid group.) The subjects were observed for an average of 6 months (range of 4–8 months). Skin thickness was measured 5 cm distal to the antecubital fold over the dorsal antebrachioradialis muscle. At the end of the study, 4-mm punch biopsies were taken from the test and control sites of eight subjects and an additional 3-mm punch biopsy was taken from six of these eight subjects for use in electron

microscopy. Two-layer skin thickness was significantly increased at the test site as compared to the control site; the AHA-treated site increased 25% from baseline, while the control site decreased 2% from baseline. No significant difference in response was observed among the acids. Microscopically, the mean epidermal thickness of the acid-treated sites was significantly greater than the control sites. Inflammation was not observed. The researchers reported that a "reversal of basal cell atypia, dispersal of melanin pigmentation, and a return to a more normal rete pattern" were observed. They also reported that "the basal layer of the epidermis showed a more uniform basal keratinocyte nuclei, less clumping of tonofilaments with the cytoplasm, and the formation of microvilli."

Ten subjects completed a pilot study that examined the effects of monthly serial 70% Glycolic Acid application for 4 months; five of the subjects also applied a moisturizer that contained 10% Glycolic Acid twice daily (Piacquadio et al., 1996). The monthly applications were initially for 3 min, and the time was increased by 1 min with each application. Clinical scoring, the number of actinic keratoses, and patient self-assessment were done prior to the study and at study termination. Three-millimeter punch biopsies were taken 2 weeks after the last application, and optical profilometry was done.

No conclusive differences were observed microscopically between the two groups. At study termination, patient self-evaluation noted significant improvement in both groups. Expert scoring recorded "notable" improvement in roughness and fine wrinkling; the changes were primarily seen in the group that applied the Glycolic Acid lotion daily. However, no statistically significant differences were observed between the two treatment groups. Optical profilometry evaluation reported mild improvement in three subjects that used the daily Glycolic Acid lotion and in one subject who received monthly applications only. Actinic keratosis counts improved in both groups.

A "leg regression efficacy assay" was conducted using 10 subjects with moderate to severe ichthyosis/xerosis of the lower legs and 8% Glycolic Acid, partially neutralized to pH 4.4, to examine the microscopic changes in the skin (DiNardo et al., 1994). After a 2-week pretrial conditioning program in which no moisturizers, sunscreens, or any other topical products were applied, the subjects applied Glycolic Acid to mapped sites (BID) daily for 3 weeks. Shave biopsies, which included the papillary dermis, were taken at study initiation, weekly during the study, and 1 week postapplication. Application of 8% Glycolic Acid resulted in a 25% reduction in the thickness of the stratum corneum and a 36% increase in thickness of the viable epidermis. Glycosaminoglycan content was increased 400% from the baseline value and collagen disposition increased 260% from baseline. Also in this leg regression efficacy assay, clinical evaluations for dryness, electroconductance (EC) values, and

TEWL measurements were made at study initiation, weekly during the study, and 1 week postapplication. A 73% decrease in skin roughness was observed as determined by an expert grader. EC measurements demonstrated a 302% increase in skin moisture, and desorption curve data reported that the skin's ability to bind water was increased by 75%. TEWL values indicated a 43% increase in water loss.

DiNardo et al. (1996b) performed a leg regression assay following the procedures described in DiNardo et al. (1994), with the exception that two groups of 10 subjects with moderate to severe ichthyosis/xerosis were used. Group I received applications of an 8% Glycolic Acid formulation at a pH of 3.25, 3.80, or 4.40. Group II received applications of a formulation with a pH of 3.80 containing 3.25, 6.50, 9.75, or 13% Glycolic Acid. For group I, a 22, 32, and 25% reduction in stratum corneum thickness and an 18, 21, and 36% increase in viable epidermis thickening was observed with a pH of 3.25, 3.80, and 4.40, respectively. Glycosaminoglycan content was increased by 350, 33, and 300% over baseline and collagen deposition was increased by 54, 128, and 160% over baseline for pH 3.25, 3.80, and 4.40, respectively. For group II, a 44, 55, and 22% reduction in stratum corneum thickness and a 50, 56, and 42% increase in viable epidermis thickening was observed with 3.25, 6.50, and 9.75% Glycolic Acid, respectively. However, a 23% increase in stratum corneum thickness and a 25% decrease in viable epidermis was observed with 13% Glycolic Acid. Glycosaminoglycan content was increased by 267, 167, 25, and 167% over baseline and collagen deposition was increased by 29, 21, 55, and 250% over baseline with 3.25, 6.50, 9.75, and 13% Glycolic Acid, respectively. In this assay, effects on hydration were again examined using EC and TEWL. For group I, a 41, 66, and 73% decrease in skin roughness was observed, as determined by an expert grader, for the 8% Glycolic Acid formulation at pH 3.25, 3.80, and 4.40, respectively. EC measurements reported a 197, 203, and 302% increase in skin moisture content for the pH 3.25, 3.80, and 4.40 formulations, respectively. Desorption curve data indicated that the skin's ability to bind water was increased by 60–70%. TEWL values indicated a slight increase in water loss compared to baseline values; the difference "was not considered clinically meaningful." For group II, a 38, 36, 38, and 44% decrease in skin roughness was observed, as determined by an expert grader, for the 3.25, 6.50, 9.75, and 13% Glycolic Acid formulations, respectively. EC measurements indicated a 162, 144, 163, and 144% increase in skin moisture content for the 3.25, 6.50, 9.75, and 13% formulations, respectively. Desorption curve data indicated that the skin's ability to bind water was increased by 70–80% for concentrations of 6.50–13% Glycolic Acid and by 40% for 3.25% Glycolic Acid. TEWL values indicated a slight increase in water loss compared to baseline values; again, the difference "was not considered clinically meaningful."

The effect of Glycolic Acid on skin hydration and TEWL was evaluated using 30 subjects, 15 males and 15 females, that had atopic dermatitis (Morganti et al., 1996a). A day and a night cream containing 10% Glycolic Acid, gelatin, glycine, and arginine, pH 5.5, were each applied to the forearm for 30 days. Ten normal subjects served as a control group. TEWL and capacitance values were measured prior to application of the creams and after 30 days. Prior to application, TEWL values for atopic and normal skin were approximately 35 and 5 $g/m^2\ h^{-1}$, respectively, and capacitance values were approximately 11 and 95 (arbitrary units), respectively. After 30 days of application of the creams, TEWL values for atopic and normal skin were both approximately 5 $g/m^2\ h^{-1}$, and capacitance values were approximately 75 and 91, respectively.

The effect of 10% Glycolic Acid on the hydration of psoriatic skin was also examined (Morganti et al., 1996a). Groups of 12 and 13 female subjects applied creams, pH 5.5, containing 10% Glycolic Acid, gelatin, glycine, and either arginine or lysine, respectively, to one forearm and vehicle to the other forearm twice daily for 30 days. Five subjects were used as an untreated control group. Hydration was measured every 5 days. Skin hydration values were greater throughout the study for the areas to which the Glycolic Acid creams were applied.

A study was performed that compared the pathological changes induced by the application of 70% Glycolic Acid and 35% trichloroacetate (TCA), alone and in various combinations, to a non-sun-damaged area of the arm of a patient with Fitzpatrick type II skin (Murad and Shamban, 1994a). Microscopic examination of the skin was made at 2 days, 2 weeks, 2 months, and 19 months. At 2 days, the Glycolic Acid-treated skin had epidermal spongiosis whereas upper epidermal necrosis was observed in the skin treated with TCA. The skin treated with Glycolic Acid, TCA, and Jessner's solution (14% Lactic Acid, 14% salicylic acid, and 14% resorcinol in an ethanol base [Premo, 1995]) had massive necrosis of the epidermis. At 2 weeks, the skin treated with Glycolic Acid had a mild acanthosis, and the TCA-treated skin had epidermal acanthosis. Orthokeratosis, mild acanthosis, and a perivascular infiltrate were observed in the skin treated with the combination. At 2 months, the epidermis was similar for all three specimens. However, the Glycolic Acid-treated area had a greater increase in collagen and elastin fibers as compared to the combination-treated skin. At 19 months, the skin had features of its prepeel state. The researchers stated that the preliminary results indicated that Glycolic Acid induced more changes in the papillary dermis than in the epidermis, and the reverse was true for TCA. Therefore, they argued that, theoretically, by prewounding the skin with TCA instead of Glycolic Acid, the increased epidermolysis allows deeper penetration of Glycolic Acid, augmenting its dermal effects.

Seven Glycolic Acid formulations, 50–70% and pH range 0.08–2.75, were applied to the unpretreated forehead of one male subject and the

Table 30. Effect of Glycolic Acid on elderly skin with actinic damage

	Subject 1	Subject 2
70% Glycolic Acid, pH 0.6	Epidermal crusting; focal subepidermal vesiculation	Epidermal crusting; partial epidermal necrosis; upper dermal perivascular infiltration
70% Partially Neutralized Glycolic Acid, pH 1.8	Normal stratum corneum	Focal epidermal spongiosis; epidermal crusting
70% Partially Neutralized Glycolic Acid, pH 2.25	Focally absent stratum corneum; focal parakeratosis	Remnant of stratum corneum
70% Partially Neutralized Glycolic Acid, pH 2.75	Normal stratum corneum	Remnant of stratum corneum; epidermal spongiosis
70% Esterified Glycolic Acid, pH 0.08	Epidermal scaling and crusting; focal subepidermal vesiculation	Epidermal spongiosis; upper dermal lymphocytic infiltrate
50% Glycolic Acid, pH 1.0	Absent stratum corneum; basal cell degeneration; upper dermal edema	Remnant of stratum corneum
50% Glycolic Esterified Acid, pH 0.08	Focal parakeratosis; thinned stratum corneum	Remnant of stratum corneum

preauricular skin of another male subject; both subjects were elderly and had skin with actinic damage (Becker et al., 1996). The test solutions were applied by wetting the skin and neutralizing the formulation after 30 min. After 48 h, 2-mm punch biopsies were taken and examined microscopically. The results are shown in Table 30.

A study was performed in which a micropeel was performed with and without 30% Glycolic Acid using 10 and 5 female subjects, respectively, whose skin had signs of environmental damage but who did not have any systemic or dermatological disorders (Milmark Research, Inc., 1994). For the test group, on day 1, the face was cleaned with a cleanser and acetone, the facial skin was dermaplaned, a 30% Glycolic Acid solution was applied for a maximum of 2 min, the skin was neutralized with sodium bicarbonate solution, and an iceball (CO_2 [dry ice] in gauze dipped in acetone) was rolled over the skin. The same method was followed for the control group with the exception that the Glycolic Acid step was deleted. The micropeel was performed at 2, 4, 6, 8, 10, and 12 weeks for the test group and at 2, 4, and 6 weeks for the control group. The subjects were

strongly encouraged to follow a home regimen which included applying 4% hydroquinone cream or 3% Melanex and 0.1% Retin-A daily unless otherwise instructed. Ultrasound B-mode scans of the skin were done using the left outer canthus of the eye on six subjects of the test group comparing day 1 to weeks 2, 6, and 12 and on three subjects of the control group comparing day 1 to weeks 2 and 6.

For the test group at week 2, decreased density of the epidermis and dermis, indicating increased hydration, was observed for two of the subjects and increased cellularity with a uniformity of skin structure and increased density of epidermal and dermal component were observed in three of the subjects. At week 6, decreased density of the epidermis and dermis was observed in three of the subjects and increased cellularity and increased density of epidermal and dermal components were observed in two of the subjects. For one subject, decreased density of the dermis, increased cellularity, and increased density of epidermal components were observed. A week 10 scan was done in one subject and decreased density of the epidermis and dermis was observed. At week 12, one subject had decreased density of the epidermis and dermis, three subjects had increased cellularity and increased density of the epidermal and dermal components, and one subject had decreased density of the dermis, increased cellularity, and increased density of epidermal components. For the control subjects at week 2, one subject had decreased density of the epidermis and dermis, one had increased cellularity and increased density of the epidermal and dermal components, and one had no changes. The same observations were made at week 6.

Glycolic Acid is used in the treatment of acne because it can interfere with the abnormal keratinization associated with acne and can "unroof" the developing papule (Murad and Shaman, 1994b). Glycolic Acid has synergistic behavior with topical tretinoin in the treatment of acne.

The depigmenting activity of creams, pH 5.5, containing 10% Glycolic Acid, 10% Glycolic Acid and gelatin, glycine, and arginine, or 10% Glycolic Acid and gelatin, glycine, and lysine were evaluated using three groups of 10 female subjects (Morganti et al., 1996a). The creams were applied twice daily for 3 months to the back of one hand that had hyperpigmented lentigo; the other hand served as an untreated control. The intensity of the color was measured with a chromameter. All three formulations statistically significantly lightened the age spots, with the most noticeable depigmentation occurring with the Glycolic Acid, gelatin, glycine, and arginine and Glycolic Acid, gelatin, glycine, and lysine formulations.

Lactic Acid

Ammonium Lactate. In the leg regression efficacy assay described earlier by DiNardo et al. (1994), the pathologic changes produced by

12% Ammonium Lactate, pH 4.4, were also evaluated using 10 subjects with moderate to severe ichthyosis/xerosis of the lower legs. Application of 12% Ammonium Lactate resulted in a 41% reduction in the thickness of the stratum corneum and a 4% decrease in thickness of the viable epidermis. Glycosaminoglycan content was increased 200% from the baseline value and collagen disposition increased 210% from baseline. DiNardo et al. (1994) also examined the effects of application of 12% Ammonium Lactate on hydration by use of EC and TEWL in this assay. An 82% decrease in skin roughness was observed as determined by an expert grader. EC measurements indicated a 333% increase in skin moisture and desorption curve data indicated that the binding of water by the skin was increased by 66%. TEWL values indicated a 24% increase in water loss.

A double-blind study was conducted using 40 female subjects with xerosis, minimum severity 5/9, to determine the effects of Ammonium Lactate (Morganti et al., 1996b). Eight or 14% ammonium gelatin–glycine–arginine–lactate lotions were applied to one side of the face, lower legs, or the forearm twice daily for 4 weeks and compared to the vehicle, which was applied to the opposite side. Each formulation was applied with and without a 2-week pretreatment period. TEWL, hydration, and surface lipids were measured 4 weeks prior to dosing, at weeks 2, 4, 8, and 12 of dosing, and after 16 and 20 weeks. The amino acid content of the skin was determined 4 weeks before dosing, at weeks 4 and 12 of dosing, and after 16 and 20 weeks. Stratum corneum turnover time was also determined using dansyl chloride in petrolatum. Both test formulations statistically significantly increased TEWL, skin hydration, and surface lipids, with average increases of 12–20%, 50–63%, and 26–30%, respectively. Greater and faster results were seen with the 14% formulation. The increases were still observed after treatment was discontinued. Amino acid content also was increased significantly. Epidermal renewal time increased 20% using the vehicle alone and increased 50 and 80% upon application of the 8 and 14% lotions.

Two groups of 30 female subjects with xerosis on both lower legs, minimum severity 7/9, were used in a double-blind study to examine the effects of Ammonium Lactate (Morganti et al., 1994b). The two groups applied base lotions containing 8 or 14% Ammonium Lactate to their lower legs twice daily for 28 days after using a bath oil that contained Ammonium Lactate (concentration not stated) and other ingredients. The severity of xerosis was evaluated on days 0, 4, 7, 14, 21, and 28. TEWL, skin hydration, and the amount of surface lipids were also measured. After 28 days of treatment, during the regression phase, the 8% group discontinued applying lotion. The 14% Ammonium Lactate group applied the 8% lotion for an additional 21 days. Evaluations were made on days 28, 35, 42, and 49. Within 1 week, the severity of xerosis was significantly decreased for the legs treated with Ammonium Lactate as

compared to the vehicle controls. On days 14, 21, and 28, the scores were significantly lower for the 14% group as compared to the 8% group. Skin hydration and the amount of surface lipids were also improved for both test lotions and the vehicle. The improvement in severity scores was maintained for both groups during the regression phase.

Twenty-four female subjects with dry skin, nine of which had atopic dermatitis, applied an oil-in-water emulsion of 12% Ammonium Lactate, pH not specified, to their legs twice daily for 1 month (Vilaplana et al., 1992). Clinical evaluations for dryness, desquamation, folliculitis, and pruritus, biophysical noninvasive measurements, i.e., skin hydration via EC, skin surface lipid level, TEWL, and skin surface topography, and measurement of the biomechanical properties of the skin, i.e., extensibility and firmness, were performed prior to study initiation, after 14 days, and at the termination of treatment; scores were assessed for 24 subjects on day 15 and for 22 subjects on day 30. Stinging and irritation were not reported. Dryness, desquamation, and pruritus were significantly reduced by day 15, and the scores on day 30 were not significantly different than those recorded on day 15. EC and lipid content of the skin were significantly increased from initial values after 15 and 30 days, but TEWL was not. Skin surface topography, evaluated by scanning electron microscopy and image analysis, was reduced in roughness and there was a smoothing and flattening of the skin. Extensibility and firmness were significantly improved after 15 and 30 days.

Ethyl Lactate. Ten percent Ethyl Lactate in formulation with glycerol and ethanol and applied as a lotion or under occlusive patches was effective in treating acne (Opdyke and Letizia, 1982). Application of a 5% solution of Ethyl Lactate to female patients with facial seborrhea resulted in skin clearing and decreased oiliness, with a decrease in lipolytic activity of the sebum.

DERMAL IRRITATION: COSMETICS

Yu and Van Scott (1996) stated that stinging and irritation upon application of an AHA-containing product can be due to a low pH of the formulation, the AHA itself, or the organic or inorganic alkali used in partial neutralization. They have found "that Glycolic Acid or Lactic Acid formulations are more irritating to sensitive skin or atopic skin when ammonium hydroxide instead of organic amines are used for partial neutralization."

Glycolic Acid

A mini-cumulative irritation patch assay was performed on a variety of cosmetic formulations containing Glycolic Acid (CTFA, 1995h). Approximately 0.2 mL of the material was applied undiluted to the back under

an occlusive patch for 4 consecutive days. The patches were removed approximately 24 h after each application. Irritation was scored 5 h after removal of the fourth patch. The sites were not scored daily; however, if a score of 2/4 (moderate erythema) was observed following immediate removal of any patch, no further patching was done and the score was recorded under that patch application and as the final score. The results of the mini-cumulative irritation patch assays using Glycolic Acid are summarized in Table 31.

Three groups of 10 female subjects with normal to dry and slightly sensitive skin were used to evaluate the irritation potential of three creams that contained 10% Glycolic Acid (Morganti et al., 1996a). A day and night cream, pH 5.5, containing Glycolic Acid and vehicle, Glycolic Acid, vehicle, gelatin, glycine, and arginine, or Glycolic Acid, vehicle, gelatin, glycine, and lysine were applied to one side of the face for 7 days. The vehicle only was applied to the other side of the face. Erythema was evaluated on a scale of 0–3 on days 0–7 and on day 15. Scores of ≥ 2 were observed on days 0–7 with the Glycolic Acid-only containing cream, while scores of <1 were observed for the other two creams and the vehicle. A score of <1 was observed for the Glycolic Acid-only cream on day 15, while scores of 0 were observed for the other creams and the vehicle.

Table 32 presents the results of a series of 14-day cumulative irritation assays; the cumulative values are presented as well as the normalized scores. The normalized scores are interpreted as follows: 0–0.23, no experimental irritation; 0.24–0.95, probably mild in normal use; 0.96–2.14, possibly mild in normal use; 2.15–2.76, experimental cumulative irritant; 2.77–3.0, experimental primary irritant. The maximum value of 3.0 corresponds to the maximum cumulative irritation score (e.g., 966).

A 14-day cumulative irritation assay was performed using 21 subjects in which 0.2 mL of 8% Glycolic Acid, partially neutralized, pH 4.4, was applied under a semi-occlusive patch to the upper back of each subject daily for 14 days (DiNardo et al., 1994). The patches were applied for 24 h during the week and for 48 h on Saturday for 2 weeks. Test sites were scored daily for erythema on a scale of 0–4. Glycolic Acid, 8% with pH 4.4, had an irritation value of 1/882; this corresponds to a normalized score of 0.003.

A 14-day cumulative irritation assay was also performed using 21 subjects with creams containing 9 and 13% Glycolic Acid and lotions containing 8 and 13% Glycolic Acid, all at pHs of 3.25, 3.80, and 4.40 (DiNardo, 1994). The cumulative irritation values for 8% Glycolic Acid were 1/882, 49/882, and 119/882 at pH 4.40, 3.80, and 3.25, respectively; the normalized scores were 0.003, 0.17, and 0.40, respectively. A 13% Glycolic Acid formulation (not stated whether cream or lotion), pH 4.40, had a cumulative value of 33/882, corresponding to a normalized value of 0.11; this value was compared with a marketed 12% Lactic Acid

Table 31. Clinical cumulative irritation potential of Glycolic Acid applied under occlusive patch for four consecutive days

Product form	Conc. (%)	pH	Number of subjects	PII[a]	Drops[b]	Conclusion
Cream	2.0	3.7	20	0.63	0	Mildly irritating
Lotion	2.0	3.9	20	0.78	0	Mildly irritating
Lotion	2.0	4.0	20	0.65	0	Mildly irritating
Cream	4.0	3.7	20	0.30	0	Essentially nonirritating
Cream	4.0	3.7	20	0.33	0	Slightly irritating
Cream	4.0	3.7	19	0.79	0	Mildly irritating
Cream	4.0	3.7	20	0.83	0	Moderately irritating
Cream	4.0	3.7	20	0.95	1	Moderately irritating
Lotion	4.0	3.7	19	1.03	0	Moderately irritating
Cream	4.0	3.7	20	1.03	0	Moderately irritating
Cream	4.0	3.7	20	1.03	1	Moderately irritating
Cream	4.0	3.7	20	1.08	1	Moderately irritating
Cream	4.0	3.7	20	1.25	1	Moderately irritating
Cream	4.0	3.7	19	1.29	2	Moderately irritating
Cream	4.0	3.7	19	1.32	0	Moderately irritating
Cream	4.0	3.7	19	1.47	0	Moderately irritating
Cream	4.0	3.7	20	1.60	2	Severely irritating
Cream	4.0	3.8	20	0.28	0	Essentially nonirritating
Cream	4.0	3.8	19	0.45	0	Slightly irritating
Cream	4.0	3.8	20	0.55	0	Mildly irritating
Lotion	4.0	3.8	20	1.20	1	Moderately irritating
Cream	4.0	3.8	20	1.40	1	Moderately irritating
Cream	4.0	3.9	20	0.23	0	Essentially nonirritating
Lotion	4.0	3.9	20	0.33	0	Slightly irritating
Cream	4.0	3.9	19	0.42	0	Slightly irritating
Lotion	4.0	3.9	19	0.55	0	Mildly irritating
Lotion	4.0	3.9	20	1.03	1	Moderately irritating
Cream	4.0	3.9	20	1.25	3	Moderately irritating
Lotion	4.0	4.0	20	1.15	1	Moderately irritating
Cream	8.0	3.6	20	0.72	0	Mildly irritating
Lotion	8.0	3.7	19	0.89	0	Moderately irritating
Lotion	8.0	3.7	19	1.08	0	Moderately irritating
Lotion	8.0	3.7	19	1.11	0	Moderately irritating
Lotion	8.0	3.8	19	0.92	0	Moderately irritating
Cream	8.0	3.8	20	1.08	2	Moderately irritating
Cream	8.0	3.8	20	1.53	4	Severely irritating
Cream	8.0	4.0	20	0.45	0	Slightly irritating
Lotion	10.0	3.6	20	1.25	2	Moderately irritating
Cream	10.0	3.9	20	0.53	0	Mildly irritating
Cream	10.0	3.9	20	0.63	0	Mildly irritating
Cream	10.0	3.9	20	1.25	3	Moderately irritating

[a]PII = Primary irritation index.

[b]Drops denotes the number of test subjects that had a grade 3 response and did not receive all four patches.

Table 32. Results of 14-day cumulative irritation assays using Glycolic Acid

pH	Conc. (%)	Cumulative value	Normalized value	Indication	Reference
2	10	768/966	2.39	Experimental cumulative irritant	DiNardo, 1995
2.4	5	770/966	2.38	Possibly mild in normal use	DiNardo, 1995
2.5	10	746/966	2.31	Experimental cumulative irritant	DiNardo, 1995
3	10	631/966	1.96	Possibly mild in normal use	DiNardo, 1995
3.25	8	119/882	0.40	Probably mild in normal use	DiNardo, 1994
3.25	9	481/966	1.49	Possibly mild in normal use	DiNardo, 1995
3.25	10	404/966	1.25	Possibly mild in normal use	DiNardo, 1995
3.6	8	148/966	0.46	Probably mild in normal use	DiNardo, 1995
3.6	8	258/966	0.80	Probably mild in normal use	DiNardo, 1995
3.8	8	49/882	0.17	No experimental irritation	DiNardo, 1994
3.8	9	7/882	0.02	No experimental irritation	DiNardo, 1994
3.8	10	38/966	0.12	No experimental irritation	DiNardo, 1995
3.8	10	21/882	0.07	No experimental irritation	DiNardo, 1994
3.8	15	14/966	0.04	No experimental irritation	DiNardo, 1995
3.8	20	37/966	0.11	No experimental irritation	DiNardo, 1995
4.4	8	1/882	0.003	No experimental irritation	DiNardo, 1994
4.4	8	1/882	0.003	No experimental irritation	DiNardo et al., 1994
4.4	10	18/966	0.06	No experimental irritation	DiNardo, 1995
4.4	12	30/882	0.10	No experimental irritation	DiNardo, 1994
4.4	13	33/882	0.11	No experimental irritation	DiNardo, 1994

product, pH 4.40, that had a cumulative value of 30/882 and a normalized value of 0.10. The 9% Glycolic Acid cream at pH 3.80 had a cumulative value of 7/882 and a normalized value of 0.02 and was compared to a marketed 10% Glycolic Acid product, pH 3.80, that had a cumulative value of 21/882 and a normalized value of 0.07. Figure 4 shows the cumulative irritation as a function of Glycolic Acid concentration, vehicle pH, and vehicle type, and compares these values to two marketed AHA products. The researcher stated that "it appears that the Glycolic Acid irritation potential is regulated by a pH mechanism and is not concentration dependent for the concentrations tested."

A 14-day cumulative irritation assay using 23 subjects was performed with a formulation containing 10% Glycolic Acid at pH 2.0, 2.5, 3.0, 3.25, 3.8, and 4.4 to examine the effect of the pH of a formulation on cumulative irritation (DiNardo, 1995). Formulations containing 15 and 20% Glycolic Acid, pH 3.8, and four available formulations containing 5–9% Glycolic Acid, pH 2.4–3.6, were also used. Approximately 0.2 ml of each test material was applied to the upper back of each subject under semi-occlusive patches for 24 h during the week and for 48 h on Saturday for 2 weeks. The test sites were evaluated daily for erythema on a scale of 0–4, and the scores were calculated via summation of the irritation values for each day. The maximum score per product was 966. For the 10% formulation, the following cumulative scores were reported: pH 2.0, 768; pH 2.5, 746; pH 3.0, 631; pH 3.25, 404; pH 3.8, 38; pH 4.4, 18; these scores corresponded to normalized values of 2.38, 2.31, 1.96, 1.25, 0.12, and 0.06, respectively. The 15 and 20% Glycolic Acid formulations, pH

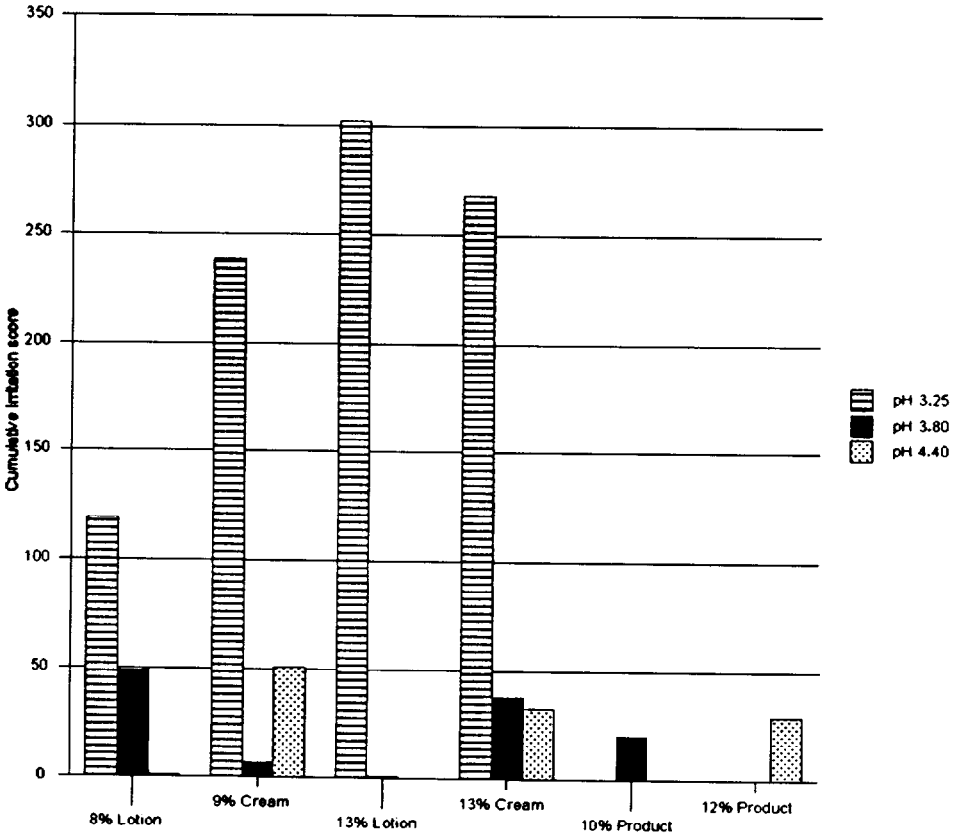

Figure 4. Cumulative irritation scores in 21 subjects using creams containing 9 and 13% Glycolic Acid and lotions containing 8 and 13% Glycolic Acid, each at three pH levels, 3.25, 3.80, and 4.40, compared to a marketed 12% Lactic Acid product at pH 4.40 and a marketed 10% Glycolic Acid product at pH 3.80 (maximum irritation score = 882) (DiNardo, 1994).

3.8, had cumulative values of 14 and 37, respectively, and normalized values of 0.04 and 0.11, respectively. Commercially available Glycolic Acid formulations had the following cumulative values/normalized values: 5.0% and pH 2.4, 770/2.39; 9.0% and pH 3.25, 481/1.49; 8.0% and pH 3.6, 258/0.80; 8.0% and pH 3.6, 148/0.46. The cumulative irritation of all products tested (the commercial formulations being marked with an asterisk) are presented graphically in Figure 5 as a function of pH and in Figure 6 as a function of concentration. The researcher concluded that "a product's pH, as opposed to Glycolic Acid content and/or formula composition, appears to be the major contributing factor governing cumulative irritation potential."

A 21-day cumulative irritation assay was completed using 18 of 21 subjects in which eight test materials, four of which were Glycolic Acid-containing creams with a pH range of 3.8–4.0, were applied to sites on the paraspinal region of the back under occlusive patches for 23±1 h; the

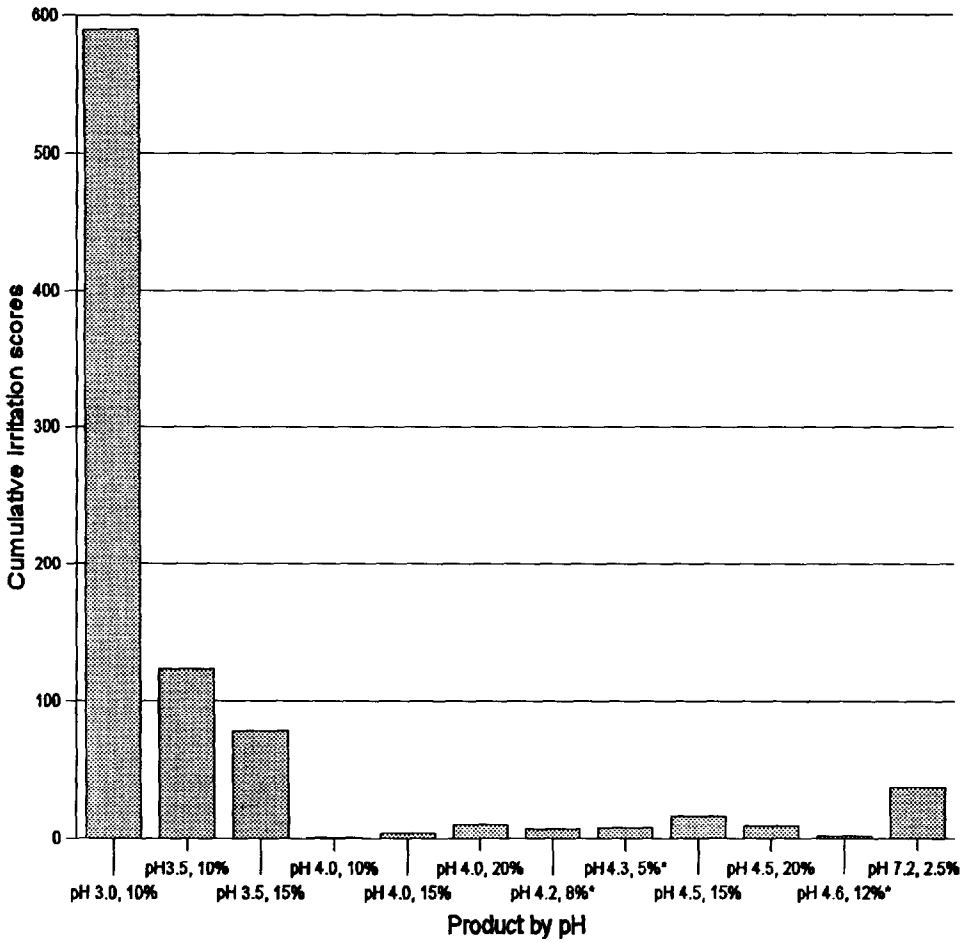

Figure 5. Cumulative irritation scores (maximum score = 966) as a function of pH of Glycolic Acid treatment. A total of 23 subjects were tested with a formulation containing 10% Glycolic Acid at pH 2.0, 2.5, 3.0, 3.25, 3.8, and 4.4. Formulations containing 15 and 20% Glycolic Acid at pH 3.8, and four commercially available formulations containing 5–9% Glycolic Acid at pH 2.4–3.6 (see asterisk) were also used for comparison (DiNardo, 1995).

sites were scored 24 h after patch removal and new patches were applied (Hill Top Research, 1994a). A positive control, 0.1% sodium lauryl sulfate (SLS), and a negative control, saline, were applied to two of the sites. Applications were made for 21 consecutive days. Group total scores (base 10) of 57.4 and 93.1 were obtained for two creams containing 4% Glycolic Acid; these creams were classified as "probably mild in normal use." Group total scores (base 10) of 225.2 and 267.8 were obtained for two creams containing 8% Glycolic Acid; these creams were classified as "possibly mild in normal use." No adverse effects were reported. A 21-day irritation assay was completed using 14 of 15 subjects following

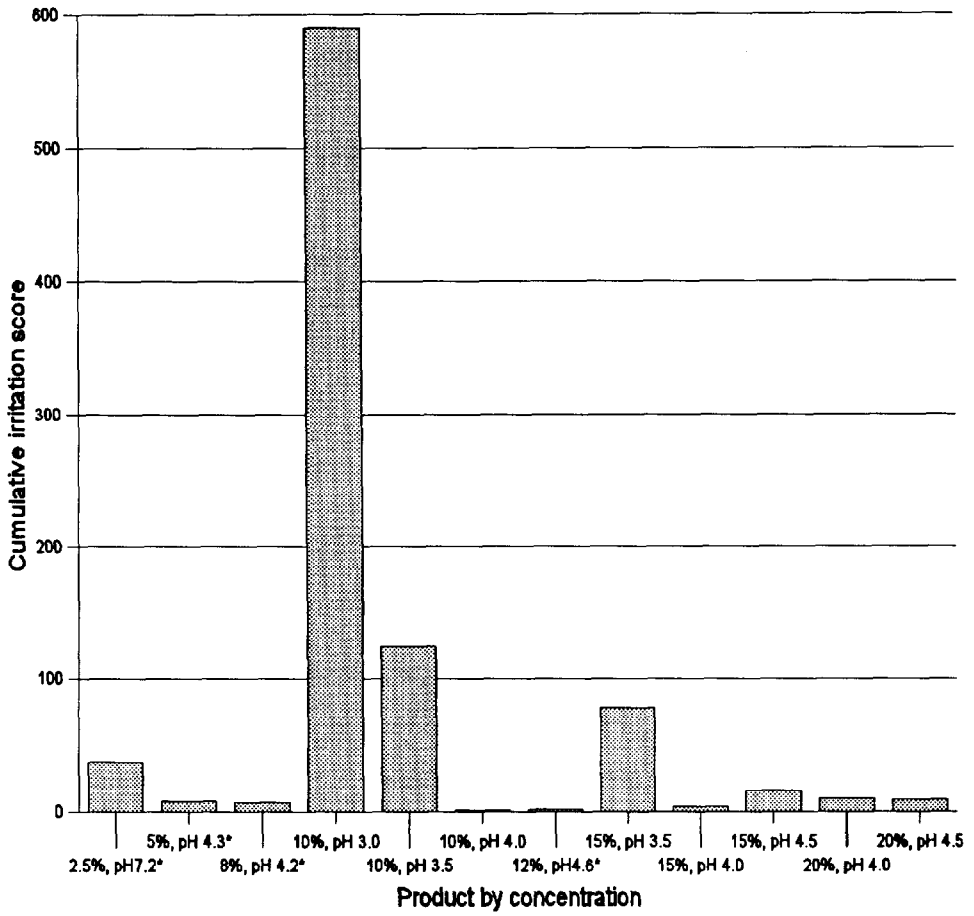

Figure 6. Cumulative irritation scores as described in Figure 5 as a function of concentration of the preparation. Asterisk denotes commercial preparations (DiNardo, 1995).

the same procedure as above (Hill Top Research, 1994b). Glycolic Acid-containing lotions were applied to four of the sites; the same positive and negative controls were used. Group total scores (base 10) of 135.1 and 158.5 were obtained for two lotions containing 4% Glycolic Acid; these lotions were classified as "probably mild in normal use." Group total scores (base 10) of 338.3 and 374.3 were obtained for two lotions containing 8% Glycolic Acid; these lotions were classified as "possibly mild in normal use." No adverse effects were reported.

A 21-day irritation assay was completed using 16 of 18 subjects following the same procedure as above with the exception that nine materials were tested (Hill Top Research, 1995). Lotions containing 8% Glycolic Acid were applied to six of the sites; the same positive and negative controls were used. Group total scores (base 10) of 73.8, 191.1, and 194.3 were obtained for three of the Glycolic Acid lotions, and these were

classified as "probably mild in normal use." Group total scores (base 10) of 211.1, 221.8, and 225.0 were obtained for the other three Glycolic Acid lotions, and these were classified as "possibly mild in normal use." No adverse effects were reported.

A single-insult patch test was performed by Avon using cosmetic formulations containing 4–10% Glycolic Acid (CTFA, 1994c). The PII was 0.03–0.50.

The primary irritancy potential of a mixed fruit acid (MFA) product containing 38–39% sugar cane extract (assumed to be Glycolic Acid) was determined by applying 10% MFA once daily for 10 days using nonocclusive patches to the volar forearms of 15 subjects, 6 males and 9 females (Dermatech of Conn., Inc., 1993). Lactic Acid, 4%, was used as a control. Clinical evaluations were made daily. Three subjects reacted to Glycolic Acid, with mild erythema being observed for two subjects on day 8 and three subjects on days 9 and 10. A total of seven subjects reacted to Lactic Acid; mild erythema was observed in one subject on days 3 and 5, two subjects on days 4 and 7–9, three subjects on day 6, and four subjects on day 10; moderate erythema was observed in one subject on day 7 and for two subjects on days 8–10.

A test was performed in which 20 female subjects applied a lotion containing 10% Glycolic Acid, pH 3.8, to arms, hands, and legs twice daily for 14 days (CTFA, 1991b). Three subjects had a history of eczema and developed the following responses on the last day of dosing: One subject had diffuse grade 1 erythema on the outer left forearm; one subject had diffuse grade 1 erythema on the outer right and left forearms; one had a small erythematous patch on the outer right forearm and approximately nine small excoriated papules above the left ankle. Five subjects experienced substantial stinging when the product was applied to freshly shaved legs.

A 3-month study was performed in which 25 female subjects applied a lotion containing 10% Glycolic Acid, pH 3.8, twice daily to the arms, legs, and hands; the lotion was not to be applied within 24 h of shaving (CTFA, 1992a). Subjective discomfort, i.e., mild itching and burning, was reported by a total of six subjects (24%); clinical irritation, i.e., mild erythema in the flexural area and general irritation was reported by five (20%) and two (8%) subjects, respectively. Subjective and clinical irritation was reported for a total of eight (32%) of the subjects, with onset for three (12%) subjects occurring during the first 2 weeks and for five (20%) subjects occurring during weeks 3–7. One subject, who had significant irritation, was sensitized to the fragrance in the lotion.

A number of facial discomfort assays were performed using a procedure similar to that developed by Frosch–Kligman (in which the thermal chamber is eliminated) on formulations containing Glycolic Acid to measure their potential to cause facial stinging (CTFA, 1995i). Female subjects, who were selected for their high degree of sensitivity to

topically applied materials and who were screened with 10% aq. Lactic Acid, were used in a 1-day split face test in which 0.4 mL of the test or control material was applied to the subject's face from the nasolabial fold to the upper cheek area; the product was not rubbed in. Water was used as the negative control. The subjects recorded all sensations at 0, 2.5, and 5.0 min and rated the intensity of the response. The delayed mean sting score (DMS) was calculated by averaging the intensity of discomfort at 2.5 and 5.0 min. These studies are summarized in Table 33.

Table 33. Human facial discomfort assay using Glycolic Acid

Product form	Conc. (%)	pH	Number of subjects	Discomfort[a]	TSS[b]	DMS[c]	Discomfort category[d]
Lotion	2.0	3.8	20	13	21.0	0.43	Nonstinging
Cream	4.0	3.7	19	9	15.0	0.32	Nonstinging
Cream	4.0	3.7	15	9	21.5	0.33	Nonstinging
Cream	4.0	3.7	22	14	16.5	0.36	Nonstinging
Cream	4.0	3.7	22	14	16.5	0.36	Nonstinging
Cream	4.0	3.7	22	14	20.0	0.38	Nonstinging
Cream	4.0	3.7	19	10	19.5	0.45	Nonstinging
Cream	4.0	3.7	22	12	26.0	0.50	Nonstinging
Lotion	4.0	3.7	22	15	31.5	0.55	Slight
Cream	4.0	3.7	18	14	22.5	0.56	Slight
Cream	4.0	3.7	22	15	29.5	0.58	Slight
Cream	4.0	3.7	20	15	29.5	0.60	Slight
Cream	4.0	3.7	19	14	27.5	0.61	Slight
Cream	4.0	3.7	22	17	32.0	0.61	Slight
Cream	4.0	3.7	20	14	28.5	0.65	Slight
Cream	4.0	3.7	20	15	30.5	0.68	Slight
Cream	4.0	3.7	20	15	34.0	0.73	Slight
Cream	4.0	3.7	20	15	34.0	0.73	Slight
Lotion	4.0	3.8	20	13	21.5	0.41	Nonstinging
Lotion	4.0	3.8	20	11	20.0	0.46	Nonstinging
Cream	4.0	3.8	22	16	37.0	0.75	Slight
Cream	4.0	3.8	21	17	50.0	0.92	Moderate
Cream	4.0	3.8	20	16	51.5	0.98	Moderate
Lotion	4.0	3.9	22	10	23.0	0.40	Nonstinging
Lotion	4.0	3.9	20	12	24.5	0.50	Nonstinging
Lotion	4.0	3.9	20	14	28.0	0.54	Slight
Cream	4.0	4.6	21	13	27.5	0.51	Slight
Cream	4.0	5.4	21	16	32.5	0.60	Slight
Cream	8.0	3.5	19	15	40.0	0.97	Moderate
Cream	8.0	3.6	21	17	31.0	0.58	Slight
Cream	8.0	3.6	22	17	45.0	0.80	Slight
Lotion	8.0	3.7	22	13	25.5	0.42	Nonstinging
Lotion	8.0	3.7	22	14	31.5	0.54	Slight
Cream	8.0	3.8	19	15	43.0	0.95	Moderate
Cream	8.0	3.8	20	18	71.0	1.23	Moderate
Cream	8.0	3.9	21	10	24.5	0.45	Nonstinging

(Table continued on next page.)

Table 33. Human facial discomfort assay using Glycolic Acid (*continued*)

Product form	Conc. (%)	pH	Number of subjects	Dis-comfort[a]	TSS[b]	DMS[c]	Discomfort category
Cream	8.0	3.9	22	15	34.0	0.60	Slight
Cream	8.0	3.9	22	15	34.0	0.60	Slight
Cream	8.0	4.0	21	13	22.5	0.36	Nonstinging
Cream	8.0	4.0	20	15	32.0	0.73	Slight
Cream	8.0	4.3	21	8	10.0	0.21	Nonstinging
Lotion	10.0	3.7	19	17	54.5	1.09	Moderate
Lotion	10.0	3.8	20	17	57.5	1.09	Moderate
Cream	10.0	3.9	20	12	22.5	0.48	Nonstinging
Cream	10.0	3.9	20	15	28.5	0.60	Slight
Cream	4% w/2% Lactic Acid	3.8	19	9	18.5	0.36	Nonstinging

[a]Discomfort denotes the number of test subjects that perceived discomfort.
[b]TSS denotes the total sting score, which is the sum of all scores at 0, 2.5, and 5.0 min.
[c]DMS denotes delayed mean sting score.
[d]Discomfort Category denotes the degree of overall discomfort based on historical performance of a variety of products.

A sting test was performed by Consumer Product Testing Co. (1993a) with a lotion containing ~1.5% Glycolic Acid using 20 females subjects who had reacted at least moderately to a 5% aq. Lactic Acid solution. The test solution was applied to either the left or right nasolabial fold and cheek using a finger cot; a commercial AHA lotion was applied to the opposite side. Stinging was evaluated at 10 s, and 2.0, 5.0, and 8.0 min. Four subjects, 20%, had a moderate sting response to the test article, and it was concluded that it "exhibits a potential for a sting response."

A Lactic Acid sting test was performed by DiNardo (1994) using 12 subjects that demonstrated moderate stinging to 5.0% Lactic Acid. Subjects were placed in an environmental chamber until profuse sweating was induced and a nonencapsulated and a liposome-encapsulated formula containing 7.0% Glycolic Acid, pH 3.25, were applied to the nasolabial fold and cheek areas. At 2.5 and 5.0 min after application, the subjects evaluated sting potential on a scale of 0–3. Four subjects had a sting response to the nonencapsulated Glycolic Acid formulation, and one subject had a sting response to the encapsulated formulation.

Stinging was correlated with irritancy in a Lactic Acid sting test (Frosch and Kligman, 1977). Comparative irritancy of four AHAs, including Glycolic and Lactic Acid, at concentrations of 5 and 15%, was determined by 24-h occlusive patch tests on the forearms of three stingers. Glycolic Acid was more irritating than Lactic Acid, with 15% Glycolic Acid producing severe erythema and vesiculation. Correspondingly, Glycolic Acid produced more stinging than Lactic Acid, and the difference was not pH related.

Another sting test was performed according to the methods of Frosch and Kligman using four groups of 10 female subjects that were classified as "stingers" (Morganti et al., 1996a). After perspiration was induced, two groups applied a day cream and a night cream, each pH 5.5, containing 10% Glycolic Acid, vehicle, gelatin, glycine, and arginine to the right or left nasolabial fold and cheek and the corresponding vehicle was applied to the other side. The other two groups applied creams, pH 5.5, that contained lysine instead of arginine in the same manner. Stinging was evaluated on a scale of 0–3 at 10 s after application, and after 2.5, 5.0, and 8.0 min. The mean sting scores 10 s after application of the arginine- and lysine-containing formulas were 0.4 and ~0.3/3, respectively. The DMSs were ~1.25 and 1.5 for the arginine- and lysine-containing formulas. The researchers felt that the addition of gelatin, glycine, and arginine or lysine reduced the amount of erythema that would be expected from a Glycolic Acid-only cream. The subjective skin irritation potential of Glycolic Acid was evaluated by applying 2 mg/cm^2 of Glycolic Acid in vehicle (15% ethanol [SD 40], 5% ethoxydiglycol, and 5% butylene glycol) to the nasal fold area of at least 10 subjects (Smith, 1996). Irritation was graded on a scale of 0–4 every minute for 15 min. The irritation scores, as an average of the summation of each individual irritation score over the 15-min test period, were 27.2–44.1 at pH 3, 24.3–37.1 at pH 5, and 15.4–21.9 at pH 7 for 0.5–1.5 M Glycolic Acid, respectively.

A number of clinical use studies have reported subjective discomfort or follicular reactivity to products containing Glycolic Acid. These studies are summarized in Table 34.

Klein (1994) stated that glyco-citrate formulations retained the cosmetic effects of pure Glycolic Acid but reduced irritability and that "virtually no reports of allergy or other untoward effects" have been reported with use of glyco-citrate formulations.

Lactic Acid

Mini-cumulative irritation patch assays were performed on a variety of cosmetic formulations containing Lactic Acid to determine the irritation potential (CTFA, 1995h). The procedure has been described earlier. Results ranged from nonirritating to severely irritating, but with no clear relation to concentration or pH. The results of these assays using Lactic Acid are summarized in Table 35.

A 14-day cumulative irritancy patch test was performed using 23 subjects with three formulations containing 10, 15, and 20% Lactic Acid across a pH range of 3.5–4.5 to examine the effect of the pH of a formulation on cumulative irritation (Essex Testing Clinic, 1996). Four commercially available formulations, three containing 5–12% Lactic Acid, pH 4.2–4.6, and one containing 2.5% Lactic Acid, pH 7.2, were also used.

Table 34. Clinical use test for subjective discomfort or follicular reactions to Glycolic Acid products

Product form	Conc. (%)	pH	Number of subjects	Method	Complaints/reactons	Reference
Gel	2	3.9	10 gel 20 vehicle	Follicular irritation chest test in which gel/vehicle was applied 2×/day for 7 days.	"no significant follicular reactivity..."	CTFA, 1991e
Gel	2 4	3.9 3.9	20- 2% 10- 4% 10- vehicle	Follicular irritation chest test in which gels/vehicle were applied 2×/day for 7 days.	2%: 10% (2/20) follicular activity 4%: 40% (4/10) follicular activity	CTFA, 1991f
Gel	2 4	3.9 3.9	10- 2% 20- 4%	Follicular irritation chest test in which the 2% gel was applied 2×/day for 7 days and the 4% gel was applied 1×/day for 14 days	2%: 10% (1/10) significant follicular irritation 4%: 30% (6/20) significant follicular irritation Vehicle: no follicular activity	CTFA, 1991f
Lotion	10	3.8	20 females	Lotion was applied to arms, hands and legs 2×/day for 7 days.	1 when applying the product to freshly shaved legs No clinical reactivity was observed	CTFA, 1991c
Cream Control Lotion	4 4	3.7 3.8	29	Supervised 2-wk split-face use test in which the Glycolic Acid lotion and a control cream were applied 1×/day; subjects applied their normal moisturizer during the study.	1 subject perceived discomfort (tingling) to the test lotion and 2 subjects perceived discomfort (acne and bumps) to the control cream 1 subject had mild flaking with both substances	CTFA, 1992b
Cream	4	5.4	20 females	Supervised 2-wk use test in which a Glycolic Acid cream and a control cream were applied to the face 2×/day for 11 days; one application was made on day 12.	4 subjects had burning/stinging within the first 4 days of use with the Glycolic Acid cream; 1 of these subjects also had burning with the control No clinical reactions were observed	CTFA, 1990a
Cream	4	3.7	28	Supervised 4-wk split face use test using Glycolic Acid-containing creams which were applied 1×/day for wks 1–2 and 2×/day for wks 3–4; observations were made at 2 wks and at study completion. Subjects applied their normal moisturizer during the study.	2 subjects had discomfort with one cream, 1 had discomfort with the second cream, and 3 subjects had discomfort with both creams	CTFA, 1992c

Cream	4	3.8	52	4-wk split-face test was done using the test cream and a moisturizer.	9 (17%) with the Glycolic Acid cream; mostly (7) of burning, stinging, or tingling; these reactions were generally mild.; 2 "unconfirmed transitory bumps or raised areas" with itching during wks 1–2 3 (6%) with the moisturizer	CTFA, 1990b
Lotion	4 8	3.8 3.7	34	4-wk split-face test was done in which subjects applied the lotions 2×/day.	15 with the 8% lotion; 12 also to the 4% lotion; mostly stinging/burning which was more intense/frequent with the 8% lotion; 1 of severe scaling of the chin that was equal on both sides, disappeared upon dose discontinuation; did not reappear upon resuming dosing; 2 unconfirmed 1 with small bumps, 1 with flaking and drying 0 reactions to the 4% lotion	CTFA, 1994d
Lotion	6	3.9	45 males	Supervised 4-wk use test in which the lotion was applied to the face 2×/day for 4 wks. A control was not used.	11 subjects had perceived discomfort/irritation; most complaints were stinging/burning, 8 had this, 6/8 after shaving, and 3 had itching 5 subjects had erythema; 4/5 was non-product-related sunburn	CTFA, 1993
Lotion	~1.5	3.7-4.1	95/100 females	6-wk clinical study in which subjects applied lotion 1×/day to entire face in the evening. Evaluations were made at the lab on days 21 and 42 for irritation.	2 adverse experiences that were "probably product related" resulting in lotion discontinuation 1 of transient stinging and hypopigmentation after 3 days of application; 1 of mild itching and erythema after 1 application. 17–18% of the subjects reported transient irritation, dryness, itching, or stinging	TKL Research, 1994a

(*Table continued on next page.*)

Table 34. Clinical use test for subjective discomfort or follicular reactions to Glycolic Acid products (*continued*)

Product form	Conc. (%)	pH	Number of subjects	Method	Complaints/reactons	Reference
Cream	~0.5% GA with Lactic Acid	3.6–4.0	102/112 females	6-wk clinical study in which subjects applied lotion 1×/day to entire face in the evening. Evaluations were made at the lab on days 21 and 42 for irritation.	3 adverse experiences that were "probably product related": on day 1, prior to application to the face, application to the hand resulted in immediate swelling, redness, and itching: between days 27 and 31, a subjects' eyes became red and itchy within 15 min of application; after 5 days of use, a subject experienced a burning sensation and continued use resulted in persistent itching 26% of the subjects reported irritation, such as itchiness and slight acne	TKL Research, 1994b
Lotion	2	3.8	10 females	2-mo chest use test in which the subjects applied the lotion 2×/day. Skin was examined visually in "daylight" and with "black light" at 2-wk intervals.	1 subject had a minor follicular response at 4 wks and at 8 wks 1 subject had a subjective response of feeling "bumpiness" in the chest area at 8 wks	CTFA, no date
Cream	10	3.8	16 females per gp	A 2-mo use test in which one group applied the Glycolic Acid cream and one group applied the same cream without the Glycolic Acid.	1 subject had a sporadic erythematous rash after 4 wks of application; subject then used the control instead of the test cream for the remainder of the study and no response was evoked 6 subjects had a strong transitory burn/sting response upon application of the test cream; there were no responses evoked by the control cream	CTFA, 1990c

Cream	10	4.0	26 females	Unsupervised 2-mo use test in which the cream was gently massaged into the entire area above the upper lip 2×/day.	No clinical or subject-perceived responses	CTFA, 1989
Gel	2	3.8	23	6-mo efficacy study in which the 2% gel was applied 2×/day to the upper chest and neck.	1 subject had papules in the neck area within the first 2 wks of dosing; application was discontinued in this area for 5 days and then resumed without adverse effect	CTFA, 1992d
Cream	4 8	?	20 females per gp	6-mo efficacy test in which the creams were applied once daily for 2 wks and then twice daily.	No dermatologist-observed irritation 14 and 33% tester-perceived discomfort with 4% (slight burning/stinging for a few minutes) and 8% Glycolic Acid cream (slight burning/stinging for most; moderate response lasting >5 min for 2 subjects), respectively 5% and 19% tester-perceived irritation with 4% (1 person developed 2 large acne-like bumps) and 8% Glycolic Acid cream (3 subjects had slight redness with flakiness; 1 subject developed bumps over entire face), respectively	CTFA, 1991d

Table 35. Clinical cumulative irritation potential of Lactic Acid applied under occlusive patch for four consecutive days

Product form	Conc. (%)	pH	Number of subjects	PII[a]	Drops[b]	Conclusion
Lotion	4.0	4.3	20	0.93	0	Moderately irritating
Lotion	6.0	3.8	19	0.66	0	Mildly irritating
Lotion	6.0	3.8	19	0.76	0	Mildly irritating
Lotion	6.0	3.8	19	1.08	0	Moderately irritating
Lotion	6.0	3.9	20	0.25	0	Essentially nonirritating
Lotion	6.0	4.2	20	0.25	0	Essentially nonirritating
Lotion	6.0	4.2	19	0.28	0	Essentially nonirritating
Lotion	6.0	4.2	20	0.40	0	Slightly irritating
Lotion	6.0	4.2	19	0.68	0	Mildly irritating
Lotion	6.0	4.2	20	0.73	1	Mildly irritating
Lotion	6.0	4.2	19	0.87	0	Moderately irritating
Lotion	6.0	4.2	20	0.95	0	Moderately irritating
Lotion	6.0	4.2	20	1.13	0	Moderately irritating
Lotion	6.0	4.2	20	1.88	1	Severely irritating
Lotion	6.0	4.3	20	0.65	1	Midly irritating
Lotion	6.0	4.3	19	1.24	1	Moderately irritating
Lotion	6.0	5.0	20	0.25	0	Essentially nonirritating
Lotion	8.0	4.1	20	0.74	0	Mildly irritating
Lotion	8.0	4.3	20	0.70	0	Mildly irritating

[a]PII = Primary irritation index.

[b]Drops denotes the number of test subjects that had a grade 3 response and did not receive all four patches.

Approximately 0.2 mL of each test material was applied to the upper back of each subject under semi-occlusive patches for 24 h during the week and for 48 h on Saturdays for 2 weeks. The test sites were evaluated daily for erythema on a scale of 0–4, and the scores were calculated via summation of the irritation values for each day. The maximum score per product was 966. For the 10% Lactic Acid experimental formulation, the following cumulative scores were reported: pH 3.0, 590; pH 3.5, 124; pH 4.0, 1; these scores correspond to normalized values of 1.83, 0.39, and 0.003, respectively. For the 15% experimental formulation, the following cumulative scores were reported: pH 3.5, 78; pH 4.0, 4; pH 4.5, 16; these scores correspond to normalized values of 0.24, 0.01, and 0.05, respectively. For the 20% experimental formulation, cumulative scores of 10 and 9 were recorded at pH 4 and 4.5, respectively; both correspond to a normalized value of 0.03. The commercial products containing Lactic Acid had the following cumulative irritation scores: 2.5%/pH 7.2, 37; 5%/pH 4.3, 8; 8%/pH 4.2, 7; 12%/pH 4.6, 2; these scores

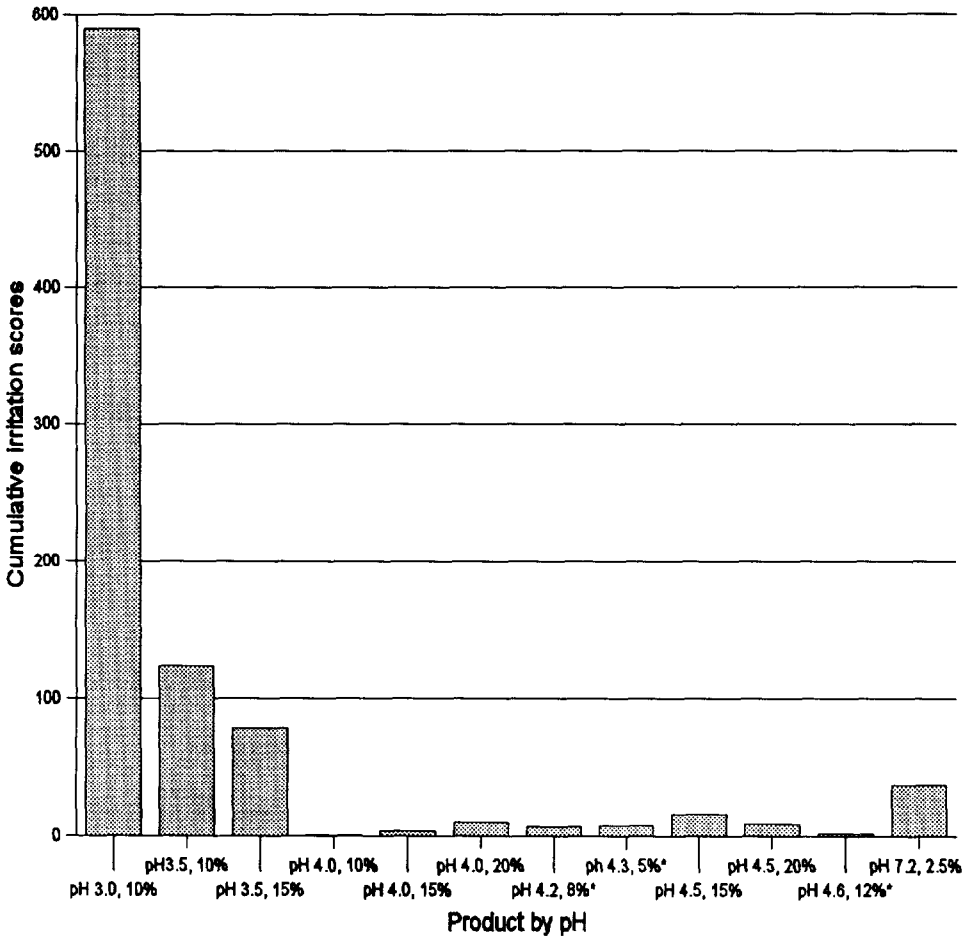

Figure 7. Cumulative irritation scores (maximum score = 966) as a function of pH of Lactic Acid treatment. A total of 23 subjects were tested using three formulations containing 10, 15, and 20% Lactic Acid at pH 3.5–4.5. Four commercially available formulations (see asterisk), containing 2.5–12% Lactic Acid, pH 4.2–7.2, were used for comparison (Essex Testing Clinic, 1996).

correspond to normalized values of 0.11, 0.02, 0.02, and 0.006. The researchers stated that the score of 37 obtained with the 2.5%/pH 7.2 formulation was due to one subject having a score of 36. (The other subjects all had scores of 0.) These results of all products tested (the commercial formulations being marked with an asterisk) are presented in Figure 7 as a function of pH and Figure 8 as a function of concentration.

Facial discomfort assays were performed on a variety of formulations containing Lactic Acid to determine the potential to cause facial stinging (CTFA, 1995i). The procedure has been described previously. Again, no clear relationship of effect to pH or concentration was evident. The results of these assays using Lactic Acid are summarized in Table 36.

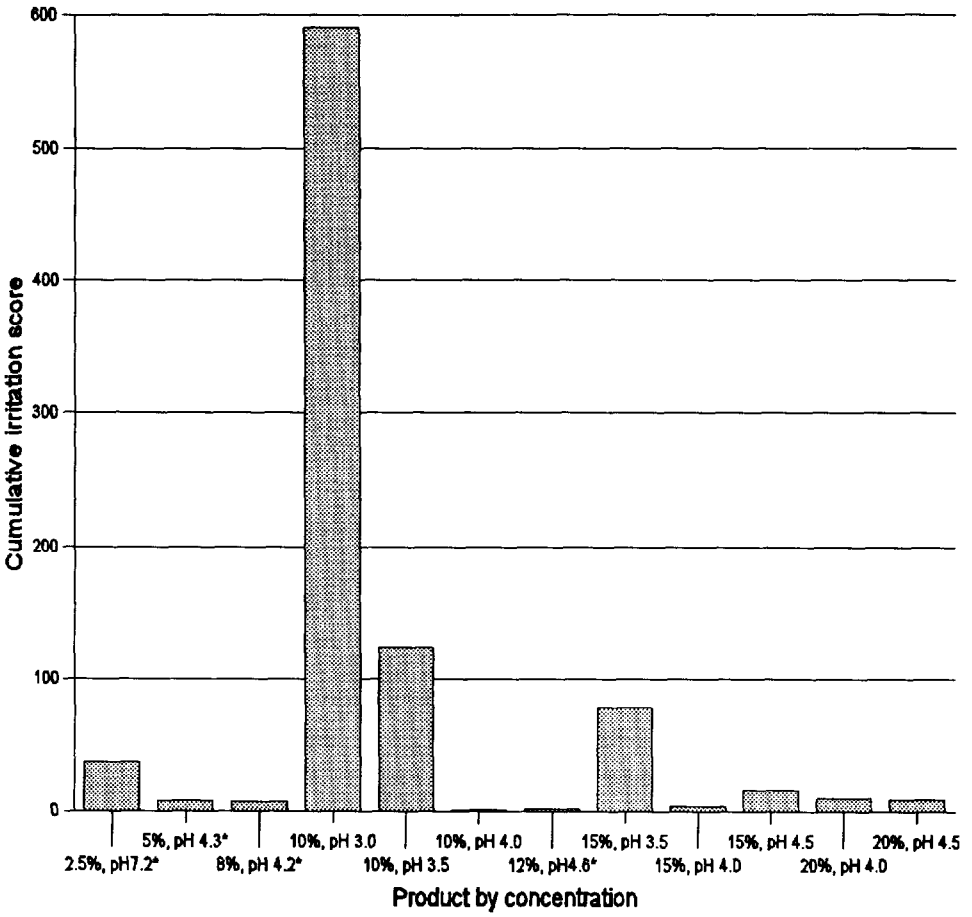

Figure 8. Cumulative irritation scores as described in Figure 7 as a function of concentration of the formulation. See asterisk for commercial preparations (Essex Testing Clinic, 1996).

A Lactic Acid "sting test" was performed using 30 subjects, 15 males and 15 females; it was noted that stinging potential was not strictly related to cheeks, and stinging sensation was scored after 10 s, 2.5 min, and 5 min on a scale of 0–4 (Frosch and Kligman, 1977). Five "stingers" were identified, four women and one man. All five stingers reported that they thought they had unusually "sensitive" skin because of past trouble with soaps and cosmetics. The stingers were also reactive to a variety of chemicals. Three stingers were then used to examine multiple versus single applications. Lactic Acid, 5%, was applied to one side of the face every 5 min for a total of five applications; the other side of the face received one application at the time of the fifth application to the first cheek. The intensity of stinging increased with each application. The effect on stripped skin was also examined. One cheek of three nonstingers

Table 36. Human facial discomfort assay using Lactic Acid

Product form	Conc. (%)	pH	Number of subjects	Discomfort[a]	TSS[b]	DMS[c]	Discomfort category[d]
Lotion	4.0	3.7	6	4	5.0	0.29	Nonstinging
Cream	4.7	3.3	19	14	31.0	0.69	Slight
Lotion	4.7	4.3	21	18	46.0	0.83	Moderate
Lotion	4.7	4.3	21	18	49.0	0.95	Moderate
Lotion	6.0	3.8	11	5	8.0	0.16	Nonstinging
Cream	6.0	3.8	22	16	30.0	0.60	Slight
Lotion	6.0	3.9	22	14	16.5	0.32	Nonstinging
Lotion	6.0	4.2	21	13	20.0	0.40	Nonstinging
Lotion	6.0	4.2	21	13	29.0	0.55	Slight
Lotion	6.0	4.2	20	13	34.5	0.70	Slight
Lotion	6.0	4.3	21	11	17.0	0.33	Nonstinging
Lotion	6.0	4.3	19	15	28.5	0.62	Slight
Lotion	6.0	4.3	21	17	40.0	0.82	Moderate
Lotion	8.0	4.3	18	11	22.0	0.51	Slight
Cream	10.0	3.8	19	15	45.0	0.96	Moderate

[a]Discomfort denotes the number of test subjects that perceived discomfort.
[b]TSS denotes the total sting score which is the sum of all scores at 0, 2.5, and 5.0 min.
[c]DMS denotes delayed mean sting score.
[d]Discomfort category denotes the degree of overall discomfort based on historical performance of a variety of products.

was Scotch-tape stripped to the "glistening layer"; half that number of strippings were taken from the other cheek. After 15 min of sweating, 5% Lactic Acid was applied to both cheeks. Severe stinging was felt immediately on the completely stripped side and less, but appreciable stinging was felt on the other side. The duration of stinging on stripped skin of nonstingers was shorter than on normal skin of stingers, generally fading within 2.5 min. Lactic Acid, 5%, was then applied to the stripped skin of the nonsweating back of three stingers and three nonstingers. Stinging was equally intense in both groups upon application and declined rapidly within a few minutes.

The subjective skin irritation potential of D- and L-Lactic Acid was evaluated by applying 2 mg/cm^2 Lactic Acid in vehicle (15% ethanol [SD 40], 5% ethoxydiglycol, and 5% butylene glycol) to the nasal fold area of at least 10 subjects (Smith, 1996). Irritation was graded on a scale of 0–4 every min for 15 min. The irritation scores, as an average of the summation of each individual irritation score over the 15 min test period, were 24–40.8 at pH 3, 21.8–36.3 at pH 5, and 13.3–21.2 at pH 7 for 0.5–1.5 M D-Lactic Acid, respectively, and 21.2–26.7 at pH 3, 15–25.6 at pH 5, and 11–17.1 at pH 7 for 0.5–1.5 M L-Lactic Acid, respectively.

In a series of sting tests, a 10% aq. solution of Lactic Acid was applied to the nasolabial fold on one side of the face (ESLUR, 1994a).

Median erythema grades were similar to those produced by distilled water. The majority of the subjects reported no or slight stinging (for example, 17/24 subjects; 22/24 subjects), with fewer experiencing moderate stinging (6/24 subjects; 2/24 subjects). Severe stinging was occasionally reported by one subject in one study.

Lactic Acid, 20%, in distilled water was applied to the face of 20 subjects, 5 males and 15 females, by placing a filter paper disk on the flat surface of a short plastic cylinder called the "occluder," wetting the filter paper with the test solution, and pressing the occluder against the cheek for 3 min; an occluder wet with distilled water was applied to the other cheek simultaneously (Green and Bluth, 1995). The 3-min trials were repeated twice more with the test solution, alternated with 3-min applications of vehicle only; the vehicle-only applications were made first. Capsaicin and ethanol were also being tested. Subjects rated sensation intensity based on a labeled magnitude scale of barely detectable to strongest imaginable at 1-min intervals during each 3-min application. The ratings for Lactic Acid had a periodicity in phase with application and removal. Lactic Acid penetrated the cornified epithelium and reached sensory nerves within 1 min of application, and irritation began to decline within 1 min of removal of the filter paper. Large individual differences were observed. Fifty-five percent of the individuals had at least a moderate response to Lactic Acid, and the group means approached moderate. The predominant sensation produced was stinging, with some reports of burning and itching.

Six subjects from the previous study, three "high reactors" and three "low reactors," were chosen for a retest (Green and Bluth, 1995). Similar consistency in results was obtained for each subject as compared to the first test. A 3-month clinical study of a gel containing 6.0% Lactic Acid, pH 3.9, was completed with 30 male subjects who applied the gel twice daily (CTFA, 1994e). Dermatologic examinations were done prior to gel use initiation and 4, 8, and 13 weeks after application. No adverse reactions were reported during the study by the subjects or upon dermatologic examination.

A 6-month clinical study of a lotion containing 6.0% Lactic Acid, pH 4.2, was completed using 41 female subjects, some of whom had rosacea (CTFA, 1994f). After a 2-week preconditioning period, the lotion was applied to the face once daily for the first 2 weeks and then twice daily. Irritation was not reported, and the lotion was "well tolerated, even among those with sensitive skin."

Ammonium Lactate. In the 14-day cumulative irritation assay performed by DiNardo et al. (1994) described earlier for Glycolic Acid, 12% Ammonium Lactate, pH 4.4, was tested concurrently. Ammonium Lactate, 12%, had an irritation value of 30/882.

Six male subjects received open applications of 0.02 mL of 12% buffered Ammonium Lactate on the ventral forearm daily for 4 weeks and six male subjects had occlusive patches of 0.02 mL 12% buffered Ammonium Lactate placed on the ventral forearm three times weekly for 3 weeks (Lavker et al., 1992). No evidence of irritation was observed, and discomfort was not reported.

A 21-day cumulative irritation test with 25 subjects used 8 and 12% Ammonium Lactate lotions; these lotions were compared to 14 other test and control compounds using a double-blind comparison technique (FDA, 1988). The test solutions were applied under occlusive patches to the back; the patches were removed after 24 h, and the sites were evaluated using a scale of 0–4. A total of 18 applications were made over a 21-day period. Both 8 and 12% Ammonium Lactate lotion produced minimal irritation. In a 21-day cumulative irritation and sensitization test with 25 subjects, a 12% Ammonium Lactate lotion was compared to 13 other test compounds by means of a randomized double-blind comparison technique (FDA, 1988). The irritation portion of the study was performed as described above, with the Ammonium Lactate lotion being applied to duplicate test sites. Ten days after the last patch, a 24-h challenge patch was applied to a previously untreated site on 15 subjects, and the sites were evaluated at 24 and 48 h. A 12% Ammonium Lactate lotion produced moderate irritation, with total scores of 311 and 218 and mean scores of 12.0 and 8.4, respectively. Of the 15 subjects challenged after 10 days, one subject had a score of 3+ (erythema, with marked edema) after 24 and 48 h.

A paired comparison facial irritancy study compared an 8 and a 12% Ammonium Lactate lotion (number of subjects not specified) by applying aliquots of the lotions to the faces of the subjects twice daily for 10–12 days (FDA, 1988). Skin irritation was defined by the degree of erythema, stinging, burning, and scaling during the application period. Both lotions were associated with irritation in all subjects, and the researcher concluded "that the lotions were not suitable for use on the face of fair complexioned Caucasian females."

TEA-Lactate. Published clinical dermal irritation data for TEA-Lactate were not found. Studies included in the Safety Assessment on TEA (Elder, 1983) reported TEA, and cosmetic products containing TEA, produced mild dermal irritation at concentrations of >5%.

Ethyl Lactate. Application of Ethyl Lactate (concentration not specified, but believed to be 8%) to the volar forearm or back of 25 subjects, 15 males and 10 females, under an occlusive patch for 48 h did not produce any irritation (Kligman, 1976a).

Butyl Lactate. Application of Butyl Lactate (concentration not specified, but believed to be 1%) to the volar forearm or back of 25 female

subjects under an occlusive patch for 48 h did not produce any irritation (Kligman, 1976b).

Cetyl Lactate. A study included in the original safety assessment of Cetyl Lactate (Elder, 1982) reported that 2.5 and 5% aq. Cetyl Lactate elicited minimal transient reactions.

DERMAL IRRITATION: MEDICAL/THERAPEUTIC

Glycolic Acid

A study was performed in which a micropeel was done with and without 30% Glycolic Acid using 10 and 5 female subjects, respectively, whose skin had signs of environmental damage but who did not have any systemic or dermatological disorders (Milmark Research, Inc., 1994). For the test group, on day 1, the face was washed using a cleanser and acetone, the facial skin was dermaplaned, a 30% Glycolic Acid solution was applied for a maximum of 2 min, the skin was neutralized with sodium bicarbonate solution, and an iceball (CO_2 [dry ice] in gauze dipped in acetone) was rolled over the skin. The same method was followed for the control group with the exception that the Glycolic Acid step was deleted. The micropeel was performed at 2, 4, 6, 8, 10, and 12 weeks for the test group and at 2, 4, and 6 weeks for the control group. The subjects were strongly encouraged to follow a home regimen that included applying 4% hydroquinone cream or 3% Melanex and 0.1% Retin-A daily unless otherwise instructed. Following the peel procedure, 9/10 test subjects and 2/5 controls had irritation; the investigators attributed the irritation to either the dermaplaning technique or the application and/or removal of Glycolic Acid. A comparison of irritation of day 1 to weeks 2, 6, and 12 was made for the test group and of day 1 to weeks 2 and 6 for the control group. For the test group: 6/10 subjects had irritation at week 2; 4/9 subjects (one subject was dropped from the study at 3.5 weeks) had irritation at week 6; 0/9 subjects had irritation at week 12. For the control group: 1/5 subjects had irritation at week 2; 0/5 subjects had irritation at week 6.

SENSITIZATION

Glycolic Acid

The results of all studies described in this section are summarized in Table 37. A repeat-insult patch test (RIPT) was performed according to the methods of Kligman and Epstein (1975) to determine the irritation and sensitization potential of a formulation of 50% Glycolic Acid in a cyclodextrin complex (Richerche e Technolgie Cosmetologiche [RTC],

1996). A preliminary test was first performed to determine the test concentrations. In the preliminary study, one subject was tested with 0.4 mL of aqueous 0.5, 2.5, and 5.0% and 0.5, 1.5, and 2.5% of the formulation under semi-occlusive and occlusive patches, respectively. On day 1, three semi-occlusive and three occlusive patches of each concentration were applied using the right and left arms. A semi-occlusive and occlusive patch at each concentration was removed after 4, 24, and 45 h. All sites were assessed on a scale of 0–6 immediately and 1 h after patch removal. Minimal reactions were generally observed, with the exception of moderate erythema and strong erythema with edema and papules immediately and 45 h after removal of the 5% semi-occlusive patch, respectively. The test dose selected was 2.5% using an occlusive patch. Twenty-eight subjects completed the primary study, in which occlusive patches of 0.4 mL of aqueous 2.5% solution of a 50% Glycolic Acid in a cyclodextrin complex, pH 2.2, were applied to one arm for 48 h twice a week for 2–3 weeks, giving a total of five induction patches. After a 2-week nontreatment period, a 47-h challenge patch was applied to both arms. The sites were assessed 72 or 96 h after each induction application and 48 and 96 h after the challenge application. The researchers concluded that, under an occlusive patch, 2.5% of the formulation induced "very strong irritation reactions during induction in the majority of subjects" and that the "challenge reactions were stronger and more persistent than those during induction, suggesting sensitization." A rechallenge consisting of a 21-day in-use test followed by a 48-h patch test using 2.5% of the formulation, pH 5.16, was performed on 10 and completed on 9 subjects that had questionable reactions. One retested subject had a sensitization reaction during the in-use test, and the other nine subjects did not have sensitization reactions but did have irritation reactions.

RIPTs were performed using products containing Glycolic Acid to determine the irritation and sensitization potential of these products; some of the products may also have contained a mixed fruit acid (designated MFA Complex). A dose of 0.2 mL or 0.2 g of the test article was applied under an occlusive patch to the back of the subjects for 24 h. Patching was done three times/week for 3 consecutive weeks for a total of 9 (AMA Laboratories, Inc., 1993a,b, 1994a,b; Essex Testing Clinic, Inc., 1994 a–i) or 10 applications (Consumer Product Testing Co., 1993b). The challenge patch, using the same dose as in the original patch, was applied after a 10–14-day nontreatment period. The sites were scored 24 and 48 h after patch application. The results were primarily negative.

A number of RIPTs were performed on formulations containing Glycolic Acid following similar procedures as outlined above with the

Table 37. Results of sensitization studies using Glycolic Acid

Test	Product form	Conc.	pH	Number of subjects (final/initial)	Conclusion	Reference
RIPT	50% GA in cyclodextrin complex	2.5%	2.2	28/30	Strong irritation reactions were induced in most subjects during induction Stronger, more persistent reactions were observed during challenge, indicative of sensitization	RTC, 1996
RIPT	Cream	~0.5% w/Lactic Acid	3.6–4.0	95/106	Did not induce irritant or allergic contact dermatitis; 3 barely perceptible to mild responses which were not considered irritant or allergic	ETC, 1994a[a]
RIPT	Lotion	~1.5%	3.7–4.1	104/112 (20M, 84F)	No indication of irritation/sensitization potential	CPT, 1993b[b]
RIPT	—	2%	5.5 ± 0.1	51/56 (13M, 38F)	Nonprimary irritant Nonprimary sensitizer	AMA Labs., Inc., 1993a
RIPT	—	3% 1% MFA	3.8 ± 0.1	53/57 (15M, 38F)	Nonprimary irritant Nonprimary sensitizer	AMA Labs., Inc., 1993b
RIPT	Lotion	4%	3.8–4.0	198/212	Did not induce irritant or allergic contact dermatitis; 1 barely perceptible response which was not considered irritant or allergic	ETC, 1994b
RIPT	Lotion	4%	3.8–4.0	198/212	Did not induce irritant or allergic contact dermatitis; no reactions were observed	ETC, 1994c
RIPT	Cream	4%	3.8–4.0	198/212	Did not induce irritant or allergic contact dermatitis; no reactions were observed	ETC, 1994d
RIPT	Cream	4%	3.8–4.0	198/212	Did not induce irritant or allergic contact dermatitis; no reactions were observed	ETC, 1994e

RIPT	—	6% 1% MFA	3.8 ± 0.1	56/58 (13M, 43F)	Nonprimary irritant Nonprimary sensitizer	AMA Labs., Inc., 1994b
RIPT	—	6% 2% MFA	3.8 ± 0.1	56/61 (12M, 44F)	Nonprimary irritant Nonprimary sensitizer	AMA Labs. Inc., 1994a
RIPT	Lotion	8%	3.8–4.0	198/212	Did not induce irritant or allergic contact dermatitis; 1 barely perceptible response which was not considered irritant or allergic	ETC, 1994f
RIPT	Lotion	8%	3.8–4.0	198/212	Did not induce irritant or allergic contact dermatitis; 1 moderate response which was not considered irritant or allergic	ETC, 1994g
RIPT	Cream	8%	3.8–4.0	198/212	Did not induce irritant or allergic contact dermatitis; no reactions were observed	ETC, 1994h
RIPT	Cream	8%	3.8–4.0	198/212	Did not induce irritant or allergic contact dermatitis; no reactions were observed	ETC, 1994i
Maximization	Lotion	2.0%	3.8	27/27	No sensitization	CTFA, 1995j
Maximization	Cream	4.0%	3.7	26/27 (10M, 16F)	No sensitization	CTFA, 1995j
Maximization	Lotion	4.0%	3.9	25/25	No sensitization	CTFA, 1995j
Maximization	Lotion	8.0%	3.9	25/26	No sensitization	CTFA, 1995j
Maximization	Cream	8.0%	3.9	25/27	No sensitization	CTFA, 1995j
Maximization	Lotion	10.0%	3.8	25/26 (7M, 18F)	No sensitization	CTFA, 1995j

[a]ETC = Essex Testing Clinic, Inc.
[b]CPT = Consumer Product Testing Co.

exception that semi-occlusive patches were used (Essex Testing Clinic, Inc., 1994b–i). The results of these studies were negative.

Maximization tests were performed on a variety of cosmetic formulations containing Glycolic Acid to determine its sensitization potential (CTFA, 1995i). The induction phase consisted of application of 0.1 mL of 0.5% aq. SLS under an occlusive patch to a site on the upper outer arm, volar forearm, or back of each subject for 24 h. After 24 h, the SLS patch was removed, and 0.1 mL of test material was applied to the same site under an occlusive patch for 48 or 72 h. This procedure was continued for a total of five induction applications. If irritation developed during the induction phase, the 24 h SLS pretreatment patch was eliminated and the test patch was applied after a 24-h nontreatment period. After a 10-day nontreatment period, the challenge application was with SLS pretreatment. Approximately 0.1 mL of a 10.0% aq. SLS solution was applied under an occlusive patch for 1 h to a previously untreated site. Upon SLS patch removal, the test material was applied to that site under an occlusive patch for 48 h. At 1 and 24 h after patch removal, the application site was scored for sensitization. The results of the maximization studies were negative.

Lactic Acid

A RIPT was completed using 99 of 115 initial subjects to determine the primary or cumulative irritation and/or sensitization potential of anhydrous emulsions containing 2.0, 3.0, 4.0, or 5.0% Lactic Acid (Consumer Product Testing Co., 1993c). Approximately 0.2 mL of each test material was applied for 24 h to the upper back (between the scapulae) of each subject using semi-occlusive patches three times/week for a total of 10 applications. Around 14 days after the last application, an open patch challenge application was made to the original site and to a previously untreated site on the volar forearm. The sites were scored 24 and 48 h after application. One subject had a response of mild erythema at the original test site 48 h after application of the formulation containing 2.0% Lactic Acid; another subject had the same response to the 3.0% formulation at the test site after 48 h. A third subject had a response of mild erythema to the 3.0, 4.0, and 5.0% Lactic Acid formulations at the previously untreated site. No responses were recorded for the other subjects. The three subjects that had a reaction were rechallenged as previously described for the original challenge. A reaction of mild erythema was recorded after 24 h, but not 48 h, at the previously untreated site for the subject that had a reaction to the 2.0% formulation; the response was considered weak and transitory and clinically insignificant. No reaction was observed upon rechallenge of the subject that had a reaction to the 3% formulation. Upon rechallenge of the

Table 38. Sensitization potential of Lactic Acid determined via maximization test

Product form	Conc. (%)	pH	Number of subjects (final/initial)	Conclusion
Lotion	6.0	3.9	25/27	No sensitization
Lotion	6.0	4.2	26/27	No sensitization
Cream	10.0	3.7	25/26	No sensitization

subject that reacted to the 3.0, 4.0, and 5.0% Lactic Acid formulations, a response to the test materials of mild erythema was observed at the previously untreated site after 24 and 48 h; the researchers stated that the response could be due to hypersensitivity and could probably be considered clinically insignificant. The researchers concluded that studies with anhydrous microemulsions containing 2.0, 3.0, 4.0, and 5.0% Lactic Acid "do not indicate a significant potential for dermal irritation or sensitization."

Maximization tests were performed on three cosmetic formulations containing Lactic Acid to determine its sensitization potential (CTFA, 1995j). The maximization study procedure was described earlier. The results of these studies, which were negative, are summarized in Table 38. A report described a case of contact dermatitis resulting from topical treatment of warts by a solution containing Lactic Acid (Tabar et al., 1993). In subsequent patch testing, the subject had a 1+ reaction (not defined) to 3% aq. Lactic Acid.

Ammonium Lactate. Two modified Draize prophetic patch tests were conducted, each using 203 subjects, to investigate the contact sensitization potential of a 12% Ammonium Lactate lotion (FDA, 1988). In both studies, the lotion was applied to the back under occlusive patches three times per week, for a 48-h period during the week and a 72-h period over the weekends, for a total of 10 applications. After a 2-week nontreatment period, a challenge patch was applied to an untreated site for 72 h. No sensitization was reported in either study.

Sodium Lactate. A RIPT was completed using 101 of 137 initial subjects with a completely neutralized cream containing 1.0% Sodium Lactate to determine sensitization potential (Stephens and Associates, 1992). At least 20 μL of the test material was applied to the backs of the subjects for 48 h under occlusive patches 3 days per week for 3 weeks. The challenge patches were applied for 48 h 17–23 days after the last induction application to a previously untreated site on the upper central aspect of the right or left arm; the site was scored 48 to 96 h after application. No adverse or unanticipated clinical reactions were observed.

Reactions to the cream ranged from 0 to +0.5 during the induction phase, and no reactions were observed at challenge.

TEA-Lactate. Published clinical sensitization data for TEA-Lactate were not found. Studies included in the Safety Assessment on TEA (Elder, 1983) reported TEA, and cosmetic products containing TEA, produced very little sensitization.

Ethyl Lactate. A maximization test was performed with SLS pretreatment using 25 subjects, 15 males and 10 females, to determine the contact sensitization potential of Ethyl Lactate (concentration not specified, but believed to be 8%) (Kligman, 1976a). No sensitization reactions occurred at challenge.

Butyl Lactate. A maximization test was performed with SLS pretreatment using 25 female subjects to determine the contact sensitization potential of Butyl Lactate (concentration not specified, but believed to be 1%) (Kligman, 1976b). No sensitization reactions occurred at challenge.

Myristyl Lactate. A study included in the original safety assessment of Myristyl Lactate (Elder, 1982) reported that a lipstick formulation containing 13.8% Myristyl Lactate produced no evidence of irritation or sensitization in a RIPT using 200 subjects.

Cetyl Lactate. A study included in the original safety assessment of Cetyl Lactate (Elder, 1982) reported that 5% aq. Cetyl Lactate was nonirritating and nonsensitizing in a RIPT using 200 subjects.

PHOTOSENSITIZATION/PHOTOTOXICITY

Glycolic Acid

The photosensitization potential of two creams containing 4 and 5% Glycolic Acid, pH 3.7 and 3.9, respectively, was evaluated with a maximization test using 25 subjects/test (CTFA, 1994g). The minimal erythema dose (MED) of each subject was determined by exposing one side of the midback to a series of exposures 1 cm in diameter in 25% increments using a xenon arc simulator (150 W). The induction phase consisted of applying 10 $\mu L/cm^2$ of test material to a site on the lower back under an occlusive patch for 24 h and then, upon patch removal, exposing the site to three MEDs from the xenon arc solar simulator. This procedure was repeated after 48 h at the same site; the sequence was done twice weekly for 3 weeks. At 10 to 14 days after the last induction exposure, the test material was applied as before to two previously untreated sites under an occlusive patch. After 24 h, one patch was removed, and the site was irradiated with 4 J/cm^2 of UVA using a 1-mm-thick Schott WG-345 filter (50% cutoff at about 335 nm); the second site was not irradiated and

served as a control. The test sites were scored 48 and 72 h after UVA exposure. Neither of the Glycolic Acid creams produced a sensitization reaction at the irradiated or nonirradiated sites.

The photoallergy potential of a product containing ~1.5% Glycolic Acid, pH 3.7–4.1, was evaluated in a photoallergy study using 26 subjects, 7 males and 19 females (Consumer Product Testing Co., 1994a). The MED of each subject was first determined using a xenon arc lamp (150 W) that produced a continuous emission spectrum in the UVA and UVB range. The induction phase consisted of applying 0.2 mL of test material to two sites on the lower back under a patch for 24 h and then, upon patch removal, exposing one of the sites to two MEDs using a continuous emission spectrum. This procedure was repeated twice weekly for 3 weeks. Test and control sites were evaluated every weekday following the initial application for a total of 14 evaluations. Approximately 2 weeks after the last evaluation, the test material was applied as before to two previously untreated sites on the lower back. After 24 h, the patches were removed and one treated and a nontreated site were irradiated for 3 min with UVA (nonerythemogenic) light for a total dose of 6.3 J, using a Schott WG-345 filter to eliminate UVB wavelengths. The second treated site was not irradiated. The challenge sites were scored 24, 48, and 72 h after UVA exposure. The product containing ~1.5% Glycolic Acid "did not induce a response indicative of a photoallergic reaction."

The photoallergy potential of a cream containing ~0.5% Glycolic/Lactic Acid mix, pH 3.6–4.0 was evaluated in a photoallergy study completed by 27 subjects, 5 males and 22 females (Harrison Research Laboratories [HRL], 1994a). Each subject's skin type and MED was first determined. The induction phase consisted of applying 0.2 g of test material to a site on the volar forearm and to a site on the left scapular area of the back under an occlusive patch for 24 h. Upon patch removal, the treated site as well as an untreated site on the forearm was exposed to 15 min of UVA irradiation from four F40BL fluorescent tubes, which deliver a dose of approximately 0.22 J/cm^2 min^{-1} at 15 ± 2 cm, for a total dose of 3.3 J and to UVB light from a Solarium 300, which delivers a dose of approximately 1.2 mJ/cm^2 min^{-1} at 22 ± 2 cm, for a dose of two MEDs or for a period of 135 s. This procedure was repeated twice weekly for 3 weeks. Test sites were evaluated upon patch removal and immediately following irradiation. Approximately 2 weeks after the last patch, the test material was applied to a previously untreated site on the ulnar side of the volar forearm and to the right scapular area of the back. After 24 h, the patches were removed, and the forearm was irradiated with UVA. The challenge sites were scored upon patch removal, immediately following irradiation, and 24 and 48 h after irradiation.

During induction, one subject had a 2-level reaction (erythema, edema, and/or papules within patch margins) at the irradiated treated and untreated sites, 22 subjects had low-level reactions at the irradiated

treated site, one subject had a low-level reaction at the nonirradiated treated site, and 16 subjects had low-level reactions at the irradiated nontreated sites. No reactions were observed at the original test sites during the 2-week nontreatment period or at challenge. The researchers concluded that a cream containing ~0.5% Glycolic/Lactic Acid mix "did not induce contact dermal photoallergy or contact dermal sensitization in human subjects."

In studies performed by Avon, cosmetic formulations containing 4 and 4.5% Glycolic Acid, 25 subjects, were not photosensitizers (CTFA, 1994c).

A human contact phototoxicity study was performed in which 50 μL of a cream containing 4.0% Glycolic Acid, pH 3.7, was applied under occlusive patches at duplicate sites to the lower midback of 10 subjects (CTFA, 1994h). Twenty-four hours after application, one patch was removed and the test site was immediately exposed to 30 J/cm^2 of UVA (320–400 nm); the light source was a 150-W compact xenon arc source that used a 1-mm-thick Schott WG-345 to eliminate UVB wavelengths and a 1-mm-thick UG11 filter to remove reflected infrared and visible radiation. The other test site served as a nonirradiated control. An adjacent skin site, which served as a control, was treated with hydrophilic ointment USP and exposed to UVA. Reactions were scored immediately, 24 h, and 48 h after irradiation. The cream (4.0% Glycolic Acid, pH 3.7) was not phototoxic.

A human phototoxicity study was performed in which each subject's MED was first determined and then approximately 0.2 mL of a product containing ~1.5% Glycolic Acid, pH 3.7–4.1, was applied under occlusive patches to two sites on the lower back of 10 subjects (Consumer Product Testing Co., 1994b). A third site was not treated. Twenty-four hours after application, the patches were removed, and one test site and the untreated site were irradiated with a timed UVA exposure, 5–8 min for a total dose of 10.5–16.8 J, to achieve one MED; the light source was a Solar UV Simulator with a xenon arc lamp (150 W) and a Schott WG-345 filter to eliminate UVB wavelengths. Test and control sites were examined 15 min, 24 h, and 48 h after irradiation. A product containing ~1.5% Glycolic Acid "did not induce a response indicative of a phototoxic reaction."

A phototoxicity study was performed in which approximately 0.2 g of a cream containing ~0.5% Glycolic/Lactic Acid, pH 3.6–4.0, was applied under occlusive patches to duplicate sites on the volar forearms of 10 subjects, 3 males and 7 females (HRL, 1994b). Twenty-four hours after application, the patches were removed, and one forearm was irradiated for 15 min with UVA from four F40BL fluorescent tubes, which deliver a dose of approximately 0.22 J/cm^2 min^{-1} at 15 ± 2 cm, for a total dose of 3.3 J; the treated and a nontreated site were irradiated. The sites were scored upon patch removal, immediately following irradiation, and

24 and 48 h after irradiation. No reactions were seen on the irradiated or nonirradiated test sites or at the irradiated untreated site. The researchers concluded that a cream containing ~0.5% Glycolic/Lactic Acid mix "did not induce a contact dermal phototoxic response in humans."

Lactic Acid

The photosensitization potential of a lotion containing 6.0% Lactic Acid, pH 4.2, was evaluated in a maximization test using 25 subjects as described previously (CTFA, 1994g). A sensitization reaction was not produced at the irradiated or nonirradiated sites.

TEA-Lactate. Published clinical photosensitization and phototoxicity data for TEA-Lactate were not found. Studies included in the Safety Assessment on TEA (Elder, 1983) reported products containing ≤20.04% TEA were neither phototoxic nor photosensitizing.

SUNBURN CELL PRODUCTION

The short-term effects of the dermal application of Glycolic Acid on the sensitivity of skin to UV light was determined by assessing the effect on sunburn cell (SBC) production (KGL, Inc., 1996a). Ten percent Glycolic Acid in a thickened aq. vehicle, pH 3.5, was applied to a 5 × 10-cm area of the back of 15 subjects, 3 males and 12 females, at a dose of 100 mg per test area (2 mg/cm^2) once daily for 4 days; the material was rubbed over the test site using finger cots. A second test site was treated with a moisturizer containing 8% glycerin, while another site was rubbed with a moistened mechanical exfoliating sponge for 15 s each day. A fourth site was untreated. Seven subjects had Fitzpatrick skin type I, and eight had skin type II. Following dosing, the test sites were irradiated, at a distance of 12 in., using a bank of four 20-in. fluorescent FS20 bulbs filtered with a 0.15-mm-thick sheet of cellulose acetate to remove UVC. The spectral power distribution was primarily in the UVB region. A 2-cm-diameter circular area of each test site was exposed to 1 MED 15 min after the last dose. The MED of each subject was determined 1 week prior to irradiation of the test sites. Following injection of a local anesthetic, a shave biopsy (~4 mm × 4 mm) was taken from each irradiated site 20 ± 4 h after irradiation. The number of SBCs were determined in sections obtained at 50-μ intervals. A minimum of 80 high-powered fields (HPFs) from each skin specimen using a magnification of 400× were randomly counted, and the average was determined. Cells with a pyknotic nucleus and a glassy homogenous eosinophilic-staining cytoplasm were counted as SBCs. The mean MED was 52.4 mJ/cm^2, and the range was 33.1–81.6 mJ/cm^2. After four applications, the 10%

Table 39. Number of SBCs per high-power field produced by 1 MED of UV radiation as a function of pretreatment once a day for 4 days

Subject	Skin type	Glycolic Acid	Moisturizer	Sponge	Untreated
1	I	0.48	0.37	0.38	0.22
2	I	0.83	0.75	0.80	0.66
3	II	0.57	0.08	0.20	0.43
4	I	0.33	0.66	0.96	0.42
5	I	0.15	0.06	0.08	0.08
6	I	0.11	0.07	0.18	0.02
7	II	0.40	0.24	0.30	0.41
8	II	0.19	0.19	0.38	0.35
9	II	0.15	0.21	0.13	0.03
10	II	0.46	0.23	0.35	0.63
11	II	0.02	0.01	0.03	0.02
12	I	0.16	0.07	0.09	0.06
13	II	3.17	1.64	1.76	1.59
14	I	0.22	0.01	0.03	0.11
15	II	0.24	0.68	0.67	0.28
Geometric mean		**0.27**	**0.16**	**0.24**	**0.18**

Glycolic Acid formulation, pH 3.5, did not statistically significantly increase the number of SBCs when compared to the 8% glycerin, mechanical exfoliating sponge, or untreated skin (using a parametric analysis of variance (ANOVA) on log-transformed average number of SBCs per field, followed by a series of pairwise *t* tests conducted within the ANOVA to identify those treatments which differed significantly using a significance level of 0.05, with a Bonferroni adjustment). The number of SBCs for each subject and treatment is given in Table 39. To depict the variation among subjects, these same data are shown in Figure 9.

Another study (KGL, Inc., 1996b) examining the effect of Glycolic Acid application on the production of SBCs was conducted following the procedures outlined above. In this study, however, the duration of dosing was 12 weeks, and a minimum of 70 HPFs were counted for each skin specimen. One group of 16 subjects, 2 males and 14 females, was treated with a 10% Glycolic Acid formulation in a thickened aq. vehicle, pH 4.0, a moisturizer containing 8% glycerin, or a mechanical exfoliating sponge, and a fourth site was untreated; one female subject was dropped during the study due to a lack of compliance. A second group of 16 subjects, 9 males and 7 females, was treated with a 10% Glycolic Acid formulation, pH 3.5, the thickened aq. vehicle, pH 4.0, or 99.8% mineral oil, and a fourth site was untreated. No adverse reactions were reported. The mean MED was 57.3 mJ/cm^2, and the range was 26.5–102 mJ/cm^2.

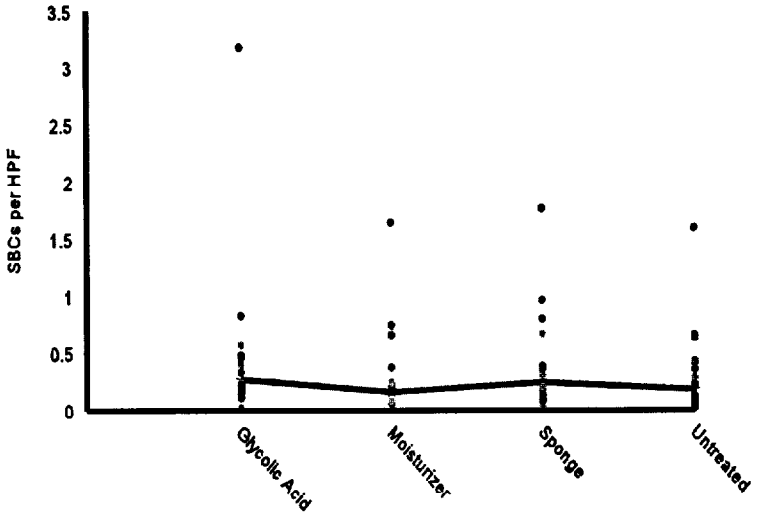

Figure 9. Number of sunburn cells produced in each of 15 subjects exposed to 1 MED of primarily UVB radiation as a function of the pretreatment regimen: 10% Glycolic Acid, moisturizer without Glycolic Acid, a mechanical sponge, and no treatment; once daily for 4 days. The geometric means are connected with a line (KGL, Inc., 1996a).

These data were analyzed by a parametric ANOVA on log-transformed average SBCs per HPF, followed by a series of pairwise t tests conducted with the ANOVA to identify those treatments that differed significantly using a significance level of 0.05, with a Bonferroni adjustment (KGL, Inc, 1996b; Battelle, 1997). In the first group, Glycolic Acid, pH 4.0, application resulted in a statistically significant increase in the number of SBCs as compared to skin treated with moisturizer and to untreated skin ($p < 0.05$). A significant difference in the number of SBCs was not observed between treatment with the moisturizer and the sponge, nor were these values significantly different from untreated skin. When comparing the Glycolic Acid groups to the mechanical sponge, there was no significant difference.

In the second group, application of Glycolic Acid, pH 3.5, resulted in a statistically significant increase in the number of SBCs as compared to skin treated with the vehicle and mineral oil and untreated skin (KGL, Inc., 1996b). There was not a significant difference in the number of SBCs observed after application of the vehicle as compared to after application of mineral oil, nor were these significantly different from untreated skin.

In analyzing the data using alternative methods (the Dunnett method for multiple comparisons and a paired t test), Glycolic Acid application resulted in a statistically significant increase in the number of SBCs as compared to the mechanical sponge ($p < 0.05$ and $p < 0.003$, respectively) (3M Health Care, 1997). Using these alternative methods,

Table 40. Number of SBCs per high-power field produced by 1 MED of UV radiation as a function of pretreatment once a day for 12 weeks—group 1

Subject	Skin type	Glycolic Acid (pH 4.0)	Moisturizer	Sponge	Untreated
1	II	0.24	0.13	0.18	0.22
2	II	1.94	0.79	0.96	0.90
3	II	0.22	0.03	0.10	0.11
4	I	0.56	0.35	0.45	0.08
5	I	0.89	1.71	1.65	2.08
6	II	0.08	0.06	0.16	0.29
7	II	0.42	0.29	0.23	0.12
8	II	1.99	0.96	0.87	0.99
9	II	11.90	2.36	3.83	0.95
10	II	0.36	0.52	0.29	0.21
11	II	1.00	0.20	0.48	0.50
12	II	2.59	2.39	1.49	1.78
13	II	0.41	0.26	0.15	0.69
14	II	0.95	0.39	0.30	0.38
15	II	1.31	0.31	0.35	0.06
Geometric mean		**0.77**	**0.38**	**0.44**	**0.37**

the statistical significance of the Glycolic Acid treatment SBC increases compared to the moisturizer (group 1), the vehicle (group 2), mineral oil (group 2), or the untreated controls (groups 1 and 2).

The number of SBCs for each subject and treatment in the groups 1 and 2 is given in Tables 40 and 41, respectively, and the data are depicted in Figures 10 and 11, respectively.

The dose–response relationship between UVB and SBC induction was examined using four male and four female subjects (skin type I or II) with a series of exposures in 25% dose increments (KGL, Inc., 1996c). A dose response was observed between the number of SBCs and the UVB dose, with a mean number of 0.05 SBCs at 0.64 MEDS, 0.41 SBCs at 1 MED, and 1.31 SBCs at 1.56 MEDs.

Battelle (1996) interpreted the results of the 12-week study (KGL, Inc., 1996b) in regard to change in the effective UV exposure by relating the number of SBCs to a UV exposure using the dose–response relationships described by KGL, Inc. (1996c). For the first group, the geometric mean effective UV dose associated with application of the 10% Glycolic Acid formulation, pH 3.5, was approximately 20 and 21% greater than that for treatment with the vehicle and untreated skin, respectively, and 15% greater than that with the sponge. For the second group, the geometric mean UV dose associated with application of the 10% Glycolic

Table 41. Number of SBCs per high-power field produced by 1 MED of UV radiation as a function of pretreatment once a day for 12 weeks—group 2

Subject	Skin type	Glycolic Acid (pH 3.5)	Vehicle (pH 4.0)	Mineral oil	Untreated
1	II	0.06	0.01	0.01	0.02
2	II	2.66	1.10	0.38	1.10
3	II	2.72	0.64	1.53	2.38
4	II	0.60	0.74	0.46	0.74
5	I	0.19	0.09	0.09	0.01
6	II	1.00	0.83	0.36	0.70
7	II	1.21	0.16	0.06	0.08
8	II	1.31	0.22	0.51	0.34
9	I	1.09	0.11	0.45	0.67
10	II	0.94	0.45	0.71	1.23
11	II	1.28	0.73	1.25	0.67
12	II	0.70	0.20	0.05	0.08
13	II	1.77	1.09	1.99	1.97
14	II	1.46	0.17	0.21	0.51
15	I	0.60	0.30	1.48	1.69
16	II	0.68	1.10	0.01	0.19
Geometric mean		**0.85**	**0.31**	**0.26**	**0.37**

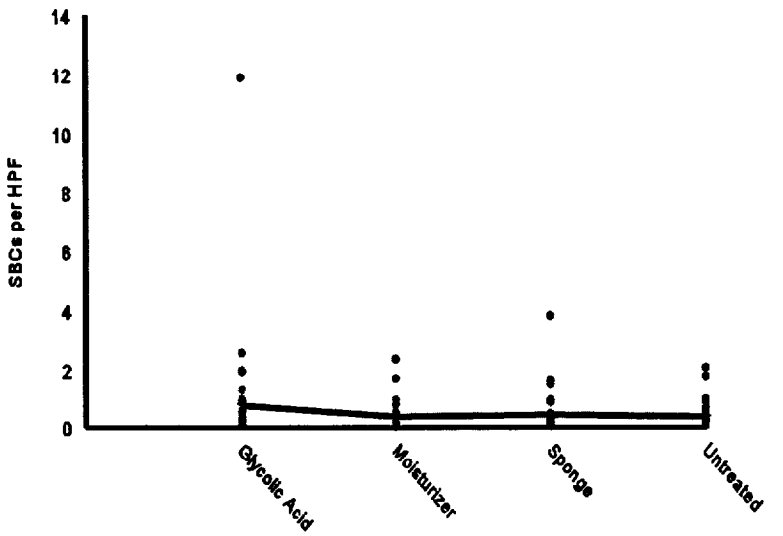

Figure 10. Number of sunburn cells produced in each of 15 subjects (group 1) exposed to 1 MED of primarily UVB radiation as a function of the pretreatment regimen: 10% Glycolic Acid, moisturizer without Glycolic Acid, a mechanical sponge, and no treatment; once daily for 12 weeks. The geometric means are connected with a line (KGL, Inc., 1996b).

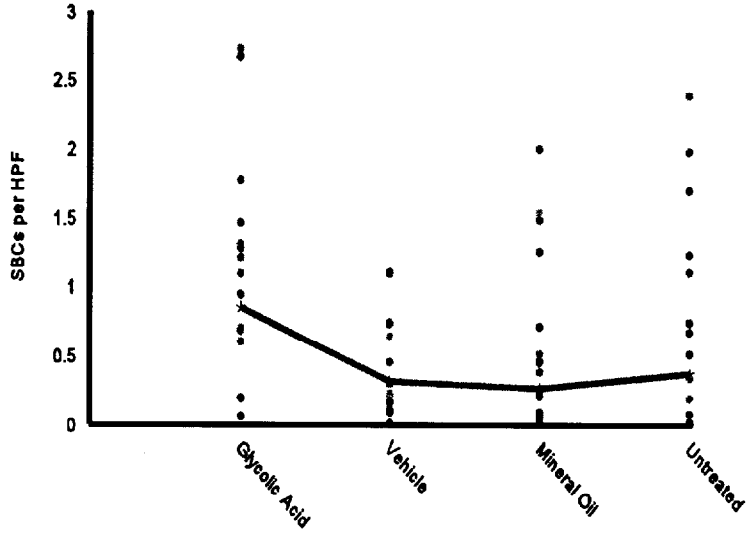

Figure 11. Number of sunburn cells produced in each of 16 subjects (group 2) exposed to 1 MED of primarily UVB radiation as a function of the pretreatment regimen: 10% Glycolic Acid, vehicle alone, mineral oil, and no treatment; once daily for 12 weeks. The geometric means are connected with a line (KGL, Inc., 1996b).

Acid formulation, pH 4.0, was approximately 25, 31, and 37% greater than that for untreated skin, skin treated with the vehicle, and skin treated with mineral oil, respectively.

The effect of application of a 4 and an 8% Glycolic Acid cream containing 1.5% ethylhexyl methoxycinnamate on the production of SBC was examined; the creams had a very low level of UV absorbance equivalent to a sun protection factor (SPF) of approximately 2.9 (De Leo, 1996). The study was carried out according to the procedure outlined previously in the study by KGL, Inc. (1996a). The test material was applied once daily for 4 days, and 15 min after the fourth exposure, a 1-cm area of each site was exposed to a dose of 1 MED from a xenon arc solar simulator (150 W); a control site was also dosed with 1 MED. A shave biopsy was obtained from each site 20 ± 4 h after irradiation. Five subjects were used, but the results from only four subjects were evaluated because one subject had a lack of SBCs at all sites. The four valid subjects had less SBCs at the treated site as compared to the untreated site. The number of SBCs at the Glycolic Acid-treated sites was similar to that seen upon incidental UV exposure. The data are summarized in Table 42.

The Unilever Research U.S., Inc. (1995) study described previously in this report, in which 8% Glycolic and Lactic Acid, pH 3.8, were applied in a double-blind manner to mild to moderately photodamaged face and forearm skin, was not conducted with the intention of investigating SBC formation. In a follow-up to that study, the punch biopsies

Table 42. Number of SBCs per high-power field produced by 1 MED of UV radiation as a function of pretreatment with 4 or 8% Glycolic Acid once a day for 4 days

Subject	Skin type	4% Glycolic Acid	8% Glycolic Acid	Untreated
1	2	0.04	0.02	0.13
2	2	0.03	0.02	2.26
3	3	0.02	0.13	0.47
4	2	0.00	0.00	1.36
5[a]	1	0.00	0.00	0.00

[a]This subject was not considered valid by the researchers.

that were obtained from forearm skin after 22 weeks of dosing (between March and June) were reexamined to determine SBC formation (Unilever Research U.S., 1996). Although the subjects were instructed to use sunscreen, actual use varied from none to frequent application. SBCs were evaluated in a blinded manner in 10 HPFs (40×) for an approximate length of 3.7 mm of epidermis. An average of SBCs in all fields were calculated for each treatment group. All results are from forearm skin. A total of 18 paired biopsies were taken from nine subjects dosed with 8% Glycolic Acid and vehicle. SBCs were not found in any field (180 total) for either the vehicle or 8% Glycolic Acid. A total of 18 paired biopsies were taken from nine subjects dosed with 8% Lactic Acid and vehicle. A total of four SBCs were identified in biopsy samples taken from Lactic Acid-treated skin (SBC average, 0.04; 180 fields examined). No SBCs were found in vehicle-treated skin samples. The increase was not considered meaningful. A total of 24 paired biopsies were taken from 12 subjects treated with 8% Glycolic and 8% Lactic Acid. In the 240 fields examined, three SBCs were identified (overall average, 0.0125). Significant dose-related SBC formation was not observed in skin treated with 8% Glycolic or Lactic Acid, pH 3.8, upon incidental sun exposure. While biopsies were obtained from March through June, six of the seven SBCs identified were found in skin from biopsies taken in March and April.

A study was conducted (according to a different protocol than that used in the studies that have been described) to examine the number of SBCs produced after application of SLS (CTFA, 1996b). SBCs were counted in sections adjacent to those that were scanned to locate at least one SBC. A correlation between the density of SBCs and the degree of injury induced by SLS was indicated.

EFFECT ON MED

Upon review of data concerning alterations in UV transmittance by skin, it was suggested that more UV is transmitted through normal,

moisturized skin versus dry skin (because dry skin scatters more light) (CTFA, 1995k). Research (TKL Research, 1995a) has indicated that application of typical cosmetic moisturizers containing 10% mineral oil or 10% glycerin decreased average MED 5 or 7.6%, respectively. Also, shaving and a cosmetic exfoliating sponge were reported (TKL Research, 1995b) to decrease MED by approximately 12%.

Seasonal and climatic changes also affect UV transmittance. In one study (KGL Skin Study Center, 1995a) it was reported that between January and April, the average MED increased by 14%. This was attributed to an increase in skin dryness and skin roughness. No change in skin pigmentation was found using a chromameter. However, Sayre et al. (1981) reported increased MED during summer months as compared to winter months, and this was attributed to greater skin pigmentation from sun exposure.

Glycolic Acid

Erythema was induced on the backs of five subjects (gender not stated) in a 2-cm template by exposure to three times the MED of UVB (Perricone and DiNardo, 1996). A 12% Glycolic Acid cream partially neutralized with ammonium hydroxide in an oil-in-water vehicle, pH 4.2, was applied to the template 4 h postirradiation four times/day. A second template was used on the subjects as a vehicle control. The site treated with Glycolic Acid had a marked reduction of erythema at 48 h as compared to the control vehicle. At 72–96 h, the treated site had hyperpigmentation, and the control site had erythema.

Five subjects (gender not specified) were used to evaluate the potential effects of Glycolic Acid on the skin before and after exposure to UVB light (Perricone and DiNardo, 1996). Four sites were exposed to UVB using a xenon arc lamp. Site 1 was a nontreated control site used to establish the MED. Site 2 was exposed to an MED series on nontreated skin and 24 h after exposure, seven daily applications of a cleanser and a lotion, both containing 8% Glycolic Acid, pH 3.25, were made to determine the effect of post-treatment with an AHA on UV radiation effectiveness in producing erythema (measured as seconds of UV exposure to produce 1 MED). Site 3 was treated with daily applications of the cleanser and the lotion for 3 weeks and irradiated with a MED series 24 h after the last application; site 4 was treated in an identical manner as site 3, but also included a 6-min chemical peel with a 50% Glycolic Acid solution partially neutralized with ammonium hydroxide, pH 2.75, 15 min prior to irradiation. Sites 1 and 2 were evaluated for erythema 1, 2, 3, 4, and 7 days after irradiation, whereas sites 3 and 4 were evaluated daily for erythema. The results are depicted in Figures 12 and 13. At site 2, treatment with Glycolic Acid resulted in a 16% reduction in irritation

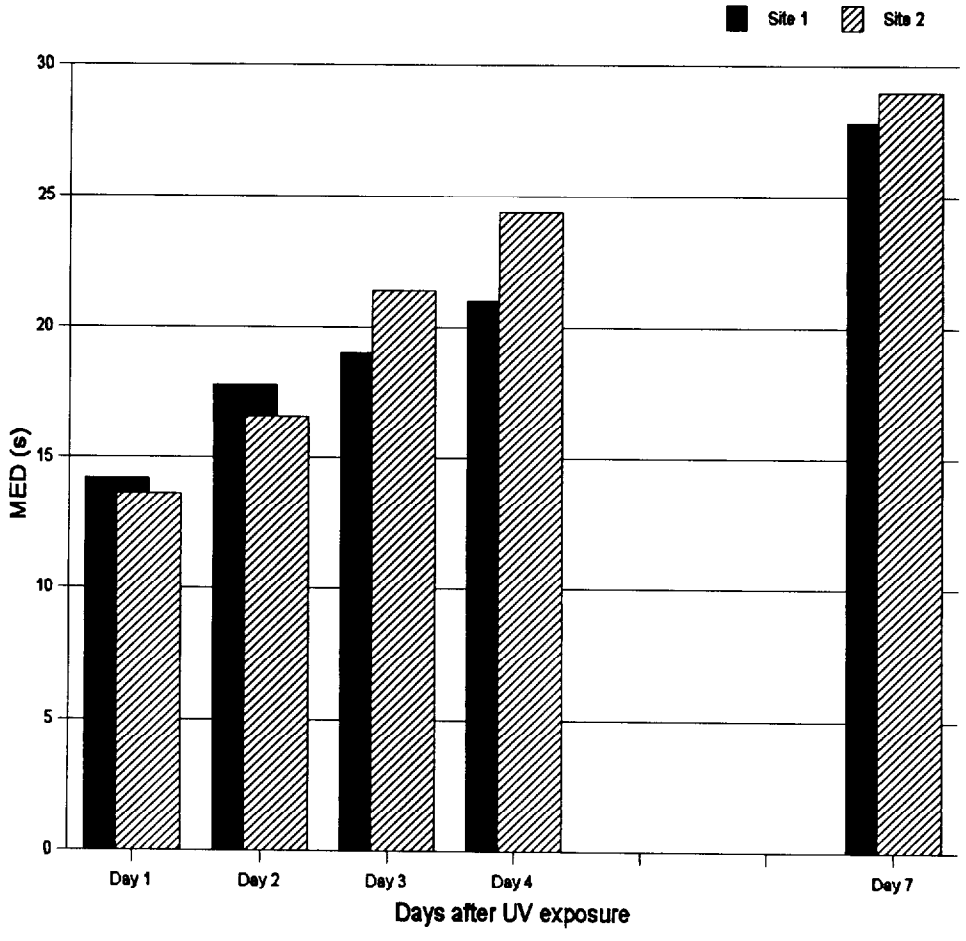

Figure 12. Effect of posttreatment (7 daily applications) with 8% Glycolic Acid, pH 3.25 (site 2), or no treatment (site 1) on erythema expressed as seconds of UV exposure to reach 1 MED (Perricone and DiNardo, 1996).

after 7 days. In comparing site 1 to site 3 (nontreated skin exposed to UVB versus skin first treated with Glycolic Acid and then exposed to UVB) a SPF of 2.4 was achieved by pretreating the skin with Glycolic Acid prior to irradiation. In comparison of site 3 to site 4 (treated skin that was not peeled subjected to UVB versus similarly treated skin that was peeled and subjected to UVB), it was observed that the chemical peel reduced the SPF by 50%; however, a SPF of 1.7 was still achieved when compared to untreated skin. According to the researcher, pretreatment with Glycolic Acid increased the skin's natural protection from UVB and minimized additional UVB damage prior to chemical peeling.

A 4% Glycolic Acid cream, pH not specified, was applied to a site on the lower back of 19 subjects twice daily in a semi-supervised manner for

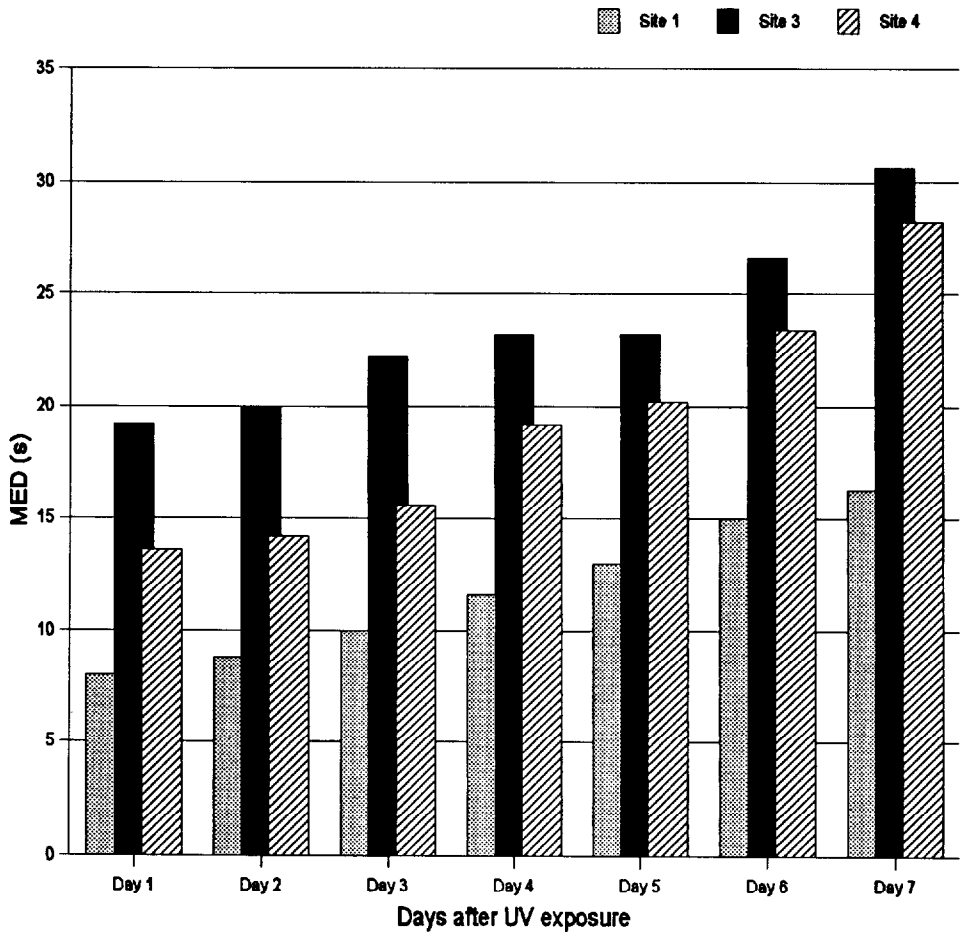

Figure 13. Effect of pretreatment (daily) with 8% Glycolic Acid, pH 3.25, for 3 weeks (site 3); the same pretreatment plus a 6-min chemical peel with a 50% Glycolic Acid solution, pH 2.75, 15 min prior to UV exposure (site 4); or no treatment (site 1) on erythema seen following UV exposure. Erythema expressed as seconds of UV exposure to reach 1 MED (Perricone and DiNardo, 1996).

12 weeks (KGL Skin Study Center, 1995b). After 12 weeks of treatment, MEDs were determined for treated and untreated skin with a series of six UV exposures in 25% increments using a 150-W xenon arc solar simulator equipped with a 1-mm WG-320 filter and a 1-mm UG11 filter. Skin that was treated with Glycolic Acid had an average MED that was 13.2% lower than that of untreated skin; this difference was statistically significant. However, less than half of the subjects (47%) had a lowered MED. A breakdown of changes in MED by skin type based on the Fitzpatrick scale is given in Table 43 and depicted in Figure 14. Average SPF for the treated site (determined by dividing the MED for the treated site by the MED for the untreated site) was 0.86. Skin dryness/roughness,

Table 43. Effect of pretreatment with 4% Glycolic Acid on MED as a function of skin type

Skin type	Number of subjects	Decrease	No change	Increase
I	2	2	—	—
II	5	3	2	—
III	10	3	6	1
IV	2	1	1	—

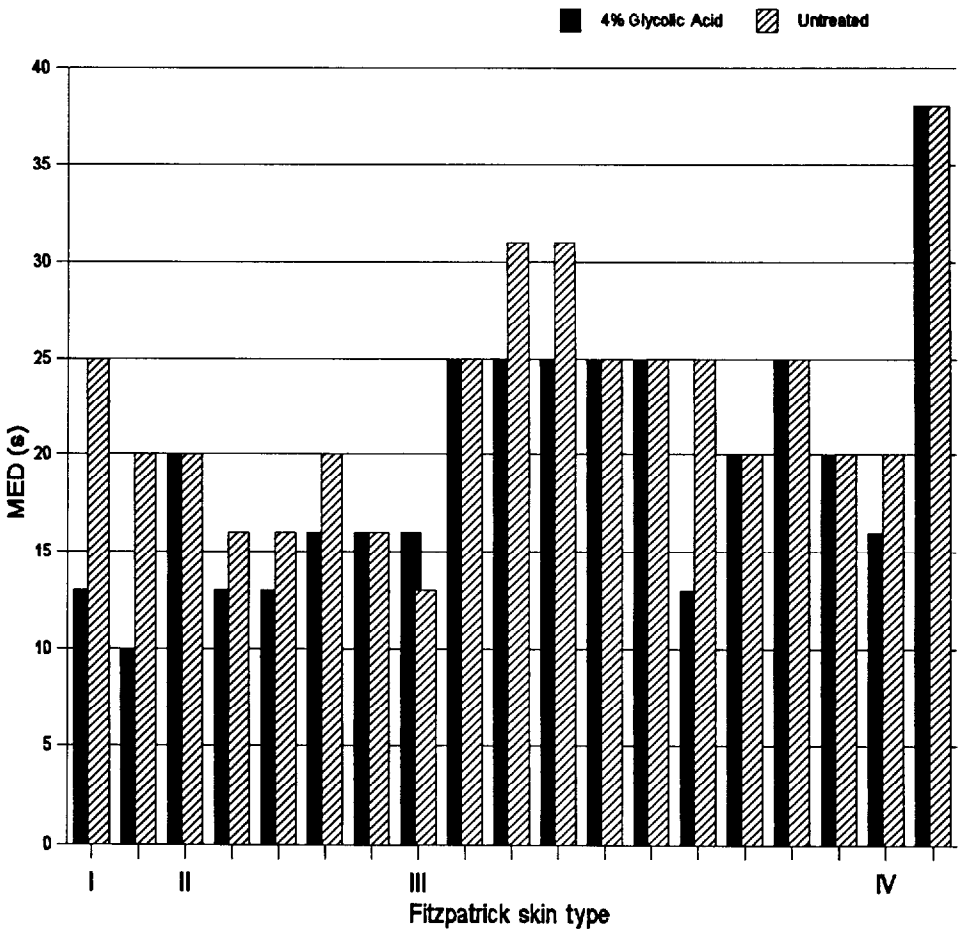

Figure 14. Time of UV exposure (in seconds) needed to reach 1 MED in 19 subjects pretreated with 4% Glycolic Acid cream (pH not stated) twice daily for 12 weeks. UV exposures were done in 25% increments using a xenon are solar simulator (KGL Skin Study Center, 1995b).

water content, and color were also determined to examine any correlation between these factors and change in MED. Dryness/roughness was determined by visual grading and use of D-Squames, water content was measured using a conductance meter, and skin color was determined using a chromameter. Scores for visible dryness were essentially the same for both the treated and untreated sites. However, the D-Squame tapes established that Glycolic Acid-treated skin was significantly less dry and significantly less rough than untreated skin. Using the conductance meter to measure water content, Glycolic Acid-treated skin had significantly greater values than untreated skin, indicating a greater stratum corneum water content. No difference in coloration was observed between the Glycolic Acid-treated sites and untreated sites. Statistical correlation suggested that MED increased with increased D-Squame scores (i.e., a higher MED is obtained with skin that is drier).

The sunscreen efficacy of a lotion containing ~1.5% Glycolic Acid, pH 3.7–4.1, was evaluated using 20 subjects in a procedure based upon the method outlined in the FDA monograph of proposed rules for sunscreen testing (FDA, 1978) (Consumer Product Testing Co., 1993d). A xenon arc solar simulator (150 W) was used as the UV light source.

Prior to testing, the MED of each subject was first determined. The test lotion and a control (8% homosalate) were applied to the back of each subject, with an adjacent site serving as an unprotected control, and the sites were irradiated 15–30 min after application; exposure times were based on the initial MED. All test sites were evaluated 16–24 h after exposure. The average SPF of the Glycolic Acid-containing cream was 8.82.

In a test following the same method outlined above, the sunscreen efficacy of a cream containing ~0.5% Glycolic/Lactic Acid mix was evaluated using 20 subjects (Consumer Product Testing Co., 1994c). The average SPF of this cream was 8.90.

Lactic Acid

Twenty subjects applied a formulation, pH 4.2, containing three AHAs (Lactic Acid, alpha-hydroxy octanoic acid, and alpha-hydroxy decanoic acid) at a concentration of 1.4% w/w to the ventral forearm twice a day for 3 months (Estee Lauder Research and Development, no date). Both forearms of the subjects were exposed to UVB from a Berger Solar Simulator after 4, 8, and 12 weeks of product application to determine if there has been a change in MED. Additionally, at study initiation and after 4, 8, and 12 weeks of application, the subjects were exposed to 1.5 times their MED at that time. Erythema was assessed using a Minolta chromameter 24 h after each UV exposure. No significant changes in skin response to UVB were observed after 3 months of application of

the test material. No changes were observed in either the MED of the application site or in the reactivity of the skin to a 1.5 MED measured at 24 h as compared to the untreated site.

URTICARIAL REACTIONS

Lactic Acid

A skin test was performed using 49 atopic and 56 nonatopic patients to determine whether application of 2.5% Lactic Acid in water produces an urticarial reaction (Lahti, 1980). Finn chambers containing 20 μL of test solution were fixed on the skin using porous tape for 20 min. Lactic Acid produced no immediate reactions.

Sodium Lactate. In the skin test described previously for Lactic Acid, application of 10% Sodium Lactate in water to 49 atopic and 56 nonatopic patients did not produce any immediate reactions (Lahti, 1980).

COMEDOGENICITY

Glycolic Acid

Comedogenicity assays were performed based on the procedure of Mills and Kligman (1982) in which 0.2 μL of a test material was applied under an occlusive patch to the upper back above the scapulae 3 days/week for 4 weeks, providing 29 days of continuous exposure (CTFA, 1995l). A nontreated site with an occlusive patch served as the control. On the Monday following the 4 weeks of applications, the test site was sampled by a cyanoacrylate "follicular biopsy" technique, and the comedogenic potential was scored on a scale of 0–3. The test sites were also examined visually for adverse effects. The results of these comedogenic assays, which were negative, are summarized in Table 44.

Table 44. Comedogenicity assay using Glycolic Acid

Product form	Glycolic Acid conc. (%)	pH	Number of subjects	Mean comedo score		Results
				Test	Control	
Lotion	2.0	3.8	6	0.00	0.07	No adverse effects
Cream	4.0	3.7	6	0.03	0.07	No adverse effects
Cream	5.0[a]	3.9	6	0.07	0.07	No adverse effects
Cream	8.0[a]	3.8	6	0.00	0.00	No adverse effects
Lotion	10.0[a]	3.8	6	0.03	0.13	No adverse effects

[a]Used semi-occlusive patches.

Lactic Acid

The comedogenic potential of two lotions containing 6.0% Lactic Acid, pH 3.9 or 4.2, was evaluated in a comedogenicity assay, as described previously, using six subjects/test (CTFA, 1995l). The mean comedo scores were 0.00 for both test groups and for the untreated control group in the test using a lotion with pH 4.2. In the test of the lotion with pH 3.9, the untreated control group had a mean comedo score of 0.03. No adverse effects were seen.

COSMETICS ADVERSE REACTIONS

Glycolic Acid

The FDA submitted to CIR 1989–1996 consumer adverse experience reports that were submitted to FDA headquarters and to FDA district offices on AHA-containing products (FDA, 1996a). Typical adverse reactions included "severe redness, swelling (especially in the area of the eyes), burning, blistering, bleeding, scarring, rash, itching, contact dermatitis, skin discoloration (reportedly permanent), and adverse neurological responses." Some of the individuals submitting an adverse experience report were seen by a physician, and at least one adverse report involved professional application and at least one involved a product prescribed by a dermatologist. FDA's submittal stated that "in addition to consumer reports of adverse reactions, letters have also been received from dermatologists treating patients suffering from injuries resulting from the use of these [AHA-containing] products." The number of reported adverse reactions to AHA-containing products and possible AHA-containing products (for this category, the reports lacked sufficient product details for accurate classification as an AHA product) is given in Table 45. The values included in Table 45 included deletions made because the originally named products do not contain any AHAs and because the ingredients named in the complaint/related information did not include Glycolic or Lactic Acid (Cosmair, Inc., 1996; FDA, 1996d). Information from a company that distributed four products containing 2–10% Glycolic Acid, pH 3.02–3.9, had average complaint rates of 8 per million units distributed (CTFA, 1995m). This company's traditional moisturizers that did not contain Glycolic Acid, pH 5.97–7.75, had average complaint rates of 3 per million. (The Glycolic Acid product had been on the market less than 2 years.)

Lactic Acid

Sodium Lactate. A company that has a product containing 1% Lactic Acid, pH 5.5, reported having 14 complaints per million units distributed

Table 45. Adverse reactions reported to FDA for products containing AHAs

Year	FDA Headquarters (1/1/89–2/9/96)		FDA District Offices (1/1/89–11/6/95)	
	AHA products	Possible AHA products	AHA products	Possible AHA products
1989	3	0	0	0
1990	1	0	0	6
1991	1	0	0	2
1992	2	0	0	4
1993	6	1	2	8
1994	36	0	10	12
1995	17	0	6	2
1996	3	0	N/A	N/A
Total	**69**	**1**	**18**	**34**

(CTFA, 1995m). This company's more traditional moisturizer had an average complaint rate of 8 per million. (The Lactic Acid product had been on the market $<1\frac{1}{2}$ years.)

MEDICAL/THERAPEUTIC ADVERSE REACTIONS

Lactic Acid

Ammonium Lactate. In a clinical study of 115 patients with ichthyosis who were treated with a 12% Ammonium Lactate lotion, a total of 65 adverse reactions were reported (FDA, 1988). The most commonly reported reactions were stinging, erythema, and burning, with the incidences being 14, 12, and 10, respectively. In a clinical study of 546 patients with xerosis who were treated with a 12% Ammonium Lactate lotion, a total of 96 adverse reactions were reported (FDA, 1988). The most commonly reported reactions were stinging, burning, and illness, with the incidences being 17, 17, and 11, respectively.

In a study of 41 patients with xerosis on both legs who were treated with a 12% Ammonium Lactate lotion to one leg and a 5% Lactic Acid and 2.5% sodium pyrrolidone carboxylic acid lotion to the other for 3 weeks, two adverse reactions, one of dryness and one of pruritus and irritation, were reported for the 5% Lactic Acid formulation causing the subjects to be dropped from the study (Rogers et al., 1989). There were also seven minor complaints: two complaints after use of 12% Ammonium Lactate lotion and three complaints after use of both of tingling, stinging, and burning; one complaint of pruritus after use of 5% Lactic Acid lotion; and one complaint of irritation after use of 5% Lactic Acid lotion.

ESTIMATION OF SAFE EXPOSURES

Glycolic Acid

Data from industry indicate that the majority of women would use between 0.5 and 1.0 g daily of a product containing 8% Glycolic Acid (ESLUR, 1994b). The expected human exposure, assuming 10% absorption and a 50-kg woman, is 0.16 mg/kg day^{-1}. The ESLUR extrapolated using the rat no-effect level, stating that studies examining the manner in which ethylene glycol in the rat was converted to oxalate reported that it was similar to that of humans. Using the male rat no-effect level of 250 mg/kg day^{-1} (Silbergeld and Carter, 1959), a safety factor of 1562.5 (250/0.16) was calculated. ESLUR (1994b) further stated that if it was assumed that all the Glycolic Acid in a skin-care product was absorbed immediately and distributed through the extracellular fluid, the plasma concentration would increase by 0.8 mg/L, an increase that would be "insignificant in view of fluctuations that could arise from diet and metabolism." Additionally, using a urinary excretion rate of 1.7 mg/h (Niederwieser et al., 1978), steady absorption of 8 mg of Glycolic Acid from an applied product throughout 24 h would result in a deliverance of 0.3 mg/h into the bloodstream. "Thus, the normal excretion of Glycolic Acid could cope easily with this additional input, even without any metabolism to reduce blood levels further." ESLUR (1994b) also examined exposure to Glycolic Acid from food, stating that it is present in a variety of foods, including boneless ham, parsley, celery, haricot beans, and coffee. One value for coffee indicated that the consumption of 30 g of filter coffee would provide 40–90 mg Glycolic Acid. If it is assumed that absorption via the gut and skin are similar, then "blood levels of Glycolic Acid from the diet are likely to be more important than those arising from the topical application of a product."

DuPont's internal safe exposure limit (acceptable exposure limit) for Glypure 99% high-purity Glycolic Acid is 10 mg/m^3, 8- and 12-h TWA (time weighted average) (Haskell Laboratory, 1996).

Lactic Acid

Again from information that estimates that the majority of women would use between 0.5 and 1.0 g of skin-care cream daily, the expected exposure to Lactic Acid, assuming 10% absorption and a 50-kg person, is 0.16 mg/kg day^{-1} (ESLUR, 1994a). The 10% absorption rate was based on studies indicating that approximately 50% of Lactic Acid applied in a cream penetrates rat skin, and that the skin of the rat is five to ten times more permeable than human skin (ECETOC, 1993). The ESLUR (1994a) states that the changes in blood and urine concentrations of Lactic Acid, assuming 100% absorption, would be nonconsequential for the

same general reasons discussed for Glycolic Acid. As with Glycolic Acid, the amount of Lactic Acid that the body would be exposed to by use of Lactic Acid in skin care products was compared to the amount of Lactic Acid contained in foods, citing examples of 500 mg Lactic Acid in 100 g of yogurt and 70 mg Lactic Acid in 100 g of wine. Again, assuming similar absorption via the gut and skin, "blood levels of Lactic Acid arising from the diet are likely to be considerably greater than that arising from the topical application of a skin-care product."

PROPOSED MECHANISMS OF ACTION

As with data included in other sections of this report, the information included in this section generally represents the opinions of the researchers. The inclusion of these references regarding proposed mechanisms is not an endorsement of their validity.

It has been claimed that AHAs have a profound effect on keratinization by modulating stratum corneum formation through diminished cellular cohesion between corneocytes at the lowermost newly forming layers of the stratum corneum, at its junction with the stratum granulosum, and not by causing disaggregation of corneocytes of the mature upper layers of the stratum corneum (Van Scott and Yu, 1984; Yu and Van Scott, 1994). These researchers stated that this [proposed] effect is clinically detectable when the stratum corneum is thick enough for it to be apparent by sheet-like separation of the stratum corneum resulting in a thinner, more flexible stratum corneum. High concentrations of AHAs, which were more penetrating but less specific, could impact on the papillary and reticular dermis, leading to dermal changes, including the synthesis of new collagen (Van Scott and Yu, 1989b).

These researchers also stated that the influence of AHAs on corneocyte cohesion appears to be due to their actions on ionic bonds (Van Scott and Yu, 1984). While acknowledging that it is unknown whether AHAs function physiologically, promoting normal desquamation by modulating diminished corneocyte adhesion, the researchers state that it could be assumed that AHAs achieve diminished corneocyte adhesion by inhibiting the biosynthesis of sulfated or phosphorylated cell surface mucopolysaccharides, glycoproteins, sterols, and lipid phosphatides.

Yu and Van Scott (1994) asserted that the [proposed] effects of AHAs on the stratum corneum were not due to their action on mitosis of basal cells; they reported that AHAs do not have an inhibitory or stimulatory effect on mitosis. They also stated that the [proposed] effects were not due to skin irritation since some gentle AHAs achieve the same effects without irritating the skin. Additionally, they reported that the effects of AHAs on the stratum corneum were neither due to keratolytic actions

nor due to any antioxidant properties; they stated that neither Glycolic nor Lactic Acid is an antioxidant. However, it has been reported that Glycolic Acid has anti-inflammatory activity with antioxidant properties (Murad and Shamban, 1994b).

Although Yu and Van Scott claim that AHAs do not work by irritating the skin, others propose that because AHAs are acids and have a low pH, they produce clinical (high concentration) or subclinical (low concentration) irritation (Jackson, 1993, 1994). This irritation is proposed to stimulate the stratum germinativum of the epidermis, increasing epidermal turnover rates and producing "fresh skin." Jackson (1994) reported that both theories could be true under different circumstances. He proposed that in mild or severe conditions of ineffective desquamation, the corneocyte adhesion loosening could be operative. He also stated that at lower concentrations, subclinical irritation could diminish fine lines and wrinkles by producing fresh skin, smooth or retexture the skin, and clarify the skin from chloasmas. Another proposed mechanism was an extension of the cell proliferation theory (Jackson, 1993). Slight edema resulted from inflammation due to exposure to the acid, plumping up the skin and minimizing the appearance of fine lines and wrinkles.

Yu and Van Scott (1994) also theorized that AHAs at greater bioavailability have deeper effects in the dermis. Topical application of Glycolic and Lactic Acids to photoaged skin has produced increased amounts of mucopolysaccharides and collagen and has increased skin thickness without detectable inflammation as determined by skin biopsies (Ditre et al., 1996). Also, topical application of AHA formulations has resulted in skin that was less wrinkled and less dyspigmented. Yu and Van Scott (1994) contended that these effects were not due to edema formation. Ridge et al. (1990) suggested increased stratum corneum hydration through the humectant qualities of AHA as a possible mechanism.

Glycolic Acid

Moy et al. (1996b) examined the effect of Glycolic Acid on the radioactive collagen production in human skin fibroblasts in culture. Fibroblast cultures initiated from biopsy of normal human skin were preincubated in a medium containing 50 μg/mL Glycolic Acid and 25 μg/mL ascorbic acid for 4 or 24 h, and the cells were then labeled with [^{3}H]-proline. Control fibroblasts were preincubated with ascorbic acid only. The synthesis of radioactive hydroxyproline in nondialyzable fraction was used as the index of procollagen production. Procollagen production was not affected by 4-h pretreatment with Glycolic Acid. However, procollagen production increased approximately 10-fold with 24-h Glycolic Acid pretreatment. Cell protein production increased almost 20-fold with Glycolic Acid pretreatment. It was suggested that the specific stimulatory effect

of Glycolic Acid could "explain some of the positive benefits from the clinical use of Glycolic Acid."

Kligman (1993) stated that Glycolic Acid causes loosening of epidermal corneocytes, leading to exfoliation of the outer cell layers of the stratum corneum. He also stated that dilute solutions act on the stratum corneum, while more concentrated solutions penetrate more deeply and cause epidermolysis. He proposed that 5–10% Glycolic Acid decreased the cohesiveness of the corneocytes by "softening the intercellular substance that holds them together," but did not state whether the cells that line the follicular epithelium will produce less coherent corneocytes. He also stated that 10% Glycolic Acid may stimulate fibroblasts and macrophages in the dermis.

As the mechanism of action of Glycolic Acid is unknown, one speculation is that, because of its small size, the molecule penetrates the skin, loosening epidermal attachments and taking its acidic characteristics with it through the epidermis into the dermis, producing inflammation followed by replacement with new cells after the sloughing of the epidermal cells (Elson, 1993). However, the researcher stated dermal activity may be significantly more complicated and no receptors of Glycolic Acid have been identified. A second speculation is that Glycolic Acid could act as a free radical scavenger, since it has been proposed that a significant portion of the photoaging process involves the formation of free radicals by supplying H^+ to use up the negativity preventing the arachidonic acid cascade (Elson, 1993). Therefore, although there appears to be no specific binding site for Glycolic Acid to function at the cellular level, there could be many nonspecific sites for this substance to react. Elson stated that others [persons not specified] "have proposed a mechanism whereby Glycolic Acid molecules may coalesce, resonate, and act as free radical scavengers in this manner."

SUMMARY

This report provides a review of the safety of Glycolic Acid, Ammonium, Calcium, Potassium, Sodium, Methyl, Ethyl, Propyl, and Butyl Glycolates, Lactic Acid, and Ammonium, Calcium, Potassium, Sodium, TEA-, Methyl, Ethyl, Isopropyl, Butyl, Lauryl, Myristyl, and Cetyl Lactates. These ingredients belong to a group of ingredients known as alpha-hydroxy acids (AHAs), the CIR review of which was accelerated due to the vast interest in these ingredients and their possible effects. Myristyl and Cetyl Lactate have previously been reviewed by CIR, but updated information is included in this report.

AHAs can function as mild exfoliants. Different grades and purities of Glycolic Acid are available, but the technical-grade Gycolic Acid is not to be used in cosmetics. Glycolic and Lactic Acid can also be used as pH adjusters, and Lactic Acid, Potassium Lactate, Sodium Lactate, TEA-Lactate, Lauryl Lactate, Myristyl Lactate, and Cetyl Lactate can function as skin conditioning agents. Frequency of use data submitted to the FDA in 1996 and concentration of use data provided by industry in 1995 are summarized in Table 46. The pH of the formulations in which these ingredients are used generally ranges from 2 to 8. The pH of 12 commercial products was determined by FDA and ranged from 2.68 to 8.19. The relationship between the total concentration of AHA, the concentration of free acid, and the pH is complicated and cannot be calculated simply on the basis of the Henderson–Hasselbalch equation.

AHAs have various noncosmetic uses, including many claims for treatment of certain diseases, but only Ammonium Lactate has been approved by the FDA (for treatment of ichthyosis vulgaris and xerosis). FDA has approved Glycolic Acid as an indirect food additive and Lactic Acid, Calcium Lactate, Potassium Lactate, Sodium Lactate, Ethyl Lactate, and Butyl Lactate have been approved as direct food additives.

Absorption of AHAs varies with the pH of the material applied. In a study using a 5% Glycolic Acid oil-in-water emulsion comparing the skin absorption at pH 3 vs. pH 7 over 24 h using *in vitro* flow-through cell techniques, 38.8% of the applied dose was absorbed at pH 3, whereas only 2.7% of the applied dose was absorbed at pH 7, with 82 and 90%, respectively, of the applied dose being recovered. In a second study in which two o/w emulsion vehicles were used, total absorption using a vehicle that included two nonionic surfactants was 24.8 and 3.9% at pH

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Table 46. Current frequency of use and concentration of use data reported to FDA

Ingredient	Frequency of use	Concentration of use[a]
Glycolic Acid	42	<1–≤20%
Ammonium Glycolate	19	—
Sodium Glycolate	1	—
Lactic Acid	342	0.1–11.8% (≤25%)
Potassium Lactate	3	<0.1%
Sodium Lactate	93	0.1–0.4% (≤50%)
TEA-Lactate	13	—(≤0.1%)
Ethyl Lactate	3	50%
Lauryl Lactate	13	0.1–5% (≤25%)
Myristyl Lactate	195	>1.5–15% (≤50%)
Cetyl Lactate	38	0.5–9% (≤25%)

[a]If the concentration of use reported to FDA in 1984 was greater than what was reported in 1996, the 1984 value is included in parentheses.

3 and 7, respectively, and total absorption using a vehicle that included a nonionic and an ionic surfactant was 34.8 and 2.3% at pH 3 and 7, respectively. In an *in vitro* skin absorption study of 10% aq. Glycolic Acid (pH not specified) using female abdominal skin, the average total absorption over 24 h was 0.15% of the applied dose.

Lactate is distributed equivalently to or slightly less than total water in the body and can diffuse readily across cell membranes, primarily by passive transport. Using a primed-constant infusion technique, the lactate turnover rate was 81–82 mg/kg h^{-1} in humans and 50–60% of lactate turnover was derived from blood glucose. In a primed infusion study using L-Lactic Acid, turnover was approximately 96 mg/kg h^{-1}, with approximately 88% oxidation to carbon dioxide.

Safe exposures estimations predict that, even upon complete absorption of Glycolic and Lactic Acid, the increase in plasma concentration would be insignificant and normal excretion could cope with additional inputs in the blood. While clinical reports suggested that Glycolic and Lactic Acid can function as a penetration enhancer and facilitate the absorption of various active ingredients, further animal and clinical tests indicated that AHA pretreatment does not enhance penetration of hydroquinone, musk xylol, hydrocortisone, or glycerin.

Acute toxicity studies (LD_{50} determinations) with various AHA ingredients have demonstrated that these ingredients are of a low order of toxicity when applied dermally or orally. In short-term oral studies, feeding rats Glycolic Acid resulted in oxalate-induced calculi formation. In chronic oral studies of Glycolic Acid using rats, an increase in renal

oxalate and nephrotoxic effects were observed in male but not female rats; chronic administration of Sodium Glycolate also resulted in oxalate production.

In a 21-day dermal study using rabbits, a 12% Ammonium Lactate lotion, pH 5–5.5, did not induce compound-related signs of toxicity, but did produce local irritation at the application site. Short-term dermal testing of facial products containing 0.10–0.15% of 60% aq. Sodium Lactate also did not cause systemic toxicity in rabbits but did cause some irritation. In subchronic dermal testing, no significant findings of toxicity were observed with application of cosmetic formulations containing 0.25 of 85% aq. Lactic Acid, 0.10 of 60% aq. Sodium Lactate, or 0.75 or 1.0%, pH 7–8, Cetyl Lactate. Application of a 12% Ammonium Lactate lotion, pH 5–5.5, to the backs of rabbits in a 90-day study caused mild irritation.

In subchronic oral studies, no significant toxicity was seen after oral administration of Lactic Acid to rats, pigs, or hamsters, but oral administration of Calcium Lactate to rats caused some nephrocalcinosis. Subchronic oral administration of Myristyl Lactate resulted in toxic effects, but the researchers concluded that it was safe for cosmetic use due to exaggerated conditions of the test. In chronic oral studies using 1–2% Glycolic Acid, decreased growth weight and increased renal oxalate content was observed for male, but not female, rats. Chronic oral administration to rabbits of Glycolic Acid and Sodium Glycolate also resulted in increased renal oxalate content.

Dermal irritation testing of products reportedly containing 15–50% Glycolic Acid, pH 4.5, (FDA analysis of a product that was reported to contain 50% Glycolic Acid found it to contain 30%) in rabbits concluded the products were nonirritating. Dermal exposure to skin cream formulations containing 0.6% of 85% aq. Lactic Acid, pH 7.5, caused mild to moderate irritation in rabbits, and undiluted 60% aq. Lactic Acid resulted in negligible irritation. A 12% Ammonium Lactate solution produced mild irritation. Facial product and hair conditioner formulations containing 0.1–0.4% of 60% aq. Sodium Lactate, pH 3.4–8.6, a nail enamel corrector formulation containing 50% Ethyl Lactate, skin and facial preparations containing 2–5% Lauryl Lactate, a foundation and lip pencil containing 7.65–11.54% Myristyl Lactate, and skin-care, facial products, lipstick, and foundation formulations containing 0.5–9.0% Cetyl Lactate, pH 6–8, caused no to mild dermal irritation; no pattern or effect as a function of pH or concentration was discernable. In other studies of Sodium Lactate using guinea pigs and rabbits, the results were similar. Undiluted Glycolic Acid (70% technical grade) caused severe irritation in one rabbit.

RIPTs and maximization tests using AHAs were negative. AHAs were not photosensitizers or phototoxins. Lactic Acid and Sodium Lactate did

not cause urticarial reactions. Lotions and creams containing 2–10% Glycolic Acid, pH 3.7–3.9, were not comedogenic.

Using *in vivo* methods, the severity of ocular irritation of lotions and creams containing 4–8% Glycolic Acid, pH 3.8–4, ranged from nonirritating to mildly irritating; undiluted Glycolic Acid was corrosive and caused irreversible effects to the eye. In *in vitro* studies, skin and lip formulations containing 2.86–14.29% aq. 70% Glycolic Acid, pH 3.5–5.5, were mild–moderate to severe irritants in the Eytex assay. In *in vivo* testing for ocular irritation with Lactic Acid, a skin cream containing 0.6% of 85% aq. Lactic Acid, pH 7.5, caused minimal irritation and a solution containing 10–20% Lactic Acid, pH not given, produced significant irritation. A lotion containing 12% Ammonium Lactate was an ocular irritant, 60% aq. Potassium Lactate, pH 8.1, was slightly irritating, and 50–70% Sodium Lactate caused no significant ocular irritation. Face and hair products containing 0.1–0.4% of 60% aq. Sodium Lactate, pH 3.4–8.6, caused no to mild ocular irritation and a 100% solution produced irritation, nail enamel correctors containing 50% Ethyl Lactate caused moderate irritation, face creams containing 5% Lauryl Lactate, pH 4.65, caused minimal to mild irritation, a foundation and lip pencil containing 7.65 and 11.54% Myristyl Lactate caused mild and no irritation, and skin, face, and lip products containing 0.5–9% Cetyl Lactate, pH 6–8, caused primarily no to mild ocular irritation. Using *in vitro* methods, face, eye and nail formulations containing 0.12–11.8% of 85% aq. Lactic Acid, pH 2.0–7.5, were minimal to moderate–severe ocular irritants, skin and hair products containing 0.15–20% of 60% aq. Sodium Lactate, pH 3.2–3.8, and eye creams containing 0.1% Lauryl Lactate, pH 5.3–6.3, were minimal irritants, a face cream containing 3.2% Lauryl Lactate, pH 3.9, was a moderate irritant, eye shadows containing 5–15% Myristyl Lactate were minimal irritants, and skin, face, and eye products containing 0.75–2% Cetyl Lactate, pH 5.3–8, were minimal to minimal–mild ocular irritants.

A developmental toxicity study using Glypure 99% high-purity Glycolic Acid reported developmental and maternal toxicity; the no-observed-effect-level was 150 mg/kg. Technical-grade 70% Glycolic Acid solution produced some fetotoxic effects, with a no-observed-adverse-effect level of 250 mg/kg day^{-1}. An *in vitro* embryo culture study suggested that pH was not a major factor in Glycolic Acid toxicity. In a study using mice, the only fetal effect observed after treatment with Lactic Acid was an increase in delayed ossification of the parietal bones.

Glycolic Acid was not mutagenic in Ames tests and was not clastogenic in a chromosome aberration assay. Lactic Acid was generally nonmutagenic in Ames tests, was not clastogenic in chromosomal aberration assays, was negative in a DNA-cell binding assay, and produced intermediate mutant yields in a reversion test. Ammonium Lactate was negative

in an Ames test, and Sodium Lactate was negative in an Ames test, chromosomal aberration assay, and forward mutation assay. In studies examining the carcinogenic potential of Lactic Acid in rabbits and Calcium Lactate in rats, no significant positive effects were observed.

Both cosmetic and medical or therapeutic skin effects of AHAs were examined clinically. In cosmetic effects studies, no adverse reactions or skin thickening was produced by Glycolic Acid. Generally, application of Glycolic Acid did not induce structural differences in the skin, although in some subjects some changes in the stratum corneum were observed. In most studies, Glycolic Acid did not change the water content of the stratum corneum, and it did not increase TEWL. In one study it was found that Glycolic and Lactic Acid increased cell renewal and that pH, cell renewal, and skin irritation were correlated, but that the ability of Glycolic and Lactic Acid to increase renewal diminished over time.

Where one study found that no adverse reactions or skin thickening, another study found skin thickness increased with Lactic Acid treatment, and Ammonium Lactate increased epidermal thickness in some studies. Lactic Acid increased skin hydration, and Lactic Acid and Sodium Lactate plasticized the stratum corneum.

Mini-cumulative irritation patch assays were performed with creams and lotions containing 2–10% Glycolic Acid at pH values from 3.7–4.0. Skin irritation ranged from essentially nonirritating to moderately irritating; no correlation between pH and/or concentration was observed. In 14- and 21-day cumulative irritation assays, mild irritation was generally observed; one researcher concluded that the irritation potential of Glycolic Acid was regulated by pH and was not concentration dependent. In facial discomfort assays with creams and lotions containing 2–10% Glycolic Acid, pH 3.5–5.4, discomfort ranged from nonstinging to moderate stinging; no correlation between pH and/or concentration was observed. In some studies in which Glycolic Acid was applied to the face or chest, subjective moderate discomfort or follicular reactions were reported.

Mini-cumulative irritation patch assays were performed with creams and lotions containing 4–8% Lactic Acid at a pH range of 3.8–5.0. Skin irritation ranged from essentially nonirritating to moderately irritating; no correlation between pH and/or concentration was observed. In facial discomfort assays with creams and lotions containing 4–10% Lactic Acid, pH 3.3–4.3, discomfort ranged from nonstinging to moderate stinging; no correlation between pH and/or concentration was observed.

In stinging assays, stinging with Lactic Acid application was observed. Ammonium Lactate, 8 or 12%, caused no to moderate irritation. However, one researcher reported some irritation in all subjects and concluded that lotions containing 8–12% Ammonium Lactate were not

suitable for use on the face of fair Caucasian females. Ethyl and Butyl Lactate were not irritating.

Studies examining the effect of Glycolic Acid on SBC production found greatly varying results among the individual subjects used in the studies. In a 4-day study, there was also no difference between skin that was treated with Glycolic Acid or vehicle and untreated skin. In a 12-week study, a statistically significant increase in SBCs was observed in skin treated with Glycolic Acid as compared to skin treated with vehicle or mineral oil or untreated skin. In a study in which creams containing 4 or 8% Glycolic Acid, SPF 2.9, were applied for 4 days, after which the test sites and an untreated control site were irradiated, less SBCs were observed at the treated sites compared to the control site. In another study, no or few SBCs were found in skin from forearms that were dosed with 8% Glycolic Acid, 8% Lactic Acid, or vehicle for 22 weeks and exposed to incidental sunlight.

A total of 69 consumer adverse experience reaction reports for AHA-containing products were submitted to FDA headquarters between 1989 and February 1996 and a total of 18 were submitted to FDA district offices between 1989 and November 1995. For a company that distributed four products containing 2–10% Glycolic Acid, pH 3.02–3.9, and a company that distributed one product containing 1% Lactic Acid, pH 5.5, the average complaint rate for the Glycolic Acid products was 8 per million units (compared to an average complaint rate of 3 per million for this company's traditional moisturizers) and for the Lactic Acid product was 14 per million units (compared to an average complaint rate of 8 per million for this company's traditional moisturizers).

DISCUSSION

For ease of discussion, Glycolic and Lactic Acid, their common salts, and their simple esters are referred to as AHA ingredients. The Expert Panel considered that there are three categories of use of AHA ingredients: consumer use, salon use, and medical use. The Expert Panel stressed that this review does not address the medical use of AHA ingredients; this review addresses only the consumer and salon use, i.e., those products available to the general public and those applied by trained estheticians, respectively.

While the Expert Panel focused on several areas of concern in its consideration of these ingredients, there is a great deal of data in the report from which it can be concluded that AHA ingredients can be used safely at certain concentrations and pH levels. For example, the Expert Panel interpreted the available data to mean that AHA ingredients are not mutagenic or carcinogenic. Likewise, data suggest that AHAs are not reproductive or developmental toxins. The Expert Panel also agreed that clinical testing supports the view that AHAs are not sensitizers.

The areas that are of concern to the Expert Panel are the known irritation potential, the potential enhancement of penetration of other ingredients, and the potential increase in sensitivity to sunlight. These latter two concerns arose from the ability of AHA ingredients to remove a portion of the stratum corneum. Since the stratum corneum is a barrier to many chemicals, its removal may increase penetration. Likewise, the stratum corneum both reflects and absorbs ultraviolet radiation (UVR), and it was suspected that alterations might result in an increase in the amount of UVR reaching sensitive skin cells. Each of these issues is considered below.

IRRITATION

The available data demonstrate that AHA ingredients can be dermal irritants. These data show an interdependence of concentration and pH. At a given pH, increasing the concentration increases irritation. At a given concentration, reducing the pH increases the irritation.

The extensive data on irritation produced by AHA ingredients suggest that concentrations of Glycolic Acid used in leave-on products no greater

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than 20% and Lactic Acid no greater than 10%, with a pH no less than 3.5, would not produce irritation to an unacceptable degree. Likewise, rinse-off uses with concentrations no greater than 30% and a pH no less than 3.0 are considered to present an acceptable irritation risk if applied in a brief, discontinuous fashion followed by thorough rinsing by trained individuals. The Expert Panel expressed concern that salon customers not be treated frequently.

Even within those concentration, pH, and training constraints, the Expert Panel stressed that it is possible to formulate in ways that would be inappropriate and, therefore, urged that products be formulated to limit irritation. For example, increased irritation sensitivity of tissue around the area of the eye led to a specific recommendation that AHA-containing products intended for use near the eye be formulated in such a way as to reduce stinging and burning reactions.

PENETRATION ENHANCEMENT

The Expert Panel agreed that animal test data indicated that pretreatment with AHA ingredients did not result in enhanced penetration of hydroquinone or musk xylol. The Expert Panel also agreed that additional human test data confirmed an absence of penetration enhancement for hydrocortisone and glycerin. Based on these data, the Expert Panel concluded that there is no need to be concerned about AHA ingredient use enhancing the penetration of other chemicals.

The Expert Panel considered data included in the report that clearly indicated that AHA ingredients themselves were absorbed across the skin, especially at lower pHs. However, as noted above, AHA ingredients have a notable lack of systemic toxicity; therefore, concern regarding the amount of absorption was not warranted.

Although animal tests did not show any enhancement in penetration, there was an increase in cell proliferation. This effect was evaluated together with data on changes in the sensitivity of human skin to sunlight.

SUN SENSITIVITY

Limited data assessing the effects on MED show that the MED was increased in one study and reduced in another by AHA application. In the study showing the reduction of the amount of UVR needed to produce reddening (potentiation of radiation damage), the Expert Panel noted there was a wide variation in the effect. While an overall 13% reduction was seen, some individuals experienced a 50% reduction.

In a more comprehensive study that used SBC production as a measure of UVR damage in volunteers pretreated with AHA ingredients at

concentrations as great as 10%, the Expert Panel noted a similar wide variation in individual response. These studies were done using volunteers preselected because their skin type makes them very sensitive to the sun. The initial statistical analysis showed a small, but statistically significant, increase in the number of SBCs produced by one MED of UVR in these sun-sensitive individuals pretreated with AHA ingredients compared with untreated, vehicle-treated, or mineral oil-treated skin. A subsequent, different statistical analysis confirmed the increase in SBCs in the AHA-treated individuals.

The Expert Panel compared the increase in the number of SBCs associated with AHA pretreatment to SBCs produced as a function of increased UV exposure alone. AHA pretreatment caused less of an increase than did raising the UV exposure to 1.56 MED. The increase in UVR damage associated with AHA pretreatment was of such a magnitude that it is easily conceivable that aspects of cosmetic product formulation could eliminate the effect. For example, inclusion of a sunscreen with an SPF of 2 would eliminate the effect. Likewise, addition of color additives or vehicles that produce even a small increase in UVR reflectance would eliminate the effect.

Based on the data, however, the Expert Panel concluded that some steps should be taken to minimize the potential that use of AHA ingredients would result in increased sun sensitivity. Accordingly, the Expert Panel admonished producers of leave-on cosmetics containing AHA ingredients to either formulate to avoid increasing sun sensitivity (as discussed above) or to provide directions for use that include the daily use of sun protection.

Because of the higher concentrations and lower pHs allowed for rinse-off products, and in consideration that application is by a trained professional, the Expert Panel was of the opinion that mandating directions for the daily use of sun protection was both necessary and sufficient for these products.

The Expert Panel expanded on the meaning of daily use of sun protection to include the American Academy of Dermatology (AAD) recommendations. The AAD recommends avoiding the sun between the peak hours of 10:00 am and 4:00 pm, using a sunscreen with an SPF of 15 or greater, and wearing protective clothing and hats.

The Expert Panel recalled that there were insufficient data to conclude that urocanic acid is safe for use in cosmetics (Andersen, 1995). Because of this, sunscreens containing urocanic acid should not be used by consumers when trying to minimize the potential of increased sun sensitivity due to AHA use. Additionally, the Expert Panel discussed the need to alert users of products containing AHA ingredients about the need to avoid exposure to the sun when using medications that are photosensitizers.

Taking each of these areas of concern into consideration (irritation, penetration enhancement, and sun sensitivity), the Expert Panel is of the opinion that a limitation on both concentration and pH is appropriate for AHA ingredients. The data support that concentrations no greater than 10% at pHs no less than 3.5 can be used safely in products intended for the retail market, i.e., products where the likely use is leave-on.

Even with these limitations on concentration, however, such products should either be formulated to avoid increasing any user's sun sensitivity or be accompanied by directions for the daily use of sun protection. The data support that for products designed for brief, discontinuous use followed by thorough rinsing, as applied by trained professional, higher concentrations and lower pHs may be used safely, providing the customer is instructed to use daily sun protection.

CONCLUSION

Based on the available information included in this report, the CIR Expert Panel concludes that Glycolic and Lactic Acid, their common salts and their simple esters, are safe for use in cosmetic products at concentrations $\leq 10\%$, at final formulation pH ≥ 3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection. These ingredients are safe for use in salon products at concentrations $\leq 30\%$, at final formulation pH ≥ 3.0, in products designed for brief, discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals, and when application is accompanied by directions for the daily use of sun protection.

Note added in proof: A recent clinical test was conducted (A. W. Johnson, Chesebrough–Ponds USA, Trumbull, CT, personal communication) with 12 healthy females using commercial skin creams containing 4 and 8% Glycolic Acid, both at pH 3.8, and sunscreens (SPF = 4). At weeks 6, 12, and 24, the subjects were exposed to 1 MED of solar simulated UV radiation and biopsied 24 h after the exposure. No sunburn cells (a measure of UV radiation damage, described in this report) were detected in treated skin, compared to a small number in skin receiving UV radiation alone. Quantification of stratum corneum cell layers showed no change or a slight increase after the 6 months of AHA treatment. This supports the idea that AHAs can be formulated to avoid increasing sun sensitivity.

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