
Safety Assessment of Alpha Hydroxy Acids as Used in Cosmetics

Status: Re-Review for Panel Review
Release Date: November 15, 2013
Panel Meeting Date: December 8-9, 2013

The 2013 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This re-review document was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer.

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume *MMF*
Senior Scientific Analyst/Writer
Date: November 15, 2013
Subject: Re-Review of Alpha Hydroxy Acids as Used in Cosmetics

The re-review of Alpha Hydroxy Acids (AHAs) as used in cosmetics is being presented to the Panel. In 1998, the Panel concluded 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. The Discussion of the report focused on three main area of concern: the known irritation potential, the potential enhancement of penetration of other ingredients, and the potential increase in sensitivity to sunlight.

Because it has been 15 years since the report was published, the Panel is being asked to determine whether there is any reason to re-open the safety assessment of these ingredients, or, if the conclusion should be reaffirmed. No ingredients are being suggested as “add-ons” for inclusion in this review.

TEA-lactate was re-reviewed in 2013 as part of the CIR safety assessment of triethanolamine and triethanolamine-containing ingredients as used in cosmetics. The Panel concluded that TEA-lactate, as part of that report, is safe as used when formulated to be non-irritating and when the levels of free diethanolamine do not exceed the present practices of use and concentration found safe for diethanolamine itself, and it should not be used in cosmetic products in which *N*-nitroso compounds can be formed. TEA-lactate was reported to be used at 0.06% in leave-on formulations, and the highest reported concentration of use of triethanolamine in a leave-on product was 6%.

The use of AHAs in cosmetic formulations has increased remarkably over the past 15 years. In the original 1998 safety assessment, glycolic acid was reported to be used in 42 formulations and lactic acid in 342 formulations. According to 2013 VCRP data, glycolic acid is now used in 337 formulations and lactic acid in 1042 formulations.

Concentration of use data were received from the Council and incorporated in the report. Most of the reported concentrations of use adhere to the concentration limitation set forth in the original report. However, a few exceptions are noted: glycolic acid is reported to be used up to 50% in face and neck products and in skin cleansing preparations (but concentrations for all other categories report use at $\leq 10\%$); ethyl lactate is used at 95% in “other” manicuring formulations and at 50% in nail polish and enamel removers; and myristyl lactate is used at up to 13.2% in lipstick formulations.

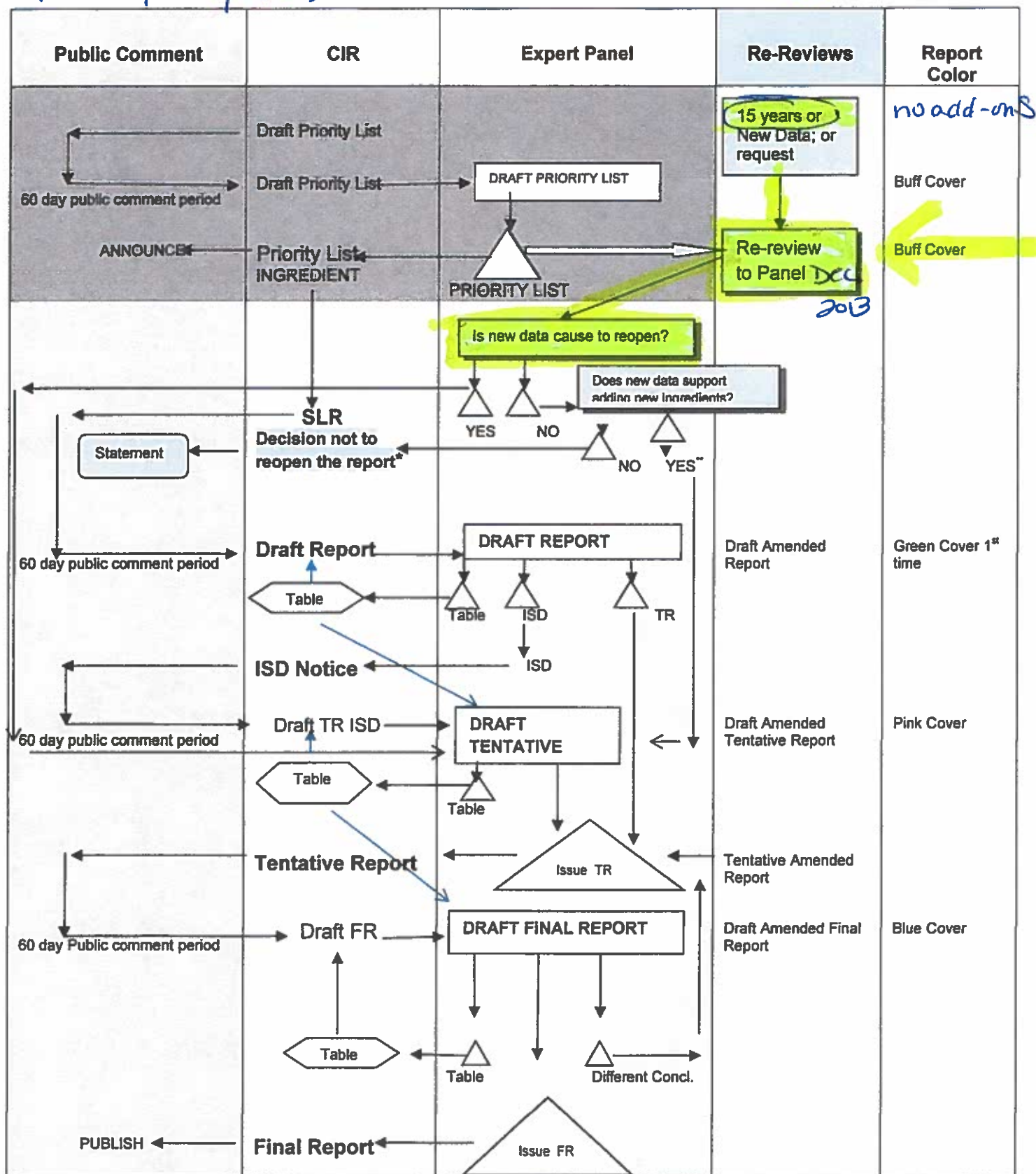
A search of the published literature was conducted, and all relevant papers were obtained. For the initial evaluation of this re-review document by the Panel, those references are listed at the end of the report, and only a summarization of significant new data is included in text.

Finally, the original safety assessment is being provided to you as part of this re-review package. For those of you that were Panel members at the time of the original review, you will recall that the assessment of this ingredient family was very thorough and the discussions were very robust. The minutes from all the Panel meetings at which the safety of these ingredients was deliberated are being included so that you have a complete history.

SAFETY ASSESSMENT FLOW CHART

Alpha Hydroxy Acids

Dec 2013



Alpha Hydroxy Acids Re-Review History

December 9-10, 2013: Re-Review

In 1998 the CIR published the report with the conclusion: The Panel concluded 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.

No add-on ingredients are proposed.

Alpha Hydroxy Acids Data Profile* - Dec 2013 - Monice Fiume

	Reported Use	Method of Mfg	Impurities	Toxicokinetics	Animal Tox - Acute, Dermal	Animal Tox - Acute, Oral	Animal Tox, Acute, Inhalation	Animal Tox - Rptd Dose, Derm	Animal Tox, Rptd Dose, Oral	Animal Tox - Rptd Dose, Inhal	Repro/Dev Tox	Genotox	Carcinogenicity	Dermal Irr/Sens	Phototoxicity	Ocular Irritation
ORIGINAL REPORT																
Glycolic Acid	X	X	X	X		X	X		X	X	X	X		X	X	X
Ammonium Glycolate	X															
Calcium Glycolate																
Potassium Glycolate																X
Sodium Glycolate	X			X		X			X		X			X		
Methyl Glycolate																
Ethyl Glycolate																X
Propyl Glycolate																
Butyl Glycolate																
Lactic Acid	X	X	X	X		X		X	X		X	X	X	X	X	X
Ammonium Lactate		X				X		X				X		X	X	X
Calcium Lactate		X							X				X			
Potassium Lactate	X	X														X
Sodium Lactate	X	X		X		X		X			X	X		X		X
TEA-Lactate	X															
Methyl Lactate		X														X
Ethyl Lactate	X	X			X	X								X		X
Isopropyl Lactate																
Butyl Lactate		X			X	X								X		
Lauryl Lactate	X					X								X		X
Myristyl Lactate	X		X			X			X					X		X
Cetyl Lactate	X		X			X		X	X					X		X

Alpha Hydroxy Acids Data Profile* - Dec 2013 - Monice Fiume																
	Reported Use	Method of Mfg	Impurities	Toxicokinetics	Animal Tox - Acute, Dermal	Animal Tox - Acute, Oral	Animal Tox, Acute, Inhalation	Animal Tox - Rptd Dose, Derm	Animal Tox, Rptd Dose, Oral	Animal Tox - Rptd Dose, Inhal	Repro/Dev Tox	Genotox	Carcinogenicity	Dermal Irr/Sens	Phototoxicity	Ocular Irritation
Re-Review																
Glycolic Acid	X			X							X		X			
Ammonium Glycolate	X															
Calcium Glycolate																
Potassium Glycolate																
Sodium Glycolate	X															
Methyl Glycolate																
Ethyl Glycolate																
Propyl Glycolate																
Butyl Glycolate																
Lactic Acid	X			X												
Ammonium Lactate	X															
Calcium Lactate	X															
Potassium Lactate	X															
Sodium Lactate	X															
TEA-Lactate	X															
Methyl Lactate	X															
Ethyl Lactate	X									X						
Isopropyl Lactate																
Butyl Lactate	X									X						
Lauryl Lactate	X															
Myristyl Lactate	X															
Cetyl Lactate	X															

*"X" indicates that data were available in a category for the ingredient

Glycolic Acid
79-14-1

Ammonium Glycolate
35249-89-9

Calcium Glycolate – not in Dictionary; not in CosIng

Potassium Glycolate – 1932-50-9 - not in Dictionary; not in CosIng

Sodium Glycolate
2836-32-0

Methyl Glycolate – not in Dictionary; not in CosIng

Ethyl Glycolate – not in Dictionary; not in CosIng

Propyl Glycolate - not in Dictionary; not in CosIng

Butyl Glycolate
7397-62-8

Lactic Acid
50-21-5; 79-33-4

Ammonium Lactate
515-98-0; 52003-58-4

Calcium Lactate
5743-47-5; 814-80-2

Potassium Lactate
85895-78-9; 996-31-6

Sodium Lactate
72-17-3; 867-56-1

TEA-Lactate
20475-12-1

Methyl Lactate
27871-49-4; 547-64-8

Ethyl Lactate
97-64-3

Isopropyl Lactate – 63697-00-7 - not in Dictionary

Butyl Lactate
138-22-7

Lauryl Lactate
6283-92-7

Myristyl Lactate
1323-03-1

Cetyl Lactate
35274-05-6

PubMed Search – 10/4,7/13

(alpha AND hydroxy AND acid) OR (Glycolic AND Acid) OR ((Ammonium OR Calcium OR Potassium OR Sodium OR Methyl OR Ethyl OR Propyl OR Butyl) AND Glycolate) OR (Lactic AND Acid) OR ((Ammonium OR Calcium OR Potassium OR Sodium OR Triethanolamine OR Methyl OR Ethyl OR Isopropyl OR Butyl OR Lauryl OR Myristyl OR Cetyl) AND Lactate)
AND (SENSITIZ* OR SENSITIS* OR PHOTOTOX* OR IRRITA* OR PHOTSENS*) - 648
AND (CARCINOGEN* OR MUTAGEN* OR GENTOX* OR CLASTOGEN* * OR (TUMOR AND (PROMOT* OR INITIAT*))) - 1488
AND ((DERMAL OR ORAL) AND TOXIC*) OR ((REPRODUC* OR DEVELOP*) AND TOX*) OR TOXICOKINETIC*
OR (DERMAL AND (ABSORB* OR ABSORP* OR PENETRAT*)) OR ((UV OR ULTRAVIOLET) AND (ABSORP* OR ABSORB*)) - 1184
– ALL FROM 1995 on
- 38 papers ordered

EU CosIng Database – 10/8/13

Glycolic Acid – SCCP position paper (on AHAs)
no restrictions: Ammonium, Sodium, and Butyl Glycolate
not listed: Calcium and Potassium Glycolate; Methyl, Ethyl, and Propyl Glycolate
Lactic Acid – SCCP position paper (on AHAs)
no restrictions: Ammonium, Calcium, Potassium, and Sodium Lactate; Butyl, Cetyl, Lauryl, and Myristyl Lactate
TEA-Lactate: III/62 – Trialkylamines, trialkanolamines, and their salts – see website for restrictions
not listed: Isopropyl Lactate

IARC – 10/8/13

nothing

NTP – 10/8/13

Glycolic Acid – photocarc study; repro effects of ethylene glycol
Glycolate – nothing
Lactic Acid – nothing
Lactate – nothing

OECD – 10/8/13

Lactic Acid – OECD; EPA/HPV
no others

REACH – 10/11/13

Glycolic Acid - http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d9b67cf-6aee-3ac1-e044-00144f67d249/DISS-9d9b67cf-6aee-3ac1-e044-00144f67d249_DISS-9d9b67cf-6aee-3ac1-e044-00144f67d249.html
Butyl Glycolate: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9875a518-a596-53d8-e044-00144f67d031/DISS-9875a518-a596-53d8-e044-00144f67d031_DISS-9875a518-a596-53d8-e044-00144f67d031.html

Lactic Acid - http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d9206e2-b2f0-4755-e044-00144f67d249/DISS-9d9206e2-b2f0-4755-e044-00144f67d249_DISS-9d9206e2-b2f0-4755-e044-00144f67d249.html
L-(+)-Lactic Acid: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d98ad08-1f3b-2a26-e044-00144f67d249/DISS-9d98ad08-1f3b-2a26-e044-00144f67d249_DISS-9d98ad08-1f3b-2a26-e044-00144f67d249.html
(R)-Lactic Acid: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9eae9ea1-66a7-0563-e044-00144f67d031/DISS-9eae9ea1-66a7-0563-e044-00144f67d031_DISS-9eae9ea1-66a7-0563-e044-00144f67d031.html
Sodium Lactate: http://apps.echa.europa.eu/registered/data/dossiers/DISS-dcd6f8da-a5c7-4638-e044-00144f67d031/DISS-dcd6f8da-a5c7-4638-e044-00144f67d031_DISS-dcd6f8da-a5c7-4638-e044-00144f67d031.html
Sodium (S)-Lactate: http://apps.echa.europa.eu/registered/data/dossiers/DISS-dffb4072-e40a-47ae-e044-00144f67d031/DISS-dffb4072-e40a-47ae-e044-00144f67d031_DISS-dffb4072-e40a-47ae-e044-00144f67d031.html
Methyl (R)-Lactate: http://apps.echa.europa.eu/registered/data/dossiers/DISS-db9c1296-a884-2ccf-e044-00144f67d031/DISS-db9c1296-a884-2ccf-e044-00144f67d031_DISS-db9c1296-a884-2ccf-e044-00144f67d031.html

Methyl (S)-(-)-Lactate: http://apps.echa.europa.eu/registered/data/dossiers/DISS-db9a2343-9144-33e1-e044-00144f67d031/DISS-db9a2343-9144-33e1-e044-00144f67d031_DISS-db9a2343-9144-33e1-e044-00144f67d031.html

ChemPortal – 10/11/13

Glycolic Acid:

HPVIS: <http://ofmpub.epa.gov/opptppv/quicksearch.display?pChem=100316>

SIDS – no

IUCLID: http://esis.jrc.ec.europa.eu/doc/IUCLID/data_sheets/79141.pdf

Butyl Glycolate:

IUCLID: http://esis.jrc.ec.europa.eu/doc/IUCLID/data_sheets/7397628.pdf

SIDS: no

Lactic Acid:

SIDS – initial profile: <http://webnet.oecd.org/Hpv/UI/handler.axd?id=240da177-beeb-4c99-b716-355be7dd4637>

EPA HPV: http://www.epa.gov/chemrtk/hpvis/rbp/Lactic%20Acid_Web_SuppDocs_August%202008.pdf

IUCLID – no

Sodium Lactate:

IUCLID: Sodium (S)-Lactate: http://esis.jrc.ec.europa.eu/doc/IUCLID/data_sheets/867561.pdf

SIDS – no

CIR Review History:

Glycolic and Lactic Acids, Their Common Salts and Simple Esters (123/84)

Scientific Literature Review: April 7, 1995

The 90-day comment period closed July 6, 1995.

A large amount of unpublished data was received from industry via CTFA. Data now included in the report that were not included in the Scientific Literature Review are highlighted.

Draft Report: August 28, 1995

Both Teams agreed to add Cetyl Lactate, Lauryl Lactate, Menthyl Lactate, Myristyl Lactate, and Sodium Isostearyl Lactate to the report as requested by industry via CTFA.

The Teams requested that the report be reorganized to separate cosmetic from medical uses of AHAs. Also, human data was moved from the General Biology section to the section on Clinical Assessment of Safety.

The Belito team requested the following data:

1. impurity data on Lactic Acid and its salts and esters;
2. information on whether AHAs decrease barrier function, and if they do, do they enhance penetration of other ingredients in the formulation (especially ingredients that CIR approved because they did not absorb); and
3. information as to what happens with skin TNF- α production upon application of AHAs.

The Schroeter team requested the following data:

1. impurity data on Lactic Acid and its salts and esters;
2. the grade of Glycolic Acid for which concentration of use data was submitted by CTFA;
3. the % aqueous of Lactic Acid for which concentration of use data was submitted by CTFA
4. the sheet used by DuPont stating that only non-technical grade Glycolic Acid (i.e., the GlyPure product) can be used for cosmetic formulation;
5. the units for formaldehyde which were omitted on DuPont's specification sheet;
6. the photoproducts/thymidine dimers and adducts produced upon application of AHAs with UV at different time intervals up to 6 wks with different dose levels; and
7. photocarcinogenicity data.

Draft Report: December 11, 1995

At the previous meeting, the Expert Panel agreed to add five additional esters of Lactic Acid to the report. However, upon researching these ingredients, it was found that two of the esters, Menthyl Lactate and Sodium Isostearyl Lactate, are not AHAs, and that Menthyl Lactate is used as a fragrance. Additionally, it was discovered that Cetyl Lactate and Myristyl Lactate had already been reviewed (JACT 1(2), 1982). These ingredients were found to be safe as used. The Expert Panel agreed to exclude Menthyl Lactate and Sodium Isostearyl Lactate from the report and to include Cetyl and Myristyl Lactate and any relevant data concerning these ingredients.

Information on the three additional esters that appear to be AHAs has been added to the report. Additionally, unpublished data that were marked confidential have been released to CIR for use in the report and have been added. The following are the new unpublished references added:

1. Avon Products, Inc. (1995a) Summary of safety data on Lauryl Lactate that includes acute oral, Draize eye, single skin, *in vitro* ocular irritation, and contact allergy tests. (95-AHA-35). (29 pp.)
2. Avon Products, Inc. (1995f) Summary of data on Myristyl Lactate 100% that includes acute oral, subchronic oral, single skin, Draize eye, and *in vitro* ocular irritation tests. (95-AHA-37). (22 pp.)
3. Avon Products, Inc. (1995g) Summary of data on Cetyl Lactate 100% that includes acute oral, subchronic dermal, single skin, contact allergy, Draize eye, and *in vitro* ocular irritation tests. (95-AHA-33). (99 pp.)
4. CTFA. (1991d) Final report on the efficacy of 4% and 8% AHA formulations. KGL #2459. Report dated July 3. (95-AHA-88). (17 pp.)
5. CTFA. (1992a). Three-month study of a hand and body lotion (86743-02) containing 10% Glycolic Acid. Study dated June 16. (95-AHA-88). (23 pp.)
6. CTFA. (1992d). Six month chest and neck study of a gel (86740-16) containing 2% Glycolic Acid. (95-AHA-65). (13 pp.)

7. CTFA (1994a) Histologic evaluation of skin effects resulting from one month usage of GA [Glycolic Acid, 8%] treatment for face. Dated December 20. (95-AHA-0062). (80 pp.)
8. CTFA (1994e). Three month clinical study of a gel containing 6.0% Lactic Acid. (95-AHA-69). (21 pp).
9. CTFA (1994f). Six month clinical study of a lotion containing 6.0% Lactic Acid. (95-AHA-70). (15 pp).
10. Unilever Research U.S., Inc. (1995) A double-blinded, vehicle-controlled, randomized study to evaluate the efficacy and safety of 8% L-Lactic Acid and 8% Glycolic Acid in the cosmetic improvement of the signs of photodamaged skin (URUS-93-MG-1). (95-AHA-0018).

Data summarized from the original Cetyl and Myristyl Lactate report have been added and are italicized. Also, information on TEA from the original report has been summarized where applicable due to the lack of information on TEA-Lactate, and this information is also italicized.

FDA requested that a conclusion not be made at this meeting because they are preparing a data submittal.

The Expert Panel tabled this review until the next meeting in order to have the opportunity to review data presented by industry at this meeting.

In addition, the Expert Panel identified the following ongoing data needs:

1. pH vs. concentration irritation data for Lactic Acid
2. rinse-off pH vs. concentration data irritation data for Glycolic and Lactic Acids
3. Lactic Acid impurity data
4. form used by DuPont stating that the technical grade Glycolic Acid is not allowed for use in cosmetics
5. units for formaldehyde impurity in Glycolic Acid
6. concentration and pH limitations for professional products containing AHAs from the American Beauty Association (ABA)
7. information on training/qualifications of beauty salon personnel from ABA

Draft Report: March 4-5, 1996

The information that was presented to the Expert Panel at the first meeting, and other published data, were added to the report and highlighted. The following is a list of references that were added:

1. CTFA (1995e) Effect of Alpha Hydroxy Acids on human skin barrier function. A report of *in vivo* effects of Glycolic and Lactic Acids on improved resistance of an SLS challenge.
2. CTFA (1995k) Changes in UV transmittance. Section III (pp 15-20) of *alpha-Hydroxy Acids and the skin barrier*.
3. DiNardo JC. (1995) Effect of pH and concentration on the cumulative irritation potential of Glycolic Acid-based products.
4. Goldstein M, Bruck R. (1994) Evaluation of Glycolic Acid permeation through skin. [Abstract.] *Pharm Res* 11:S-180. PD 7024.
5. KGL, Inc. (1995) Effect of 4% Glycolic Acid on skin barrier integrity.
6. KGL Skin Study Center. (1995a). Seasonal variation of minimal erythema dose (MED) - influence of dryness/roughness.
7. KGL Skin Study Center. (1995b). Effect of 4% Glycolic Acid (GA) on skin dryness, roughness, and minimal erythema dose (MED).
8. Sayre et al. (1961) Skin type, minimal erythema dose (MED), and sunlight acclimation. *Am Acad Dermatol* 5(4):439-43.
9. TKL Research. (1995a) Effect of emollients on the minimal erythema dose (MED).
10. TKL Research. (1995b) Effect of mechanical exfoliation on the minimal erythema dose (MED) response.
11. Viapiana et al. (1992) Clinical and non-invasive evaluation of 12% Ammonium Lactate emulsion for the treatment of dry skin in atopic and non-atopic subjects. *Acute Derm Venereal (Stops)* 7:229-33.

CIR has been told that studies on pH vs. concentration in respect to irritation that repeat the DiNardo study on Glycolic Acid using Lactic Acid are underway. To date, these data, nor any other data fulfilling the Expert Panel's requests, have not been received. Data to be submitted by FDA also have not been received as of yet.

Please note the clarifications made concerning change in MED due to Glycolic Acid pretreatment.

Prior to the meeting, the following studies were received and prepared as reports for the Expert Panel to review:

1. Natura Bissé. (1976) Dermal irritation testing using models of products containing Glycolic Acid.
2. Essex Testing Clinic. (1996) Effect of pH and concentration on the cumulative irritation potential of Lactic Acid-based products.

The FDA review of AHAs was also received between mail date and the Expert Panel meeting and was sent to the Expert Panel for their review prior to the meeting.

An addendum to the Unilever Research US, Inc. (1995) study gives concentration and pH data and that information has been added to the report.

At the meeting, Dr. Bailey presented the FDA concerns regarding the safety of AHAs and the ABA presented scientific, training, and suggested concentration/pH information to the Expert Panel.

Draft Report: June 3-4, 1996

The data that were received between the mailing for the last meeting and the respective Expert Panel meeting are summarized and highlighted in the report:

1. Essex Testing Clinic. (1996) Effect of pH and concentration on the cumulative irritation potential of Lactic Acid-based products.
2. Natura Bissé. (1996) Dermal irritation testing using rabbits of products containing Glycolic Acid.

At the March meeting, the Expert Panel recognized the following on-going data needs:

1. Effect of acute and chronic use of AHAs on the penetration of sunlight into the skin; the Expert Panel was informed that this type of study is being undertaken by industry
2. Effect of AHAs on the ability of other substances to penetrate the skin; the Expert Panel was informed that this type of study is being undertaken by FDA

The following was promised, the results of which should be submitted by December:

1. Acute comparison of AHAs vs. other normal exfoliation conditions and a 12 wk human daily application of two AHA products vs. exfoliation using sunburn cells. (Industry)
2. Effect of AHAs on the dermal penetration of other substances. (FDA)

The Expert Panel also reiterated the need for the DuPont statement that technical grade Glycolic Acid cannot be used in cosmetics, the units of formaldehyde impurity in Glycolic Acid given by DuPont, and Lactic Acid impurity data.

Since or at the last meeting, the following data have been received and summarized:

1. DiNardo JC and Grove GL. (1995) The effects of 30% Glycolic Acid chemical wash at various pH levels under exaggerated conditions of use on stratum corneum integrity.
2. EMDA. (1996a) EMDA guidelines for Alpha-hydroxy professional use only products manufacturing and distribution.
3. EMDA. (1996b) EMDA professional guidelines for Alpha Hydroxy Acid (AHA) cosmetic chemical exfoliation procedure.
4. FDA. (1996b) Adverse reaction data and survey of commercial and professional use only skin peeling products for composition and pH. Letter dated February 23 from JE Bailey, FDA, to FA Andersen, CIR. (Report dated February 15).
5. FDA. (1996c) pH of 12 AHA-containing commercial products. Report dated March 4.
6. FDA. (1996d) Percutaneous absorption of Glycolic Acid in two emulsion vehicles *in vitro* using human skin. Memo on summary of Glycolic Acid studies dated March 3 from Chief, Skin Absorption and Metabolism Section, HFS-128, to Acting Director, Office of Cosmetics and Colors (HFS-100).
7. Haskell Laboratory. (1996) Summary of a developmental toxicity study on GlyPure® 99% High Purity Glycolic Acid - crystalline using rats.
8. Yu RJ, Van Scott EJ. (1996) Bioavailability of Alpha Hydroxyacid in topical formulations.

Draft Report: December 16-17, 1996

The sunburn cell study promised by industry and the skin penetration study promised by FDA were received after the report was mailed to the Expert Panel. These data were given to the Expert Panel at the meeting. The sunburn cell studies were presented to each Team in closed session by Dr. McEwen and the skin penetration study was presented to the Expert Panel in open session by Dr. Brunaugh.

The following unpublished data were received and added to the report:

1. DiNardo JC, Grove GL, Lavker RM. (1996a) The effects of 30% Glycolic Acid chemical wash at various pH levels under exaggerated conditions of use on stratum corneum integrity.

2. DuPont Specialty Chemicals. (1996) Letter dated February 5 from DL Lohr, DuPont, to GN McEwen, CTFA, stating that formaldehyde content in Glycolic Acid is measured in ppm and giving information as to how DuPont prevents the use of technical grade Glycolic Acid in cosmetic products.
3. Recherche e Technologie Cosmetologique. (1996) Repeat insult patch test for contact sensitization of a Glycolic Acid Cyclooxetane Complex 50%. Study No. RTC/001/V. Study dated May.
4. Sah A, Mukherjee S, Wickatt RR. (1996) An *in vitro* study of the effects of formulation variables and product structure on the delivery of AHA (Lactic Acid) to dermal tissues. Poster presented at the Society of Cosmetic Chemists, May 9-10, Boston, MA.

The following published papers were added to the report:

1. Becker FF, Langford FPJ, Rubin MG, Speelman P. (1996) A histological comparison of 50% and 70% Glycolic Acid peels using solutions with various pHs. *Dermatol Surg* 22(5):463-5.
2. Carney EW, Liberacki AB, Bartale MJ, Braslin WJ. (1996) Identification of proximate toxicant for ethylene glycol development toxicity using rat whole embryo culture. *Teratology* 53:38-46.
3. Ditre CM, Griffin TD, Murphy GF, et al. (1996) Effects of α -hydroxy acids on photoaged skin: A pilot clinical, histologic, and ultrastructural study. *J Am Acad Dermatol* 34:187-95.
4. Garcia A, Fulton JE. (1996) The combination of Glycolic Acid and hydroquinone or kojic acid for the treatment of melasma and related conditions. *Dermatol Surg* 22(5):443-7.
5. Green BG, Bluth J. (1995) Measuring the chemosensory irritability of human skin. *J Toxicol - Cut & Ocular Toxicol* 14(1):23-48.
6. Komreich C, Zheng ZS, Xue GZ, Prystowsky JH. (1996) A simple method to predict whether topical agents will interfere with phototherapy. *Cutis* 57(2):113-8.
7. Morganti P, Bruno C, Randazzo SD. (1996b) Stratum corneum "turnover time" in aged skin: The effect of topical Ammonium/Aminoacid Lactate. *J Appl Pharmacol* 14, in press.
8. Morganti P, Persechino S, Bruno C. (1994b). Effects of topical alpha-hydroxy acids on skin xerosis. *J Appl Cosmetol* 12:85-90.
9. Morganti P, Randazzo SD, Fabrizi G, Bruno C. (1996a) Decreasing the stinging capacity and improving the antiaging activity of AHAs. *J Appl Cosmetol* 17:79-91.
10. Morganti P, Randazzo SD, Palombo P, Bruno C. (1994a). Topical gelatin-glycine and alpha-hydroxy acids for photoaged skin. *J Appl Cosmetol* 12:1-10.
11. Moy LS, Howe K, Moy RL. (1996b) Glycolic Acid modulation of collagen production in human skin fibroblast cultures *in vitro*. *Dermatol Surg* 22(5):439-41.
12. Moy LS, Peace S, Moy RL. (1996a) Comparison of the effect of various chemical peeling agents in a mini-pig model. *Dermatol Surg* 22(5):429-32.
13. Newman N, Newman A, Moy LS, et al. (1996) Clinical improvement of photoaged skin with 50% Glycolic Acid. A double-blind vehicle-controlled study. *Dermatol Surg* 22(5):455-60.
14. Ohta M, Ramachandran C, Weiner ND. (1996) Influence of formulation type on the deposition of Glycolic Acid and glycerol in hairless mouse skin following topical *in vivo* application. *J Soc Cosmet Chem* 47:97-107.
15. Piacquadio D, Dobry M, Hunt S, Andree C, Grove G, Hollenbach KA. (1996) Short contact 70% Glycolic Acid peels as a treatment for photodamaged skin. A pilot study. *Dermatol Surg* 22(5):449-52.
16. Stiller MJ, Bartolone J, Stern R, et al. (1996) Topical 8% Glycolic Acid and 8% L-Lactic Acid creams for the treatment of photodamaged skin. *Arch Dermatol* 132:631-6.

Final Report: June 5-6, 1997

At the December 1996 meeting, the Expert Panel issued a tentative report with a conclusion of safe in cosmetic products at $\leq 10\%$, pH ≥ 3.5 , when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection and safe for use in salon products at $\leq 30\%$, 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.

Comments on the Discussion were received from Mary Ellen Fise.

Comments on the Tentative Report were received from 3M Health Care and CTFA.

The following papers were added to the report:

1. Berardesca E, Distanti F, Oresajo C, Green B. (1997). Alpha-hydroxyacids (AHAs) modulate stratum corneum barrier function. Poster presented at the American Academy of Dermatology Annual Meeting, San Francisco, CA, March 21-6.
2. Smith WP. (1996) Comparative effectiveness of α -hydroxy acids on skin properties. *Int J Cosmet Sci* 18:75-83.

COSMETIC INGREDIENT REVIEW



MINUTES OF THE
FIFTY-SECOND MEETING

OF THE
EXPERT PANEL

September 12-13, 1994

EMBASSY ROW HOTEL

Washington, D.C.

Expert Panel Members

Wilma F. Bergfeld, M.D., Chairman

Donald V. Belsito, M.D.

William W. Carlton, D.V.M., Ph.D.

Curtis D. Klaassen, Ph.D.

Arnold L. Schroeter, M.D.

Ronald C. Shank, Ph.D.

Thomas J. Slaga, Ph.D.

Liaison Representatives

Consumer

Mary Ellen Fise, Esq.

Industry

Gerald N. McEwen, Jr., Ph.D.

FDA Contact Person

John Bailey, Ph.D.

CIR Staff

F. Alan Andersen, Ph.D.

Director/Scientific Coordinator

Alpha Hydroxy Acids

Dr. Andersen recalled that the decision for CIR to review Alpha Hydroxy Acids was made at the last Panel meeting. Specifically, the Alpha Hydroxy Acids that will be reviewed include Lactic, Citric, and Glycolic Acids, and their salts. Dr. Andersen then announced that a request to include an additional ingredient, methoxypropyl-gluconamide (MPG), in this ingredient family had been received. The ingredient is not an Alpha Hydroxy Acid, but is a derivative of gluconic acid (an Alpha Hydroxy Acid). It was noted that MPG is not on the current CIR priority list, but that it could be included in CIR's ongoing ingredient prioritization effort.

Dr. McEwen noted that MPG has been captured in the database for the CTFA Cosmetic Ingredient Dictionary, though it is not listed in the current edition of the dictionary.

Dr. Andersen said that he will be communicating with Dr. McEwen such that new cosmetic ingredients (ingredients in CTFA database that will be published in the CTFA Cosmetic Ingredient Dictionary) will be captured in CIR's ongoing cosmetic ingredient prioritization effort.

Ms. Fise favored adding MPG to the review process, but not to the family of alpha hydroxy acids slated for review. She also stated that because MPG is similar in function to the other Alpha Hydroxy Acids, the period separating the review of MPG and the Alpha Hydroxy Acids should not be lengthy.

Dr. Bailey noted that FDA's concern with Alpha Hydroxy Acids is based on their active nature. The Alpha Hydroxy Acids effect a change in the structure and function of

the skin, and this is consistent with the definition of a drug. With respect to MPG, he said that he does not visualize this same effect, at least, based on its chemical structure. Dr. Bailey recommended that MPG not be grouped with the true Alpha Hydroxy Acids, but that it should be added to the CIR Priority List. However, he also thought that the review process should allow the addition of other Alpha Hydroxy Acids to the present group, based on chemical similarity and expected action. For example, a request to include malic acid in the family of Alpha Hydroxy Acids slated for review would be considered a valid request.

Dr. McEwen asked if salicylic acid should be added to the group.

Dr. Bailey said that, from FDA's perspective, salicylic acid (a keratolytic agent) is in a somewhat different category based on its function. He does not consider this ingredient to be a true Alpha Hydroxy Acid.

Dr. Schroeter noted that salicylic acid functions in the same manner as the other Alpha Hydroxy Acids, and that it has been used for many years as a keratolytic agent in the treatment of acne. He also noted that this ingredient, like other Alpha Hydroxy Acids, can rejuvenate the skin.

Dr. Andersen agreed with Dr. Bergfeld that, from a historical perspective, CIR has grouped ingredients for review on the basis of chemical structure, and not ingredient function.

In response to Dr. Slaga's comments, Dr. Andersen said that the issue of use of combinations of Alpha Hydroxy Acids in cosmetic products should be incorporated into the Panel's future discussions on the Alpha Hydroxy Acids. For example, Glycolic, Lactic, and Citric Acids could be combined in a product to yield a higher concentration

than that which has been reported for either of the three.

It was the consensus of the Panel that MPG not be added to the review of the family of alpha hydroxy acids, but that it should be added to the CIR Priority List.

Ms. Fise asked if changes in the CIR Priority List would be made at the December 12-13, 1994 Panel meeting.

Dr. Andersen noted that, at the December Panel meeting, the Panel likely will review a new CIR Priority List with a ranking based on the factors that were discussed on the preceding day. Additions to the priority list, based on today's discussions, will also be included. Dr. Andersen also stated that he has committed to an open, public review of the CIR priority list. Therefore, after the Panel completes its planned review in December, there will be a 90-day public comment period. The priority list may be finalized at the March 1995 Panel meeting.

Ms. Fise said that in order for the Panel to have a meaningful review of the priority list in December, at the present meeting, FDA should be formally asked to provide the current list of ingredients that are being used in cosmetics.

Dr. Bergfeld stated that FDA would be asked to provide this list.

Dr. Bailey said that it was his understanding that the Panel had agreed to submit a written request for comments on CIR's prioritization scheme to FDA. He noted that FDA would be happy to review the proposed prioritization scheme and make comments.

MINUTES OF THE
FIFTY-FOURTH MEETING

COSMETIC INGREDIENT REVIEW

OF THE
EXPERT PANEL



March 16-17, 1995

LOEWS L'ENFANT PLAZA HOTEL

Washington, D.C.

Expert Panel Members

Wilma F. Bergfeld, M.D., Chairman

Donald V. Belsito, M.D.

William W. Carlton, D.V.M., Ph.D.

Curtis D. Klaassen, Ph.D.

Arnold L. Schroeter, M.D.

Ronald C. Shank, Ph.D.

Thomas J. Slaga, Ph.D.

Liaison Representatives

Consumer

Mary Ellen Fise, Esq.

Industry

Gerald N. McEwen, Jr., Ph.D.

FDA Contact Person

John Bailey, Ph.D.

CIR Staff

F. Alan Andersen, Ph.D.

Director/Scientific Coordinator

Adopted _____
(Date)

Wilma F. Bergfeld, M.D.

The Expert Panel voted unanimously in favor of issuing a Final Report with the following conclusion: The CIR Expert Panel concludes that the available data are insufficient to support the safety of Hydroxystearic Acid in cosmetic products. The data that are needed in order for the Panel to complete its safety assessment of this ingredient are listed in the discussion section of the report as follows:

- (1) Concentration of use
- (2) Chemical characterization
- (3) Dermal teratogenicity study
- (4) One genotoxicity test using a mammalian system (if the results of the genotoxicity test are positive, a dermal carcinogenicity test by NTP standards will be requested)
- (5) Skin irritation data

Formic Acid

The Expert Panel voted unanimously in favor of issuing a Final Report with the following conclusion: The CIR Expert Panel concludes that Formic Acid is safe as used as a pH adjustor with a 64 ppm limit for the free acid.

ALPHA HYDROXY ACID STATUS REPORT

Dr. Andersen indicated that the Scientific Literature Review on Alpha Hydroxy Acids is being developed, but has not been completed. He then addressed specific issues surrounding this group of ingredients. On the issue of function in cosmetics, he noted that various functions of Alpha Hydroxy Acids are included in the CTFA Cosmetic Ingredient Handbook, and that these functions are not representative of current uses. Therefore, the term exfoliant has been proposed as an additional term that describes

the cosmetic use of Alpha Hydroxy Acids.

Dr. Bergfeld asked other dermatologists on the Panel to respond to this proposal.

Dr. Schroeter said that the term, exfoliant does not represent the total function of the Alpha Hydroxy Acids, which may be categorized not only as exfoliants, but also as elements that cause new collagen formation and angiogenesis. With respect to the treatment of acne, the term exfoliant is acceptable, because most of the Alpha Hydroxy Acids cause loss of adhesions of the keratinocytes. However, in the cosmetic sense, these ingredients are doing much more than peeling the cornified layer. Dr. Schroeter expressed his preference for a broader term that describes the function of Alpha Hydroxy Acids.

Dr. Belsito favored use of the term, exfoliant only as an additional function of the Alpha Hydroxy Acids that could be added to the list already included in the Cosmetic Ingredient Handbook.

Dr. McEwen said that the Cosmetic Ingredient Handbook is not necessarily inclusive of all possible uses of any particular ingredient, but contains the primary cosmetic uses that have been recognized. The term, exfoliant (meaning mild exfoliation of the skin, ridding the skin of dead cells that have built up) would be included as an additional cosmetic use of the Alpha Hydroxy Acids. This term is not meant to describe the uses of Alpha Hydroxy Acids that may be more properly called peels or their uses in various therapies.

Dr. Bergfeld said that she is perplexed by the fact that the real use of Alpha Hydroxy Acids that is being publicized by the cosmetics industry is rejuvenation of skin.

Dr. McEwen said that he was referring to cosmetic uses of Alpha Hydroxy Acids,

and that any use that would be intended to change the structure or function of the body or to treat or prevent a mitigated disease would, by definition, be a drug use. He said that the Panel should not be concerned with drug uses of these ingredients.

Dr. Schroeter said that, in his earlier statements, he had tried to define the function of Alpha Acids based on what they actually do. He also said that in terms of what the cosmetics industry wants to market these ingredients for (rejuvenation of the skin), this is exactly what the Alpha Hydroxy Acids do (change the texture of and color the skin [hyperpigmentation]; mottling of the skin).

Dr. Andersen said that the second issue concerning the Alpha Hydroxy Acids relates to chemical classification. It was determined that Citric Acid, originally considered to be in the family of Alpha Hydroxy Acids, is not an Alpha Hydroxy Acid. Therefore, removal of Citric Acid (a beta hydroxy acid) from the group has been proposed, leaving Lactic and Glycolic Acids and their related salts and esters.

Dr. McEwen said that Citric Acid is being used in cosmetics primarily as a pH adjuster. Furthermore, based on his recollection, this ingredient is not being used as an exfoliant in cosmetics.

Dr. Bergfeld said that if Citric Acid is removed from the group, then the Panel may consider elevating its position on the CIR priority list.

Dr. Andersen reminded the Panel that the May meeting has been targeted for its review of a new CIR priority list.

The Panel voted unanimously in favor of removing Citric Acid from the list of Alpha Hydroxy Acids that will be reviewed by the Panel and consider this ingredient as a separate item at the May 22-23, 1995 Panel meeting.

Ms. Monice Fiume provided the following status report relative to development of the Scientific Literature Review on Alpha Hydroxy Acids: All of the published information on Glycolic Acid has been incorporated into the report; 25 to 50% of the publications on Lactic Acid have been incorporated. To date, the report consists of 84 pages of text, 19 pages of tables, and 17 pages of references.

Ms. Fiume also noted that many of the journal references (such as, *Cosmetic Dermatology*) that are concerned with cosmetic functions of the Alpha Hydroxy Acids cannot be retrieved using National Library of Medicine computerized databases. With this in mind, she requested that dermatologists on the Panel notify CIR of any specific publications on Alpha Hydroxy Acids that should be included in the Scientific Literature Review.

Dr. Andersen indicated that the Scientific Literature Review on Alpha Hydroxy Acids will be completed in April, and that Panel members will receive copies of this document. He also stated that data from industry will be incorporated during the 90-day comment period, and that the revised report on Alpha Hydroxy Acids will be reviewed at the August 28-29, 1995 Panel meeting.

Dr. Belsito requested that CIR redline all data from industry that are incorporated into the SLR on Alpha Hydroxy Acids during the 90-day comment period.

Dr. Bergfeld announced that the American Academy of Dermatology has completed a position paper on Alpha Hydroxy Acids, and that CIR may be interested in requesting this document.

Dr. McEwen said that industry has been assembling unpublished data on the Alpha Hydroxy Acids, much of which is anecdotal. He also said that many of the

concerns that have been raised by Dr. Bailey are being addressed by studies at the present time. Some of the studies will be included along with other industry data that will be submitted, while other studies will be ongoing at the time of data submission. Additionally, FDA will simultaneously receive copies of the industry data that will be submitted to CIR.

Dr. McEwen also mentioned that there have been newspaper reports indicating that an Oil of Olay product containing Alpha Hydroxy Acids has been recalled because of excessive eye irritation that was induced. He noted that the product did not contain Alpha Hydroxy Acids, but contained salicylic acid. Furthermore, refunds that are being offered are not based on lack of safety of the product, but on product misuse that could not possibly have been contained by the directions.

Dr. Andersen indicated that there has been an offer from one of the cosmetics manufacturers to have Dr. Van Scott address the Panel on any issues concerning Alpha Hydroxy Acids that are of particular interest.

Drs. Bergfeld and Belsito agreed that Dr. Van Scott should be invited to address studies in particular areas, rather than to give a general presentation on his clinical experiences with Alpha Hydroxy Acids. It was suggested that Dr. Van Scott address the Panel at its December 11-12, 1995 meeting.

Friday, March 17, 1995


INGREDIENTS UNDER TEST

Dr. Andersen informed the Panel that the status of all ingredients that are being

MEMORANDUM

DATE: July 5, 1995

TO: F. Alan Andersen, Ph.D.
Director/Science Coordinator

FROM: Jerry McEwen, Jr., Ph.D., J.D. 
Vice President-Science

SUBJ: Additional AHA ingredients

In addition to the Lactic Acid Salts and esters listed in the Glycolic Acid plus SLR, a company has asked that you include: Cetyl Lactate, Lauryl Lactate, Menthyl Lactate, Myristyl Lactate, and Sodium Isostearyl Lactate.

Thank You.

Aug 1995

FIFTY-SIXTH MEETING

OF THE

EXPERT PANEL

August 28-29, 1995

EMBASSY ROW HOTEL

Washington, D.C.

Expert Panel Members

Wilma F. Bergfeld, M.D., Chairman

Donald V. Belsito, M.D.

William W. Carlton, D.V.M., Ph.D.

Curtis D. Klaassen, Ph.D.

Arnold L. Schroeter, M.D.

Ronald C. Shank, Ph.D.

Thomas J. Slaga, Ph.D.

CIR Staff

F. Alan Andersen, Ph.D. (absent)

Director/Scientific Coordinator

Liaison Representatives

Consumer

Mary Ellen Fise, Esq.

Industry

Gerald N. McEwen, Jr., Ph.D.

FDA Contact Person

John Bailey, Ph.D.

Adopted _____
(Date)

Wilma F. Bergfeld, M.D.

Aug 1995

of diseases (human delayed-type hypersensitivity and contact urticaria) are needed.

The Panel voted unanimously in favor of issuing a Tentative Report on Ammonium, Potassium, and Sodium Persulfate with an insufficient data conclusion. The data needed in order for the Panel to complete its safety assessment of these ingredients (mentioned in preceding paragraph) will be listed in the discussion section of the report.

STATUS REPORT ON ALPHA HYDROXY ACIDS

Dr. Bergfeld noted that, at this meeting, both Teams reviewed the Draft Report on Alpha Hydroxy Acids for the first time. She complimented the staff at CIR and CTFA on the completeness of this lengthy (over 200 pages) document, and thanked FDA for its cooperation.

Dr. Bergfeld also noted that the Draft Report on Alpha Hydroxy Acids is being reorganized. Information pertaining to cosmetic versus non-cosmetic use will be appropriately categorized. Furthermore, this report will be reviewed in Teams and during the public session at the December 11-12, 1995 Panel meeting. Dr. Bergfeld said that there is a possibility that the Panel may arrive at conclusion on the safety of Alpha Hydroxy Acids at this meeting. She also recalled that informal data requests, generated in Teams, were submitted to Dr. McEwen.

Dr. Bailey saw the need to place the Panel's ongoing review of Alpha Hydroxy Acids in perspective. He indicated that FDA is very interested and very concerned about the proliferation and types of AHA products that are entering the market. We

view this as a real challenge to the CIR Panel, both to the process that you have as well as technologically considering the complexity of these ingredients and the many uses that they have. The Panel will have to carefully consider which safety standards will be applied in this case. In the past, the Panel has examined the toxicity of ingredients, and this is a good process. However, the Alpha Hydroxy Acids are ingredients of a different type. Thus, the standard will be pushed beyond what has been dealt with in the past. The Panel is now looking at simple toxicity, with more subtle effects and appropriate effects for cosmetic ingredients, as opposed to other types of products, namely, drugs. From FDA's perspective, the standard here is not safety and efficacy, but simply safety. Efficacy is not part of the equation. This issue deals with, to some degree, the distinction between drugs and cosmetics from a legal perspective. It is important for the Panel to examine the definitions relating to how FDA views drugs and cosmetics.

It is important for the Panel to differentiate between the uses that exist. Some of the Alpha Hydroxy Acids have legitimate uses, such as adjusting pH, and they behave like any other acid (sulfuric and hydrochloric acids) in terms of this function. The history of these uses in cosmetics does not necessarily relate to the issue that is being considered by the Panel, which is not a "pH adjuster" issue.

There is also the question of moisturizing properties. Certainly, neutralized AHA's in the pH 7 range have moisturizing properties. These need to be distinguished from what we are looking at in terms of the skin treatment products that are on the market now.

It is important to examine the categorization of products also, in the sense that we are looking at mass market products (this is FDA's perspective) that generally have AHA concentrations of less than 10%. We are also looking at the salon-use products, with typical AHA concentrations of 20% or higher, that are used by trained estheticians and trained salon beauticians who perform the "mini-peel"s. There are also the medical uses which involve AHA concentrations that are as high as 70%.

Looking at the data that were submitted, industry is to be commended for bringing this information forth. This information has been submitted to CIR and separately (from Dr. McEwen) as a package to FDA. FDA in the process of reviewing these data and has found some inconsistencies. There are reports that don't appear to be in the data submission, when referenced against the CTFA special report listing that was included. We plan to itemize these studies in the very near future such that these inconsistencies can be resolved. We are considering this information as publicly available. If someone requested this information under FOI, then it would be made available to them. FDA is conducting a review of this data, and FDA hopes to have that review completed before the next CIR Expert Panel meeting. The review will be made available if it has been completed by this time.

FDA has conducted a fairly significant examination of chemical analyses of products that are currently on the market; this includes a range of products (mass market, salon use, and medical use products). This information, which includes pH, the acid that is present, and the concentration, can also be provided as a summary report. This information can then be compared with the table that industry has provided

relative to use.

Dr. Bailey also reported that FDA is conducting skin penetration studies.

Additional information on those studies will be made available as they are completed.

This is a fairly extensive set of studies. Presently, FDA is looking at glycolic acid penetration, correlated to pH, but, is also looking at a homologous series of acids.

FDA plans to look at the effects of topically applied AHA's, and then the penetration of ingredients through skin that has been modified by AHA's. The completion of these studies could be a lengthy process [*End of Dr. Bailey's comments*].

Dr. Bronaugh said that it is anticipated that the time projected for completion of all of the studies will not exceed one year.

Dr. Bailey noted that pure AHA's are being tested in all of the FDA studies; the salts will be considered when the pH is adjusted. AHA esters will not be tested.

Dr. Bergfeld asked if FDA would be looking at technical grade and cosmetic grade AHA's.

Dr. Bailey said that if, in looking at safety, the technical grade produces a toxic endpoint, the Panel may want to consider limitations on impurities in cosmetic products.

Dr. Bailey also stated that FDA is going to provide the Panel with the adverse reactions data that have been collected over the last few years relative to Alpha Hydroxy Acid products, if such information is of interest. These data are applicable primarily to mass market products (e.g. products that may be purchased in a department store).

Dr. Bergfeld said that the Panel would like to receive the adverse reactions data

on AHA's. She also wanted to know if when a significant adverse effect is noted, whether a tracer is employed to define this effect and determine its cause.

Dr. Bailey said that FDA can provide the actual reports that were received, which include, in some cases, medical reports. However, patient names must not be visible on these reports, and FDA has to obtain clearance approval in order to release this information.

Dr. Bergfeld said that FDA's project on Alpha Hydroxy Acids seems to be an in-house review, and wanted to know if this review would be submitted to any of the FDA panels.

According to Dr. Bailey, FDA's ongoing project will not be submitted to any of the FDA review panels at this point; however, eventually, this may take place. He also said that, at this point, FDA is involved in a scientific, technical, medical type of review, which will be available as a resource for determining the next series of activities.

Dr. Bailey reminded the Panel of FDA's relationship with CIR: The agency has historically provided resources to interact with the CIR process, and that has been primarily in the form of a liaison. I am a liaison (a non-voting member of the Panel), and am here to answer questions and provide information. However, FDA does not provide a definitive position regarding any of the decisions that CIR issues. This is an industry process that is separate, obviously, from the FDA process. I think that it is important to understand that distinction and the formal working relationship that we have.

Dr. Bailey also asked for confirmation of the existence of a preliminary range-

finding study, which produced a carcinogenic endpoint for technical grade glycolic acid, and industry's decision to conduct a carcinogenicity study on this chemical. He noted that one of the issues that has been raised relates to mortalities in the range-finding study that were induced by impurities in technical grade glycolic acid.

Dr. McEwen said that the only study that he is aware of is a range-finding study on the technical grade compound, in which developmental toxicity was the endpoint. This study was submitted to Dr. Bailey and other members of the Panel. One of the impurities, present at a relatively high concentration, in the technical grade compound has been identified as a very potent developmental toxicant. Dr. McEwen added that this impurity may or may not have been responsible for the developmental toxicity that was noted in this study. He also noted that a follow-up study is being done on the cosmetic grade ingredient, and that FDA (Dr. Bailey) and CIR will be supplied with these data.

In response to Dr. Bailey's earlier comments, Dr. McEwen noted that FDA is concerned with medical uses of AHA's as well as use by estheticians. He then said that the function of the CIR Expert Panel is that of reviewing ingredients that are used in retail cosmetics, not cosmetics used in salons or by physicians. Therefore, while data based on salon or medical use of AHA's may be instructive to the Panel, salon or medical use is not a concern that should be addressed by the Panel [e.g. If the Panel determines that 50% and below is safe, the fact that the 50% concentration is being used by physicians is not the reason why it should be evaluated].

Ms. Fise said that her impression has always been that the CIR Expert Panel

reviews the safety of cosmetic ingredients used by consumers. So, in a salon setting, the Panel may not be concerned about the salon worker, but, those cosmetic ingredients that are used on a consumer are within the purview of the Panel. Ms. Fise reiterated that the Panel is concerned about consumer exposures and risks in the salon setting.

Dr. McEwen said that the Panel can establish concentration limits for ingredient use in retail products, ingredient use by a trained professional esthetician, or ingredient application by a physician. However, he said that retail use is of importance to the cosmetics industry.

Ms. Fise said that how consumers are exposed is of importance to the Panel.

Dr. Bergfeld said that on the preceding day, both Teams agreed that the data in the Draft Report on Alpha Hydroxy Acids should be organized/categorized, based on cosmetic versus noncosmetic ingredient use. She noted that many of the issues relating to salon use and medical use may be categorized as non-cosmetic use issues.

Ms. Fise said that she is aware of the difference between medical use and cosmetic use. However, the Panel has within its purview (cosmetic use) salon use, and this should be evident as the division between cosmetic and non-cosmetic use is made in the Draft Report.

With respect to the public availability of the industry data on AHA's submitted to CIR, Dr. McEwen said that CIR will make this information available to the public (upon request) after the Tentative Report on AHA's is announced. However, if there are individuals who would like to receive these data in the interim, the data may be

requested from FDA under FOI.

STATUS OF INGREDIENTS UNDER TEST

Ms. Monice Fiume made the following comments on the status of tests that are being conducted on Bisabolol and PCA and Sodium PCA:

Bisabolol

Use and concentration data were received. Additionally, mutagenicity and 28-day dermal toxicity tests are being conducted.

PCA and Sodium PCA

Use and concentration data were received. Skin penetration, 28-day dermal toxicity, and genotoxicity data are expected toward the end of this year.

Ms. Fiume noted that both ingredient reports, PCA & Sodium PCA and Bisabolol, have been tabled. She also noted that, earlier in the day, the report on Nonoxynols -1 through -8 was tabled until the December 11-12, 1995 Panel meeting.

The 56th CIR Expert Panel meeting was adjourned.

COSMETIC INGREDIENT REVIEW

FIFTY-SEVENTH MEETING

OF THE

EXPERT PANEL

December 11-12, 1995

EMBASSY ROW HOTEL

Washington, D.C.



Expert Panel Members

Wilma F. Bergfeld, M.D., Chairman

Donald V. Belsito, M.D.

William W. Carlton, D.V.M., Ph.D.

Curtis D. Klaassen, Ph.D.

Arnold L. Schroeter, M.D.

Ronald C. Shank, Ph.D.

Thomas J. Slaga, Ph.D.

CIR Staff

F. Alan Andersen, Ph.D.

Director/Scientific Coordinator

Liaison Representatives

Consumer

Mary Ellen Fise, Esq.

Industry

Gerald N. McEwen, Jr., Ph.D.

FDA Contact Person

John Bailey, Ph.D.

Adopted _____
(Date)

Wilma F. Bergfeld, M.D.

Tuesday, December 12, 1995

CHAIRMAN'S OPENING REMARKS & APPROVAL OF PREVIOUS MINUTES

The 57th Meeting of the CIR Expert Panel was called to order by Dr. Wilma F. Bergfeld on Tuesday, December 12, 1995 at 8:30 a.m., and all attendees were welcomed. Dr. Bergfeld recognized the following guests who would be making presentations later in the day: Drs. Bill Dressler and Ken Walters (Clairol presentations on the Nonoxynols), Drs. James Leyden and Daniel Sauder (CTFA presentations on Alpha Hydroxy Acids), and Paul Dykstra and Dr. Mark Lees (American Beauty Association presentations on Alpha Hydroxy Acids).

The minutes of the 56th meeting of the CIR Expert Panel were approved with corrections.

Director's Report

Dr. Andersen stated that CIR had received a letter from Dr. John Bailey, FDA Panel liaison, requesting that the Expert Panel not reach a tentative conclusion on the Alpha Hydroxy Acids at this Panel meeting. He indicated that Dr. Bailey would elaborate on the content of this letter during the Panel's discussion of Alpha Hydroxy Acids. Dr. Bailey's request is based on the expectation that FDA will submit additional data that will contribute to the Panel's eventual discussion and conclusion on Alpha Hydroxy Acids. In his letter, Dr. Bailey also raised the issue that the review of Alpha Hydroxy Acids may be problematic because of the drug-cosmetic implications for an ingredient with activity in the skin.

Dec 1995

toxicity on PEG-5 Lanolin; (4) Dermal irritation and sensitization data on PEG-5 Hydrogenated Lanolin at concentration of use; (5) Two genotoxicity tests, one in a mammalian system, on PEG-5 Lanolin; if the results are positive, then a dermal carcinogenesis study using NTP methods may be needed; and (6) A review of the literature addressing the teratogenic potential of ethylene glycol and ethylene glycol ethers will be conducted and included in the report. Depending on the results of a review of that data, teratogenicity testing may be required.

PEGs-2, -3, -5, -10, -15, AND -20 COCAMINE

The Panel voted unanimously in favor of tabling the CIR report on this group of ingredients, pending the following data that are needed: (1) Concentration of use; (2) Physical and chemical properties (including impurities and stability); (3) 28-day dermal toxicity on PEG-2 Cocamine; (4) Dermal irritation and sensitization on PEG-2 Cocamine at concentration of use; (5) Two genotoxicity tests, one in a mammalian system, on PEG-2 Cocamine; if the results are positive, then a dermal carcinogenesis study using NTP methods may be needed; (6) Ocular irritation, if available; and (7) A review of the literature addressing teratogenic potential of ethylene glycol and ethylene glycol ethers will be conducted and included in the report. Depending on the review of that data, teratogenicity testing may be required.

PEGs-2, -3, -4, -8, -9, -12, -20, -32, -75, -120, -150, AND -175 DISTEARATE

The Panel voted unanimously in favor of tabling the CIR report on this group of ingredients, pending the following data that are needed: (1) Concentration of use on one prototypical high and one prototypical low molecular weight PEG Distearate; (2) Chemical and physical properties; (3) 28-day dermal toxicity on PEG-2 Distearate; (4) Dermal irritation and sensitization on PEG-2 Distearate at concentration of use; (5) Ocular irritation, if available; (6) Two genotoxicity tests, one in a mammalian system, on PEG-2 Distearate; if the results are positive, then a dermal carcinogenesis study using NTP methods may be needed; and (7) A review of literature addressing the teratogenic potential of ethylene glycol and ethylene glycol ethers will be conducted and included in the report.

Depending on the review of that data, teratogenicity testing may be required.

ALPHA HYDROXY ACIDS - Executive Summary

During presentations to the Panel by Drs. Leyden and Sauder, a number of studies concerning the epidermal changes that are observed following the application of Alpha Hydroxy Acids (AHA's) to the skin of human subjects was summarized. Other topics that were discussed included effects on percutaneous absorption, transepidermal water loss, and UV transmission. A compilation of many of the studies summarized was provided to each Panel member at this meeting.

Mark Dykstra and Dr. Mark Lees gave presentations on the Alpha Hydroxy Acids on behalf

of the American Beauty Association. The following issues were examined: (1) What the industry has done in the past regarding safety issues relating to products containing these ingredients, (2) Industry's safety record, which includes some of the data that have been collected in the past, (3) The training of professionals in the professional beauty industry, and (4) What, if any, additional information the Panel would like the industry to provide.

Dr. Belsito requested that the American Beauty Association provide the Panel with documentation of the organization's suggested limitations on AHA concentrations and pH's, and some written documentation as to the methods of training and licensing of estheticians and what the industry is doing to restrict the distribution of professional-use products to licensed individuals.

Furthermore, Dr. Belsito said that the Panel would like to see the types of studies performed by Dr. DiNardo (dose responses and pH variations at each dose) done on Lactic Acid, because the Panel does not have well-defined dose-response and pH-adjusted response data.

Dr. Klaassen requested information concerning the chemistry of AHA's, in that the Panel had discussed regulating these compounds in relation to pH and concentration. He proposed that the Hendersen-Hasselbach equation be applied to all of the AHA's that are subject to the Panel's review, such that one knows what happens to these chemicals at the various pH's and concentrations.

Dr. Schroeter said that the Panel has to define whether the AHA's are going to be limited to peeling (destruction of the entire cornified layer) or non-peeling. If AHA's are going to include peeling, then the Panel will have to further discuss items 6 and 7 from the informal data request: (6) the photoproducts\thymidine dimers and adducts produced upon application of AHA's with UV light at different time intervals, up to 6 weeks, with different dose levels and (7) photocarcinogenicity data. Dr. Schroeter said that the photocarcinogenicity study will be needed if significant production of thymine dimers and adducts is noted after the application of AHA's in the presence of UV light.

Dr. Bergfeld noted that information would be expected from the American Beauty Association (based on today's presentation) and that FDA would submit additional information to the Panel, namely, consumer complaints information and, perhaps, information on absorption. Dr. Andersen reminded attendees that data submissions should be provided in early February.

In recognition of the data that are anticipated, the Panel postponed making a decision on the safety of AHA's until the March 4-5, 1996 Panel meeting.

Depending on the review of that data, teratogenicity testing may be required. He noted that items 1 through 6 were not received in response to the Insufficient Data Announcement that was issued, and that these data are still needed in order for the Panel to complete its safety assessment. Development of the CIR review on ethylene glycol teratogenicity is ongoing.

The Panel voted unanimously in favor of tabling the CIR report on this group of ingredients, pending the teratogenicity review on ethylene glycol.

Glycolic and Lactic Acid, Their Common Salts and Simple Esters

Dr. Bergfeld announced that Drs. James Leyden and Daniel Sauder would be making presentations on the Alpha Hydroxy Acids on behalf of CTFA. Copies of the slides used during the presentations are attached.

Dr. Leyden said that he had been asked by CTFA to present an overview of the Alpha Hydroxy Acids according to his perspective, particularly with reference to the concentrations that are in products sold by major cosmetics firms. The text of Dr. Leyden's presentation is summarized as follows:

The Alpha Hydroxy Acids were first introduced into skin care products in the early 1970's when the researchers at Unilever first found utility for these agents, specifically for the condition that we euphemistically refer to as dry skin. These agents were found to be useful because they would hold water in skin, which would make the stratum corneum more pliable and less likely to crack. Lactic Acid, and its salts in particular, have been known for many years with respect to treating dry skin. In more recent

years, with the work of Van Scott and Ray Yu, the utility in another condition in which dry skin is a major aspect, photodamage, has been described. The major signs of photodamage usually involve roughness or scaling (dreaded wrinkle and pigmentary changes in some individuals and epidermal proliferations, both benign and potentially cancerous lesions, develop in other individuals).

In the last five or six years, there has been a marked increase in the number of products containing Alpha Hydroxy Acids that are available, as well as a marked increase in the use of these ingredients at fairly high concentrations in a pulse-like fashion (pulse exposure of a relatively high concentration, often referred to as a peel or mini-peel) by dermatologists and other individuals (plastic surgeons, etc.).

Dr. Leyden indicated that he had been involved with clinical trials on the Alpha Hydroxy Acids. Following application, surface texture changes improve and, as this occurs, fine lines and wrinkles are less apparent. However, the Alpha Hydroxy Acids are not quite as effective on pigmentary changes, although they do have some effect on aspects of unwanted cosmetic effects of photodamage.

Dr. Leyden said that he views the low concentrations of Alpha Hydroxy Acids that are typically in cosmetic products as primarily having effects in the stratum corneum, primarily functioning in what is referred to as dry skin. Dry skin is an abnormality with respect to the way in which the stratum corneum desquamates into the environment. Human stratum corneum is a membrane with certain physical characteristics, including pliability. If water is added to this tissue, it becomes more pliable. If water is removed, it becomes stiffer and begins to crack, hence, the term dry skin.

In normal skin, as visualized using scanning electron microscopy, the surface is desquamating. There is an orderly orchestrated series of events by which the epidermis remains in a homeostatic condition. An important function of the skin is to produce the stratum corneum (outer layer), a constantly replenishing portion of the skin, such that cells desquamate into the environment. To ensure that this happens, signals are sent to the viable epidermis. In response to these signals, the basal layer proliferates and generates new cells that migrate to the surface and replace the desquamated stratum corneum. A lot has been learned about this process. We now know the lipid composition (consisting primarily of ceramides, fatty acids, and cholesterol esters) that is between the stratum corneum cells. Much has been learned through the work of researchers at Unilever about how these lipids encapsulate the attachment plates between stratum corneum cells. A trypsin-like enzyme near the surface causes the final breakdown of these attachment plates and allows cells to fall off into the environment.

It is now known that, in dry skin, there are profound disturbances of the normal mechanisms mentioned above. The intercellular lipids are different. Specifically, there is a decrease in ceramides and an increase in the fatty acid portion. This seems to create an environment that is less favorable for supplying the optimal amount of water that is necessary in order for enzymatic digestion to take place. This results in hyperkeratosis, a thickening of the outer membrane. As the outer membrane thickens, the outer layers become less hydrated and tend to crack. As the crack becomes more substantial, chunks of stratum corneum uplift (seen clinically as scales or clumps of

scales, recognized visually on the outer surface).

Dry skin in those genetically predisposed to chronic skin problems (atopics) is characterized by decreased ceramide in intercellular lipids. Whether this is detergent-induced, age-associated dry skin, or due to photodamage, there is a thickening or a retention hyperkeratosis with fissuring or cracking as the primary event.

Based on studies that have been done with lac hydrin (12% Lactic Acid and its salt, ammonium lactate), it has been known for some time what happens when Alpha Hydroxy Acids are applied to the skin. For example, in one of the studies (20 or 25 patients with hyperkeratosis), treatment with the lac hydrin over a three-week period caused reduction of the stratum corneum, but this effect is more correctly stated as a reduction of the thickened stratum corneum to a degree of thickness that was close to normal. With these data in mind, the Alpha Hydroxy Acids have been said to strip away the stratum corneum. However, this is not the case with the low concentrations of Alpha Hydroxy Acids that are typically found in cosmetics. When there is a retention hyperkeratosis, such as in the various forms of dry skin, the low concentrations in cosmetics normalize the stratum corneum in terms of its functional capacity. It becomes compact and no longer has cracks or fissures. Basically, the Alpha Hydroxy Acids, as formulated in cosmetic preparations, reduce abnormally thickened stratum corneum to a normal level. In the individual who has normal stratum corneum in terms of thickness, they accelerate or facilitate the normal desquamation process. However, the normal desquamation process is not exceeded.

Dr. Leyden also referred to some of the types of studies that had been done at

his laboratory:

(1) Lac hydrin (12% lactic acid and ammonium lactate) applied three times per week under an occlusive patch (right side) and dilute detergent (0.25% sodium lauryl sulfate) applied under an occlusive patch (left side). Weekly biopsies were obtained. Nothing was observed histologically at lac hydrin sites that suggested cellular injury. Damage to the stratum corneum was observed during the first and second weeks of application at sodium lauryl sulfate sites.

(2) Single applications of 4 and 8% Glycolic Acid and 12% Lactic Acid. Other sites (on same individual) served as controls. No histological changes suggestive of irritation were observed at the concentrations tested.

(3) Prolonged exposure to Alpha Hydroxy Acids. No indication of cell injury was noted using electron microscopy.

Dr. Leyden stated that each Panel member would receive a notebook of studies on the Alpha Hydroxy Acids at this meeting.

With pulse, high dose concentrations of Alpha Hydroxy Acids, he stated that one is deliberately attempting to wound skin, calling upon the skin to bring out all of its capacity for wound healing. This is the basis for the derm abrasion, phenol peels, trichloroacetic acid peels, etc. If one applies 70% Glycolic Acid (single application for 2 minutes) and then biopsies the next day, one finds that the stratum corneum is mostly gone.

The concept that low levels of Alpha Hydroxy Acids are doing something that is potentially harmful to the stratum corneum of those using them must have been due to the confusion of low concentrations with much higher concentrations of Alpha Hydroxy Acids that are used in the so-called peels.

So, he concluded that the proper perspective on Alpha Hydroxy Acids is that one takes a thickened, hyperkeratotic stratum corneum that tends to crack and replaces it

with a normal stratum corneum that, if anything, tends to function better.

Dr. Belsito wanted to know how much the concentration of an Alpha Hydroxy Acid can be increased safely before one begins to see destruction of the stratum corneum. He noted from the presentation that 70% Glycolic caused destruction of the stratum corneum, whereas 8% Glycolic Acid and 12% lac hydrin did not.

Dr. Leyden said that pH is integrated with concentration. The pH will influence how much free acid is present. The more free acid, the lower the pH, and, thus, the more damage. He said that in his experience, he has not seen anything that suggests damage or perturbation of the stratum corneum that would be clinically meaningful at concentrations up to 20% Lactic Acid or 20% Glycolic Acid.

Dr. Daniel Sauder said that the purpose of his presentation is to point out what he, as well as CTFA, feel are the defining issues relative to the Alpha Hydroxy Acids. Dr. Daniel Sauder's presentation is summarized as follows:

The issues that have been raised are: Is there a potential effect of Alpha Hydroxy Acids (AHA's) on affecting percutaneous absorption by potentially altering stratum corneum, and are there changes in UV transmission? The Panel has already heard evidence supportive of the fact that these claims are not true. In fact, Alpha Hydroxy Acids do not, at concentrations used in cosmetics, compromise the skin barrier and do not enhance percutaneous absorption; furthermore, they do not change UV transmission. Some of these data are included in the booklets that are being distributed to the Panel members today.

In terms of the barrier properties, Dr. Leyden already mentioned that the initial

suggestion that AHA's may be altering the stratum corneum is based on his studies, which indicate that AHA's reduce abnormally hyperkeratotic stratum corneum and return it to a normal level, as opposed to reducing it further.

There have been a number of studies, including the one already presented by Dr. Leyden, on the effect of AHA's on transepidermal water loss as a measure of barrier function. In a study completed recently by Gary Grove, 4% Glycolic Acid (pH 3.8) was applied to 19 subjects twice daily and transepidermal water loss was measured at baseline and 24 weeks later. The results indicated a very minimal change (not statistically significant) in transepidermal water loss. However, more water was actually being trapped in the stratum corneum, and that could have accounted for the change in transepidermal water loss. The application of Glycolic Acid enhanced the water content.

In another study by Villaplanta (published in 1992), 12% Ammonium Lactate was applied to 24 subjects. Transepidermal water loss was measured at baseline, at 15 days, and at 30 days. A very slight, if any, statistically significant change was observed at 15 days, and a slight increase was observed at 30 days. When these results are compared with some of the other ingredients (e.g. retinoic acid) that dermatologists use frequently, retinoic acid dramatically alters transepidermal water loss. At a concentration as low as 0.025% retinoic acid (Tagami, 1992), doubling or tripling of transepidermal water loss was observed.

Furthermore, if one evaluates the routine histology, either at the light microscopic or ultrastructural level, after AHA application, there is really no significant change in

terms of certain parameters. In a study by Kaby and Laughter (1994) in which 4% Glycolic Acid in a standard cosmetic preparation was applied to normal skin for 6 months, punch biopsies were submitted for histologic evaluation and ultrastructure. If one characterizes the stratum corneum in terms of histology, it really was not significantly changed compared to the control. This observation was less dramatic than what is observed following the application of commercial preparations, such as moisturizers or some of the abrasive sponge materials. When epidermal thickness (in microns) was evaluated using computer image analysis, it was determined that 4% Glycolic Acid did not cause any significant change in epidermal thickness compared to the control preparation. Clearly, if epidermal function or barrier function were disrupted or inflammation were being induced, one would have seen a hyperplastic response to, at least, some extent. Additionally, no significant ultrastructural changes were observed. One would anticipate that if the barrier were disrupted, the following ultrastructural changes could have resulted: disruption of the basement membrane, reduplication of the basement membrane, or changes in adhesion molecules. Thus, these observations suggest that the AHA's, at the concentrations noted, are not changing morphology at the light microscopic or ultrastructural level.

To reiterate what Dr. Leyden showed earlier (histological evaluations from one of his studies using 8% Glycolic Acid; 10 subjects), no significant change in stratum corneum thickness (normal skin) was observed after one month of treatment with 8% Glycolic Acid. Also, using computer image analysis, no significant change in epidermal thickness was noted.

Based on the above studies, it appears that AHA's, at the concentrations tested, do not compromise stratum corneum barrier function, and long-term application did not alter the structure or affect transepidermal water loss to any significant degree.

The next issue related to the assessment of percutaneous absorption is barrier function. Some of the studies (sodium lauryl sulfate used) mentioned earlier by Dr. Leyden will be reiterated: In two separate studies, 4% Glycolic Acid or Lactic Acid (pH = 4.0) were applied twice daily. After 28 days of use, the skin was challenged with 0.25% sodium lauryl sulfate under occlusion. One would anticipate that if the Glycolic Acid were actually changing barrier function, upon application of sodium lauryl sulfate, there would have been a significant increase in transepidermal water loss. However, the results of a comparison of 4% Glycolic Acid with application of the vehicle indicated no significant change in transepidermal water loss. Pre-treatment with Glycolic Acid actually reduced (not statistically significant) transepidermal water loss when the skin was later challenged with sodium lauryl sulfate.

Penetration through stratum corneum is affected by the following: structural integrity, the site on the body - [This is well known because cosmetic adverse reactions are more common on the eyelids, where there is a much thinner stratum corneum compared to other areas], the degree of hydration, polarity, molecular size, and the various physical properties of the ingredient to be used. Clearly, these factors can all affect the percutaneous absorption of materials. Dermatologists take advantage of this; for example, salicylic acid is added to corticosteroid preparations to enhance penetration. Enhancers such as DMSO or acetone pre-treatment in certain situations

also affect barrier function. Skin hydration also affects percutaneous absorption. This is also taken advantage of in a clinical setting. For example, use of a corticosteroid preparation in a petrolatum base enhances penetration of that corticosteroid. Therefore, a number of examples are present in terms of how one can increase percutaneous absorption.

One would anticipate that if percutaneous absorption were significantly altered with AHAs, this would have been observed in exaggerated conditions in terms of use tests. There have been 28 separate studies with exaggerated conditions (occlusion or semioclusion) using five different AHA concentrations, up to 10% at a variety of pH's, with typical cosmetic preservatives and levels. In these studies, there was no evidence of contact dermatitis. Contact dermatitis also was not observed in 10 separate human studies with 459 subjects (daily applications; extended treatment periods up to 12 months), tested with typical AHA preparations. So, one might anticipate that if, in fact, percutaneous absorption were being altered in a significant way, this should have been observed clinically as contact dermatitis. However, there was not evidence of contact dermatitis.

The final issue is effects on potentially altering UV transmission. Clearly, a smooth surface is going to allow more UV light penetration than a rough surface, simply on the basis of scatter. One would expect that if the skin were being moisturized or that its surface were being altered to some extent to make it smoother, that alteration would be visible. This is exactly what happens, and this is probably part of the mechanism of why the skin may appear a bit shinier when it is moisturized using an AHA. The flaking

and shedding of the skin surface is being altered. The extent of smoothness of the skin surface can affect UV transmission. So, skin treatments can clearly alter minimal erythema dose, the amount of UV light that is required to cause redness. In a study by TKL Research, the effects of typical moisturizers on minimal erythema dose were evaluated using 32 subjects. A moisturizing lotion containing 10% mineral oil was compared with a cosmetic lotion containing 10% glycerin in this study. At 30 minutes post-application of the lotions, sites were irradiated and minimal erythema doses were determined. In effect, the minimal erythema dose was lowered with simple moisturizers on the skin (10% mineral oil and 10% glycerin).

In another study, the surface texture of the skin was altered mechanically in ten subjects. The skin was rubbed with an exfoliative sponge, followed by shaving with a shaving cream and disposable razor. Shaved skin was compared to the skin of untreated controls. An alteration in minimal erythema doses (MED's) was observed. With the sponge alone, a fairly significant trend in terms of decreasing the MED was observed. Shaving alone was also clearly capable of altering MED's.

Climate or seasonal changes also affect MED's. As one becomes more tan, the MED is affected. In the winter months, the MED's are significantly lower than in the summer months. In a study involving 16 subjects, MED's in January and April were compared. As one would expect, as one becomes more exposed to the sun, the MED is increased.

The effect of Alpha Hydroxy Acids on UV transmission was evaluated in a study involving 19 subjects. Lactic Acid (4%) was applied twice daily for three months and

MED's at treated sites were compared with untreated control sites. There was a downward trend, although not statistically significant.

A summary of repeated applications of AHA's on the minimal erythema dose (graphic representation) indicated an alteration in the MED's at approximately the same level as shaving or using the exfoliative sponge, and slightly less than that with mineral oil or glycerin.

Thus, the studies reviewed in this presentation (also included in notebooks for Panel members) indicate that at the cosmetic levels of AHA's that have been discussed, the stratum corneum or barrier function is not being significantly compromised and there is also very little, if any, significant effect on minimal erythema dose.

Dr. Bergfeld asked for the opinions of the presenters regarding cosmetic concentrations of Glycolic Acid and pH.

Dr. Sauder said that pH plays a major role in terms of the concentrations. The concentration range in the studies that were reviewed was 3.5 to 7%. If this is used as a relative standard, the concentrations reviewed were less than 12%, which were without significant effect.

Dr. Bergfeld asked if the 3.5 to 7% concentration range is representative of the market place.

Dr. Sauder said that the vast majority of the market place is well under 12%.

Dr. Belsito said that it had been shown that after treatment with AHA's, there was no higher induction of allergic reactions to preservatives in standard cosmetics. This

presumes that AHA's have had no effect on the cutaneous immunology. However, there are data suggesting that, at least in macrophages, AHA's can induce $\text{TNF}\alpha$. He wanted to know whether the presenters had had an opportunity to look at this and determine whether there are any changes in cytokine homeostasis in skin that has been treated with AHA's.

Dr. Sauder said that he had not looked at changes in cytokines with AHA's. He said that he thinks that there are many interventions that go through a cytokine cascade. Furthermore, he said that it is very unlikely that this translates into a significant biologic effect with AHA's at concentrations that are present in moisturizers, or due to shaving or one of the minor traumas that one is exposed to on an every day basis.

Dr. Schroeter said that a reduction in MED's was noted for AHA's, although the reduction was minimal. He said that this may make a difference over a period of time for the individual who has type 1 skin.

Dr. Sauder said that he was trying to place the data in perspective by presenting data on commercial sponges, shaving, and moisturizing as well. He said that one cannot only look at the findings in terms of the actual raw data on the moisturizer preparations containing AHA's and then make an impact statement on that basis.

Dr. Bergfeld introduced Paul Dykstra and Dr. Mark Lees , who would be making presentations on Alpha Hydroxy Acids on behalf of the American Beauty Association. Paul Dykstra is Executive Director of the American Beauty Association and its subdivision, the Esthetics Manufacturers and Distributors Alliance. Dr. Mark Lees is

one of the board members of the Esthetics Manufacturers and Distributors Alliance.

Paul Dykstra said that the issues that would be addressed at this time focus on the wash-off type, in-salon applications of the Alpha Hydroxy Acids. Additionally, the following other issues will be examined: (1) What the industry has done in the past regarding safety issues relating to these products, (2) Industry's safety record, which includes some of the data that have been collected in the past, (3) The training of professionals in the professional beauty industry and (4) What, if any, additional information the Panel would like the industry to provide. Paul Dykstra's presentation is summarized as follows:

In 1994, the Esthetics Manufacturers and Distributors Alliance released a statement relating to the industry's concern about consumer safety regarding Alpha Hydroxy Acid (AHA) applications in the professional salon. This statement, which included a maximum concentration level in these products and a minimal pH level, was circulated throughout the trade media and to all professionals that practice within the industry. AHA applications are performed by licensed estheticians and cosmetologists in the professional salon environment. The intention of these applications is to enhance the cosmetic appearance of the skin.

The safety record of the professional salon industry is voluminous. Data were collected within the past several months regarding in-salon applications. These data are from two of the major suppliers of these applications within the salon environment. The two suppliers represent approximately 75% of the professional market, and are involved in FDA's voluntary reporting program. In a three-year period, there is a

potential for approximately 5 million applications of these types of chemicals, with an average concentration of between 20 and 30% and an average pH of between 3 and 3.5. Of the 5 million potential applications, there are less than ten documented cases of adverse reactions from these two manufacturers. The types of adverse reactions have been of the irritant contact dermatitis type.

Estheticians and cosmeticians who are responsible for AHA applications in the professional salon market are the most thoroughly and broadly trained of all salon professionals in the industry. They are required to attend continuous all-day seminars, even before the products can be purchased for application in the salon. The trade media have repeated articles that deal specifically with the proper and safe administration of these services within the salon. Additionally, the state boards of cosmetology, headed by the National Interstate Council of State Boards of Cosmetology, have consulted organizations such as the National Beauty Association with respect to further direction of the training that is required on the safety issues of these actual salon applications.

Mr. Dykstra stated that he would like to determine from the Panel the types of information that the industry can perhaps supply and any additional details that can be presented that can address some of the questions concerning how AHA applications are used in the professional salon.

The following comments were made by Dr. Mark Lees: The industry is aware that guidelines relative to the use of AHA's need to be established. Specifically, there should be limitations on salon use concentrations and pH, and the industry has been

working on this for two years. An irritation study was done on 26% Glycolic Acid (pH = 3 to 3.5) by the Duran Corporation. Another study has also been done at a slightly higher level, 29% Glycolic Acid (pH 3.2), by the same company.

Ms. Fise recalled that Paul Dykstra mentioned that a maximum concentration and minimum pH were established in the 1994 statement made by industry, and wanted to know what had been determined.

Dr. Lees said that the pH limitation was not lower than pH 2.85 and that the maximum concentration range was 30 to 40%.

Dr. Bergfeld confirmed with Dr. Lees that these recommended limitations on pH and concentration are current within the industry.

Ms. Fise asked whether it is possible for consumers to purchase any product at any salon for use at home.

Dr. Lees said that the salons are not supposed to allow this, and that it is unlikely that this would happen. The products are labelled, professional use only. He also said that the two major companies govern to whom their products are sold very carefully. Furthermore, if the professional products industry determines that a salon is selling the professional products for home use, the products will literally be pulled from these salons.

Ms. Fise asked approximately how many companies make up the remaining 25% of the market.

Dr. Lees said that roughly a dozen companies represent the remaining 25% of the market.

Dr. McEwen said that he presumes that there are products in the salons that are available for home use, if they are labelled correctly.

Dr. Lees agreed.

Dr. Belsito said that most of the available data relates to leave-on application, and that the Panel has little data to address the safety of Glycolic Acid in rinse-off products. Thus, any information that could be provided that would be helpful in establishing concentration limits beyond what the Panel might be able to establish for leave-on products would be needed. Dr. Belsito said that he would not be able to conclude safe for use in rinse-off products as currently used because Glycolic Acid is currently used at concentrations up to 70%, which is not necessarily a safe concentration.

Dr. McEwen asked the beauty association representatives if they would have a problem with the Panel requiring product use to be under the direction of a trained professional, making it clear that the Panel was only addressing use by someone who had actual training and not someone who was just a cosmetologist or an esthetician without direct training.

Dr. Lees said that his group would not have any problem with this. He also said that, recently, there had been some discussion on developing a set of educational standards for member companies after this has been cleared with the CIR Expert Panel. He noted that the American Beauty Association consists of 69 member companies.

Dr. Bergfeld announced that Dr. John Bailey would also be making a presentation. Dr. Bailey's comments are summarized as follows:

The data presented are very interesting, and the industry is to be commended for its effort. I wish to comment on a letter that was sent to CIR. We suggested that a decision by the Panel on the safety of Alpha Hydroxy Acids be deferred, because FDA has information that will be provided for the Panel's consideration. The point that I was trying to make in the letter is that the Panel really needs to keep in mind the different legal schemes, the regulatory schemes, that apply for cosmetics and for drugs. I know that you have been told before that this is not within your purview, that this is something that does not need to be considered, and that the Panel is only looking at safety. I tend to disagree, not from a legal point of view, but from a safety point of view.

Looking at how cosmetics are considered, there are limited requirements for insuring safety at the manufacturing and ingredient development level. Companies are given a great deal of latitude in terms of how they establish the safety of a product and an ingredient. That has worked reasonably well for cosmetics. What is important to keep in mind is that we are talking about cosmetics in the traditional sense from our perspective (lipsticks, hair products, hand and body lotions, etc.), and that legal structure is matched to these traditional cosmetics. These types of cosmetics have not presented a significant or perceived significant risk of harm when considered in the traditional sense. The question is does that legal scheme really apply when we consider AHA products that we are seeing introduced into the market. If one looks at the other side, there is a scheme for marketing drugs (drug ingredients and drug products). This scheme is very structured and addresses issues such as efficacy and indications (what the ingredient should be used for). Adverse indications, required

warning statements, and cautions, etc. do a good job of making sure that the product is used the way in which it is intended to be used and that it is safe for that use. This distinction needs to be kept in mind.

Another point is that when one approaches this from the perspective of a drug, the reference points (particularly for a physician) are traditional drugs. When looking at AHA's, one may think of trichloroacetic acid, a phenol, or other substances that are obviously drugs, which obviously have an effect. When looking at one concentration of an AHA, the effect may be mild. However, at lower concentrations there may be no effect. I think that one needs to look at AHA's from the standpoint of use in cosmetics, and the reference point that should be used should be cosmetic products in their traditional sense. In other words, are these products consistent with the traditional cosmetic scheme and the standards and reference points relative to safety?

Finally, the different ingredients, different formulations, and different pH's constitute a very complicated issue. It is important that the Panel consider drawing a reasonable line between the safe uses that are cosmetic in nature, that are in line with traditional cosmetic effects, and those that go beyond that. The issue of pH is important. This may be more important than the actual concentration of the acid. Some of the information that has been submitted to CIR will help clarify that.

Dr. Belsito said that, traditionally, cosmetics have been defined as products that are intended to beautify. Typically, up until now, they have beautified by concealing. The problem now is that AHA's potentially beautify by causing certain structural changes in the stratum corneum. So, rather than acting as a typical moisturizer, the

AHA's actually get rid of some of the thicker scale and put it back into a more normal type of configuration according to the data that were presented today. Dr. Belsito wanted to know whether Dr. Bailey considers this to be a noncosmetic effect because AHA's are beautifying by causing structural change, rather than concealing.

Dr. Bailey said that at some point, that line is crossed. Intended use is the basis that the agency has traditionally used to make a legal distinction regarding the regulation of a product that is a drug or cosmetic. That intended use is derived from what is stated on the label. The agency has never taken an action based on the pure structure-function effect. However, this is probably becoming a significant issue with the introduction of the Alpha Hydroxy Acid products.

Dr. Bailey also said that he thinks that it is important for the Panel to keep in perspective the traditional effect. The legal scheme is set up based on the traditional limited "covering up" effect, keeping in mind that anything that is applied to the skin is going to have an effect. Therefore, at what point does one go sufficiently beyond that, that the product is not safe as a cosmetic?

Dr. McEwen said that if a product causes an unsafe effect, then it is unsafe. The Panel looks at many different types of studies, and there is nothing that the Panel is precluded from looking at in terms of determining whether or not the product can be safely used as a cosmetic. A cosmetic is something that, with the labelling required, goes out on the market and is sold for home use. Dr. McEwen also said that in this particular instance, the Panel has been asked by Ms. Fise to look at the product as used in a salon and that the American Beauty Association offered to provide additional

data on salon use.

Dr. McEwen emphasized that the question is still not one of whether or not AHA's are legally drugs or whether or not FDA can regulate AHA's as drugs. He said that FDA does have adequate authority to take action against any cosmetic product. There are prohibitions in the law against any adulterated product and any misbranded product. FDA can take action against a product because it is misbranded (i.e., promises to do something that it does not do) or because it promises a drug effect. FDA can also take action if a product is hazardous or contains a hazardous substance, contains a filthy or putrid substance, or is packed or held under unsanitary conditions.

Dr. McEwen also pointed out that for OTC products, there is no requirement for full ingredient labelling, although the industry does this voluntarily. Furthermore, there is no requirement for adverse reactions reporting, and there is no voluntary program for adverse reactions reporting, as is the case for cosmetics.

Dr. McEwen said that Dr. Bailey wants to submit data to CIR, and that industry has not argued against postponement of a decision on AHA's by the Panel pending these data. However, he questioned the extent to which the data are beneficial. The data to be submitted include a summary of the AHA products that the agency has analyzed over the last three years and data on adverse reactions. Dr. McEwen said that he does not think that what is on the market is necessarily going to interfere with the Panel's determination of concentration limits. He also said that limitations should be based on data rather than current use concentrations.

On the adverse reactions data (from consumers and health professionals) on

AHA-containing products to be provided by FDA, Dr. McEwen said that 17 are confirmed for 1995. He said that he does not see the benefit in knowing that there were 17 adverse reactions, considering that millions of units were distributed in the United States during the period over which the data were collected.

Dr. Bergfeld said that the Panel is very respectful of Dr. Bailey's request that the Panel postpone making a decision on AHA's. However, the Panel's postponement of a decision is based on the fact that Panel has additional data needs that need to be answered in the scientific arena to assess safety. It is also based on the volume of material that was received, which was covered during today's industry presentations. The Panel needs to review this information and assess whether the results are credible.

Ms. Fise asked whether FDA has made a decision on drug versus cosmetic classifications, and, if not, is this decision likely to be made.

Dr. Bailey said that this decision has not been made and likely will not be made prior to the March 4-5, 1996 Panel meeting. He said that the information that is being provided and the deliberations of the Panel will play a role in that ultimate decision.

Ms. Fise also asked Dr. Bailey if he had considered salon products in terms of his interest in AHA's.

Dr. Bailey said that a cosmetic is defined as a product that cleanses, promotes attractiveness, and alters the appearance, and that this definition encompasses salon use products. Salon use products are legally cosmetics. He said that whether or not the Panel wants to consider products that are used at home or those that are sold in a

salon is strictly up to the Expert Panel.

In response to Dr. McEwen's comments, Ms. Fise said that it is very important for the Panel to note that consumers use salon products and products that are marketed for home use, and that there is concern about consumer exposure. Ms. Fise specifically recalled Dr. McEwen's comments to the effect that there is no requirement for adverse reactions reporting, implying that this is not needed. She said that FDA and the Consumer Federation of America would like to have this requirement, and that industry opposes adverse reactions reporting.

Ms. Fise also said that the fact that FDA can provide information concerning products that are on the market is very valuable to the Panel. Based on her recollection, she stated that, over the years, CTFA members have not always supplied this information.

Dr. Bergfeld noted that new data in the report on Alpha Hydroxy Acids had been reviewed in closed session on the preceding day. She said that it is the feeling of the Panel, especially after today's industry presentations, that a lot of information is yet to be reviewed by the Panel. She stated that many of the studies that were mentioned in the presentations are contained in the notebooks that industry has compiled for the Panel members. She also said that the Panel lacks information from the American Beauty Association, and that the Panel was asked to keep in mind FDA's request to submit additional information to the Panel, namely, consumer complaints information and, perhaps, information on absorption. Dr. Bergfeld said that with all of this in mind, the Panel will postpone its actual ruling on the Alpha Hydroxy Acids until the March 4-5,

1996 Panel meeting.

Dr. Schroeter said that the Panel has dealt with the salon use of agents that could be labelled by FDA as cosmetics. However, in this particular situation, the Panel will have to address salon use in the report discussion, if AHA's are agents for which the Panel wants to address safety as it relates to use by beauty salon professionals. He said that the other issue before the Panel relates to the ingredients, the Alpha Hydroxy Acids that should be reviewed in the CIR report. At the last Panel meeting, menthyl lactate and sodium isostearoyl lactylate were considered for addition to the existing report.

Dr. Belsito noted that the reasons why the two ingredients shouldn't be included is because menthyl lactate is a flavor and fragrance and sodium isostearoyl lactylate is not an Alpha Hydroxy Acid. Both Teams favored excluding these ingredients from the AHA report.

Dr. Schroeter said that the other issues that the Panel must focus on are pH and concentration. He said that the Panel will have to focus first on the desired effect for a cosmetic, e.g., determining whether or not the effect should be non-corrosive or "non-peeling". After this has been done, perhaps, the Panel will have limited its discussion and focus.

According to Dr. Schroeter, the other question that will have to be dealt with is the safety of the Alpha Hydroxy Acids in terms of their ability to promote the skin penetration of other vehicles that are formulated with them. He said that although there are limited data regarding this, indicating that AHA's do not promote the penetration of

other vehicles, this issue will also have to be further discussed. Additionally, he said that some language that incorporates a generic statement about safety into the Panel's recommendation will have to be utilized, because the Panel cannot deal with each of the formulations that may exist.

Dr. Belsito said that, as noted by Dr. Schroeter, the Panel's conclusion on the safety of Alpha Hydroxy Acids likely will be based on irritancy and the concentration at which the Panel is comfortable with irritancy. With this in mind, he said that the Panel would like to see the types of studies by Dr. DiNardo (dose responses and pH variations at each dose) done on Glycolic and Lactic Acids, because the Panel does not have well-defined, dose-response and pH-adjusted response data on Lactic Acid. Additionally, no data relating to rinse-off product use are included in the present report. These data will be of interest both for salon products and marketed facial cleansers, and will be needed in order for the Panel to make a decision on the safety of AHA's.

Dr. Belsito also said that the Panel will have to review the documents provided during today's industry presentations in order to evaluate, for example, the effect of AHA's on UV light penetration. Dr. Sauder's presentation, in particular, addressed some of the concerns that the Panel had concerning UVB light penetration, and these data will have to be evaluated closely by the Panel. Dr. Belsito wanted to know whether Dr. Schroeter's Team still wants the photoadduct thymidine dimer types of studies that were requested earlier.

Furthermore, Dr. Belsito said that he is somewhat comforted by Dr. Sauder's

response concerning the skin $\text{TNF}\alpha$ mechanisms of wounding. However, he said that there is still some concern relative to this, and that he would like to review any additional information that is available. It was also noted that there are issues that were raised in the Panel's informal data request that have not been addressed in terms of the impurities in Lactic Acid, particularly, its formaldehyde content.

Finally, Dr. Belsito said that he hopes that the American Beauty Association will provide the Panel with documentation of the organization's suggested limitations on AHA concentrations and pH's, and some written documentation as to the methods of training and licensing of estheticians and what the industry does to restrict the distribution of professional-use products to licensed individuals. He expressed concern over some of the products that reach the market place via the esthetic salons.

Dr. Schroeter said that the Panel has to define whether the AHA's are going to be limited to peeling (complete removal of the cornified layer) or non-peeling. If AHA's are going to include peeling, then the Panel will have to further discuss items 6 and 7 from the informal data request: (6) the photoproducts\thymidine dimers and adducts produced upon application of AHA's with UV light at different time intervals, up to 6 weeks, with different dose levels and (7) photocarcinogenicity data.

With respect to the other AHA's that were listed during Dr. Leyden's presentation, Ms. Fise asked if FDA could provide information on the current uses of these ingredients. She said that if these ingredients are being used, then this is an issue for the Panel, regardless or whether or not industry wants CIR to review these ingredients.

Dr. Bergfeld said that at this time, the Panel is making informal requests of the

industry (to representatives in the audience as well as CTFA) for information. She said that the Panel has agreed, and an official motion will be made, to table the report on Alpha Hydroxy Acids until the March 4-5, 1996 Panel meeting, with the intention of discussing this document in its entirety at that time.

Dr. Klaassen said that he would like to see information in regard to the chemistry of the AHA's, in that the Panel has discussed regulating these compounds in relation to pH and concentration. He said that since the AHA's have a pK_a of approximately 3.8, and if all of them don't boil down to one chemical species (that is, the free concentration), probably, the easiest way to change the concentrations of these compounds in the product is not by changing the concentration, but by changing the pH. Dr. Klaassen said that he would like to see someone apply the Hendersen-Hasselbach equation to all of the AHA's, and determine what really happens at the various pH's and at the various concentrations.

Dr. McEwen said that the work done by DiNardo shows a particular level of irritation at various pH's and concentrations. At the same relatively high pH that is close to the pK_a , there is no difference between a 5% solution and a 20% solution. However, there is a difference in the free acid concentration. In terms of the irritation seen in one study, no difference was shown. Dr. McEwen said that there must be something other than just the concentration of free acid (perhaps buffering or salt content) that accounts for this observation.

A representative from industry said that the vehicle has to be taken into consideration as well, because, in dealing with an oil-in-water emulsion, partitioning in

the water and oil phases occurs. In this case, the pK_a may not be so "clear cut".

Dr. Bailey said that in looking at the data from the presenters (given to Panel members), there seems to be a shortage of information relative to the methyl and ethyl esters of AHA's. The low molecular weight esters are really the ones that are of greater concern than some of the higher molecular weight esters. He also said that the data relative to carcinogenicity and the other toxicity endpoints seem to be missing several significant areas relative to those particular substances.

Dr. Bailey said that someone in the agency suggested to him that photocarcinogenicity may be an important issue, and that the Panel may wish to consider the need for photocarcinogenicity data.

Dr. Schroeter noted that photocarcinogenicity data is one of the items in the informal data request on AHA's. However, this request is dependent on whether or not it can be shown that there is significant production of thymine dimers and adducts. If this is true, then a photocarcinogenicity study will be needed.

Dr. Belsito asked whether the request for photocarcinogenicity was based on interference with barrier function.

Dr. Bailey said that barrier function is an issue. Additionally, the fact that the information provided shows a fairly significant change in the MED points to something happening in the skin, because Glycolic Acid is not a UV absorber.

Dr. Belsito noted that information in the CIR report suggests that pretreatment with Glycolic Acid provides photo-protection by increasing the MED.

Dr. Bailey said that the question is why is it doing that. Is it promoting healing or

are other things taking place?

The Panel voted unanimously in favor of tabling the CIR report on Alpha Hydroxy Acids until the March 4-5, 1996 Panel meeting.

Dr. Andersen reminded all of the participants in the Alpha Hydroxy Acid discussion that any data submitted for the Panel's review would have to be received in early February in order to be considered at the March 4-5, 1996 Panel meeting.

The 57th Meeting of the CIR Expert Panel was adjourned.

DEFINING THE ISSUES

POTENTIAL FOR AHA'S TO MODIFY SKIN BARRIER FUNCTION

- EFFECTS ON PERCUTANEOUS ABSORPTION
- CHANGES IN UV TRANSMITTANCE

PREMISE: AHA'S THIN STRATUM CORNEUM & COMPROMISE BARRIER FUNCTION

- AHA'S DO NOT COMPROMISE SKIN BARRIER FUNCTION
- AHA'S DO NOT ENHANCE PERCUTANEOUS ABSORPTION
- AHA'S DO NOT CHANGE UV TRANSMITTANCE ANY MORE THAN TYPICAL COSMETIC TREATMENTS OR SEASONAL/CLIMATIC CHANGES

EFFECTS OF AHA'S

ON SKIN BARRIER

PROPERTIES

MISCONCEPTION - AHA'S THIN STRATUM CORNEUM

TOPICAL APPLICATION OF AHA'S
REDUCES ABNORMALLY THICK
STRATUM CORNEUM ON SUBJECTS
WITH DRY LEGS (LEYDEN *ET. AL.*, 1992)

AHA'S HAVE MINIMAL EFFECTS ON TEWL

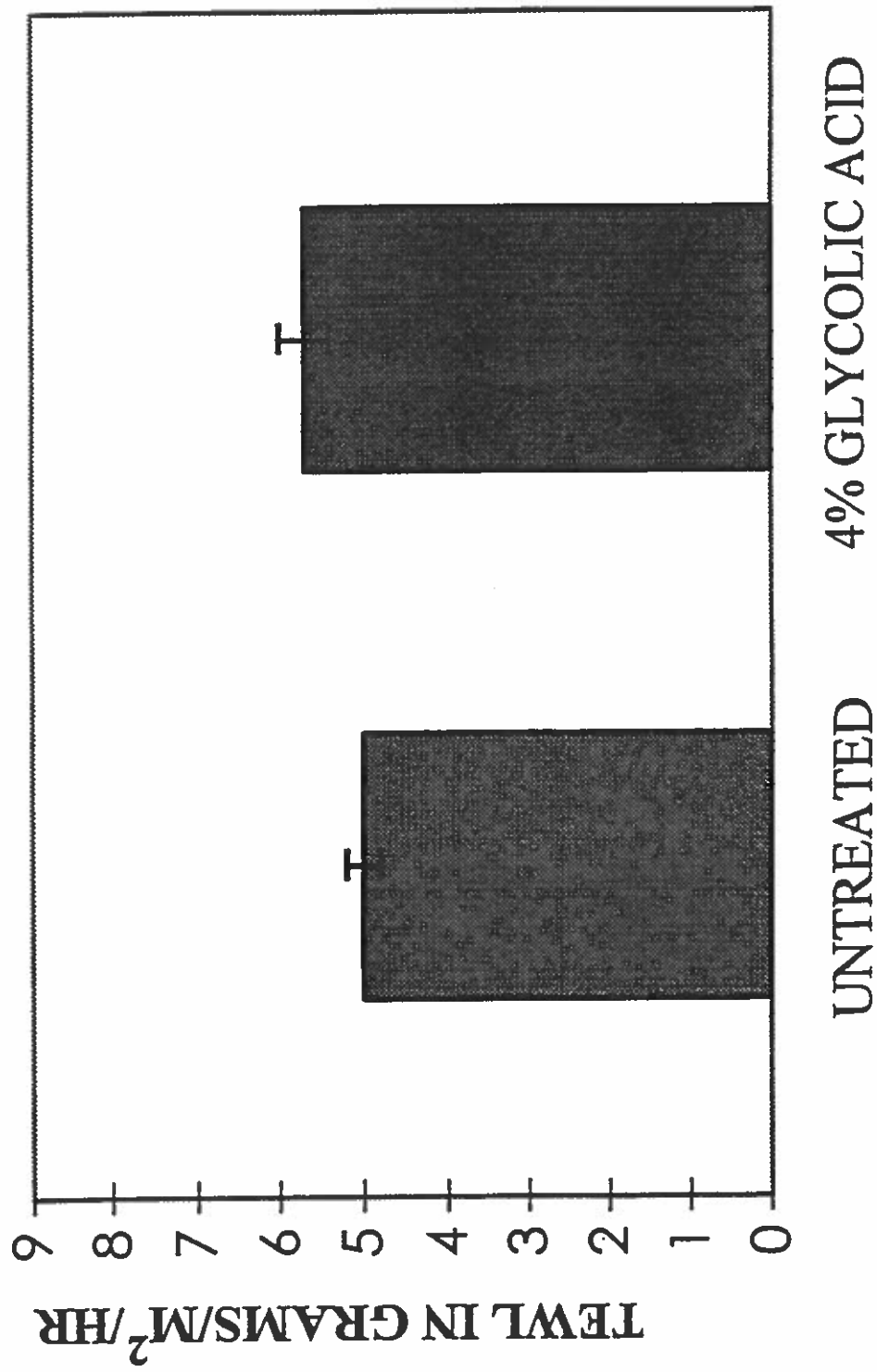
FIVE SEPARATE STUDIES

METHODOLOGY

- 4% GLYCOLIC ACID (pH 3.8) IN STANDARD COSMETIC CREAM
- 19 SUBJECTS
- APPLICATION 2x/DAY FOR 24 WEEKS TO LOWER BACK
- AM APPLICATION SUPERVISED MON. - FRI.
- TEWL MEASURED AT BASELINE AND 24 WEEKS
- STRATUM CORNEUM WATER CONTENT MEASURED AT 24 WEEKS
- COMPARISONS MADE TO ADJACENT CONTROL SITE

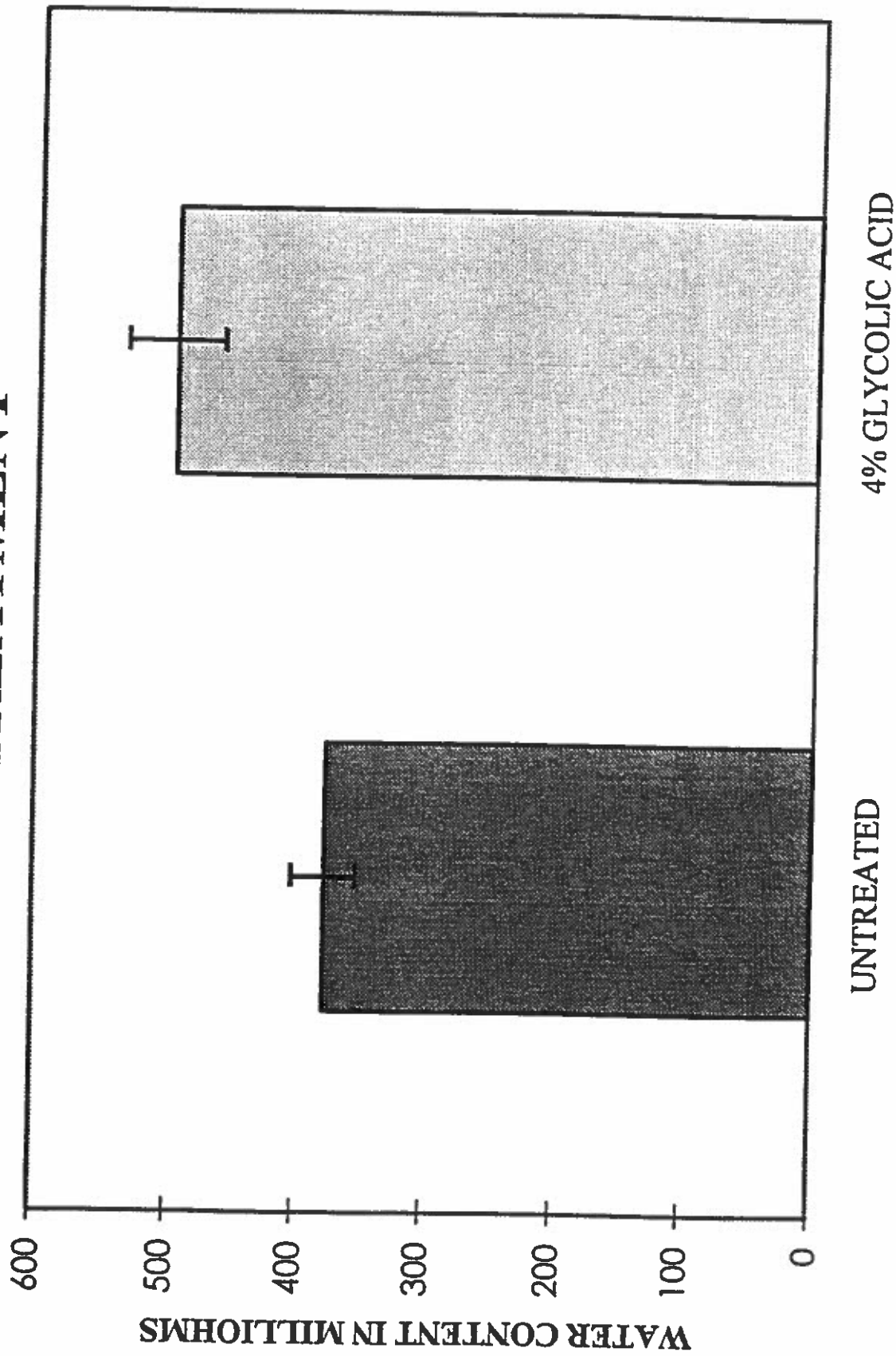
(GROVE, 1995, UNPUBLISHED DATA)

TEWL AFTER 24 WEEKS OF TREATMENT



p = 0.05

WATER CONTENT AFTER 24 WEEKS OF TREATMENT



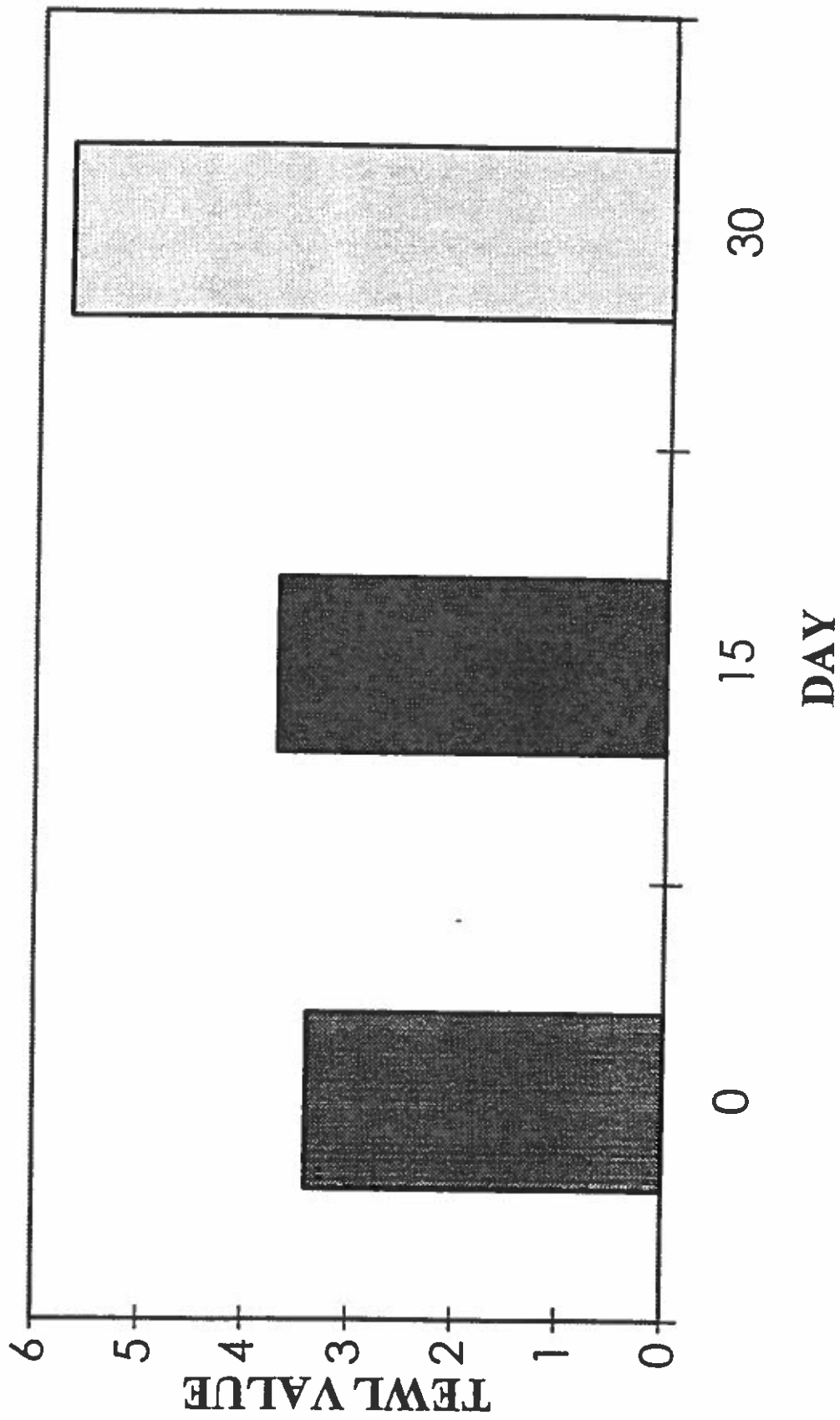
p=0.05

METHODOLOGY

- 12% AMMONIUM LACTATE PRODUCT
(KERATISIDIN)
- 24 SUBJECTS
- APPLICATION 2x/DAY FOR 4 WEEKS TO LEGS
- AM APPLICATION SUPERVISED MON. - FRI.
- TEWL MEASURED AT BASELINE, 15 & 30 DAYS

(VILAPLANA *ET. AL.*, 1992)

TREATMENT WITH 12% AMMONIUM LACTATE EMULSION



METHODOLOGY

- RETINOIC ACID CREAM (0.025, 0.05, 0.01%)
- 10 SUBJECTS/FLEXOR FOREARM
- APPLIED 1x/DAY FOR 14 DAYS
- TEWL MEASUREMENTS TAKEN AT 0, 4, 7, 12, & 14 DAYS

(TAGAMI *ET. AL.*, 1992)

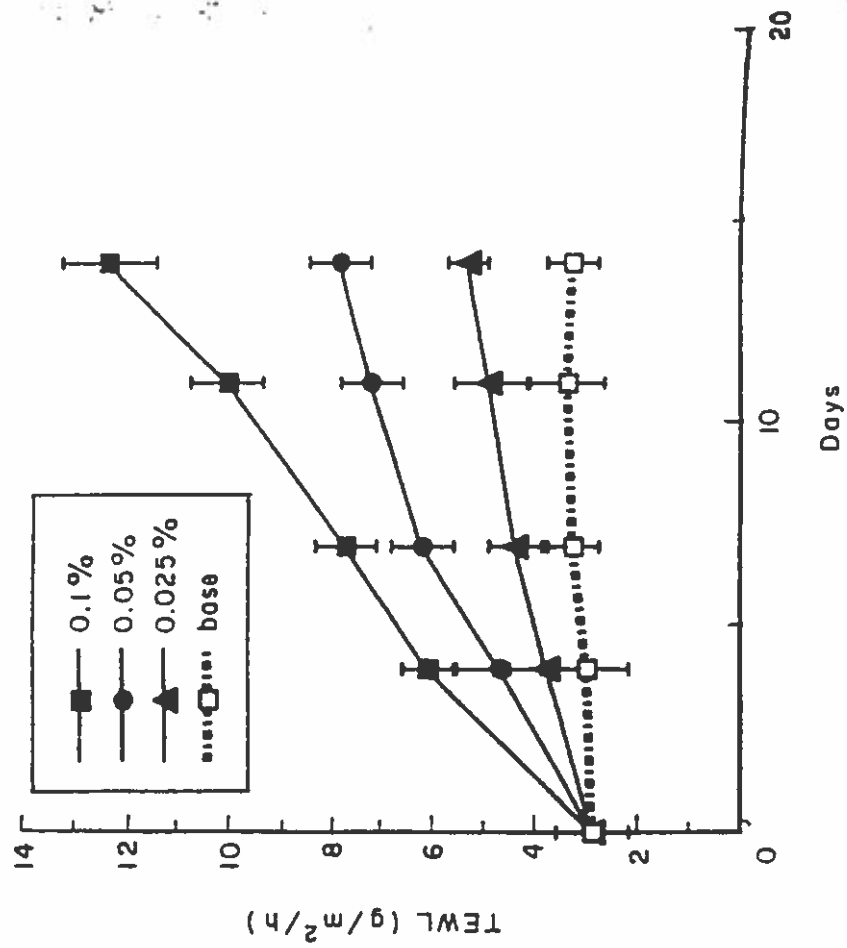


Figure 2. Transepidermal water loss (TEWL) measured on the flexor aspect of the forearm in 10 volunteers treated with various retinoid acid creams and a cream base. Data are presented as means \pm SD.

REPEATED APPLICATION

OF AHA'S DOES NOT

PRODUCE CHANGES IN:

- OVERALL SKIN STRUCTURE OR HISTOLOGY
- ULTRASTRUCTURE OF THE SKIN BARRIER
- THICKNESS OF THE STRATUM CORNEUM AND VIABLE EPIDERMIS

SIX SEPARATE STUDIES

METHODOLOGY

- 4% GLYCOLIC ACID (pH 3.8) IN STANDARD COSMETIC CREAM
- 8 SUBJECTS/VOLAR FOREARM
- APPLICATION 1x/DAY FOR 2 WEEKS THEN 2x/DAY FOR 22 WEEKS
- CONTROLS WERE LEADING COSMETIC MOISTURIZER, MARKETING COSMETIC EXFOLIATING SPONGE, & NO TREATMENT
- PUNCH BIOPSIES TAKEN AT END OF STUDY FOR HISTOLOGICAL EVALUATION

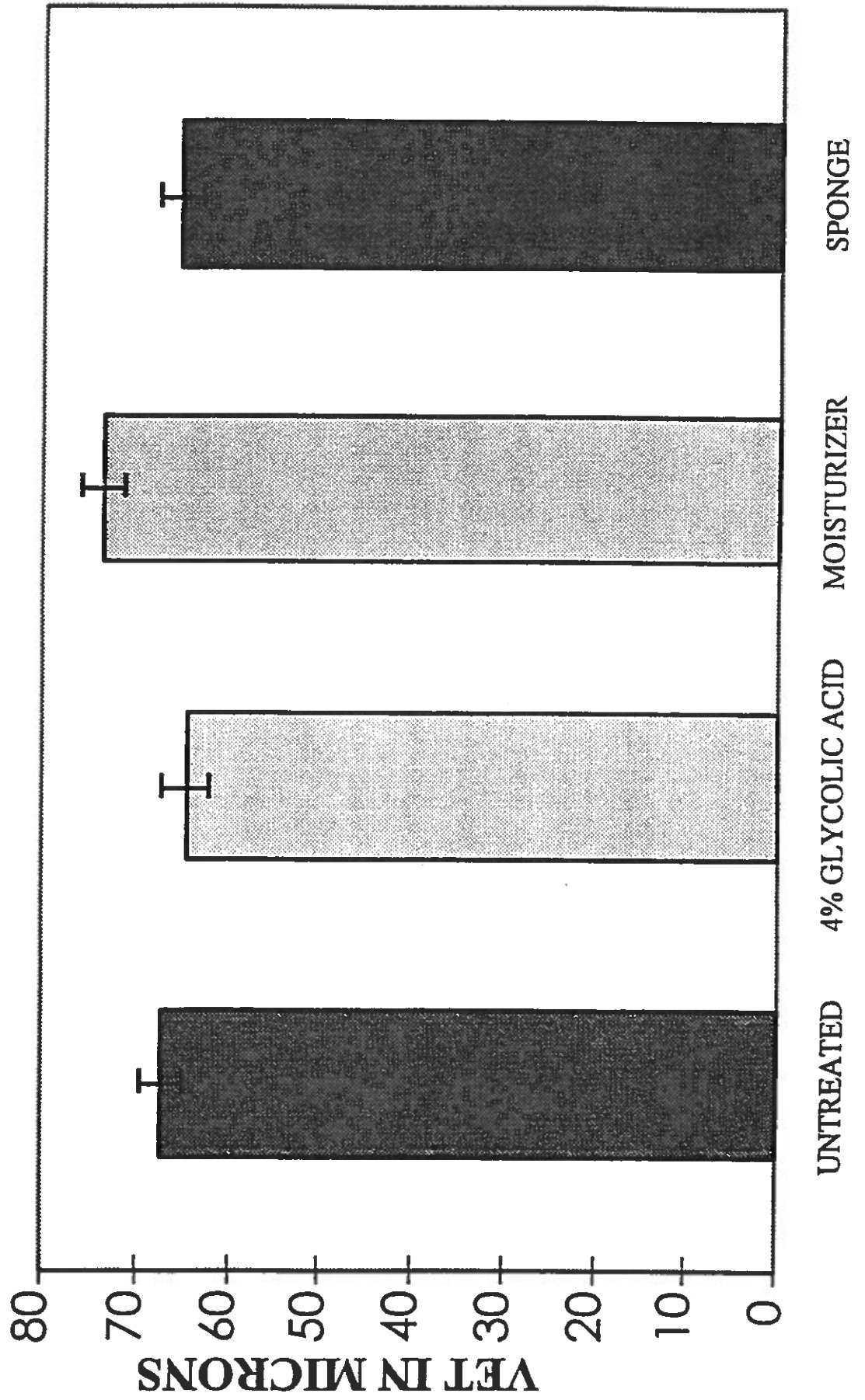
(KAIDBEY & LAVKER, 1994, UNPUBLISHED DATA)

SUMMARY OF STRATUM CORNEUM HISTOLOGY

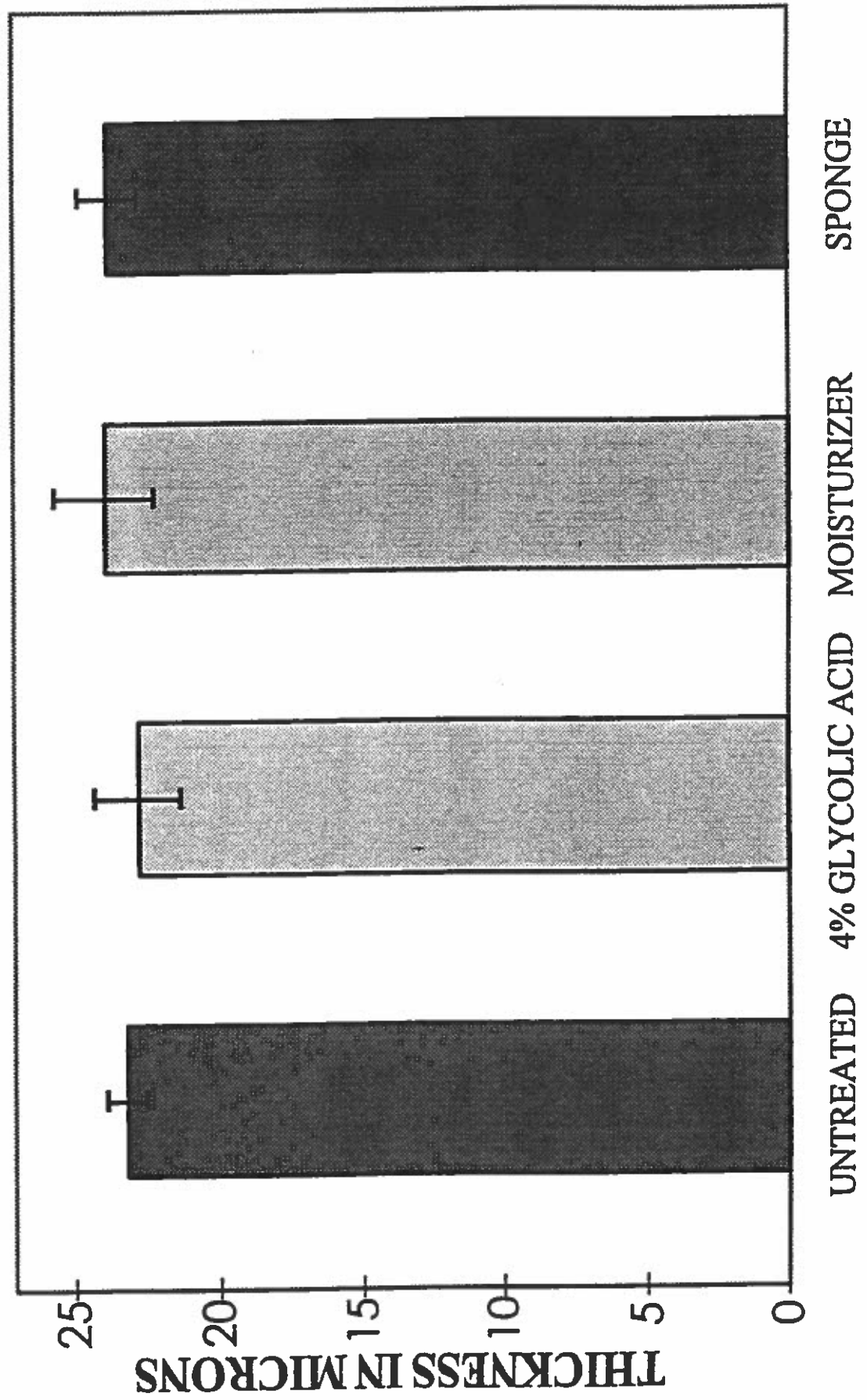
<u>SUBJECT</u>	<u>CONTROL</u>	<u>GLYCOLIC ACID</u>	<u>MOISTURIZER</u>	<u>SPONGE</u>
1	Basketweave	Basketweave	Basketweave	Basketweave
2	Basketweave	Compact	Basketweave	Slightly Thinned
3	Basketweave	Basketweave	Basketweave	Basketweave
4	Slightly Thinned	Basketweave	Thin, Compact	Basketweave
5	Basketweave	Basketweave	Basketweave	Basketweave
6	Basketweave	Thin, Compact	Very Thin	Thickened
7	Basketweave	Basketweave	Basketweave	Altered
8	Basketweave	Basketweave	Basketweave	Basketweave

NOTE: “Slightly thinned”, “compact” stratum corneum=a compressed layer of horny cells rather than basket-weave pattern.
 “Altered” stratum corneum=a stratum corneum that is discontinuous in places.

VIABLE EPIDERMAL THICKNESS AFTER 6 MONTHS OF TREATMENT



STRATUM CORNEUM THICKNESS AFTER 6 MONTHS OF TREATMENT

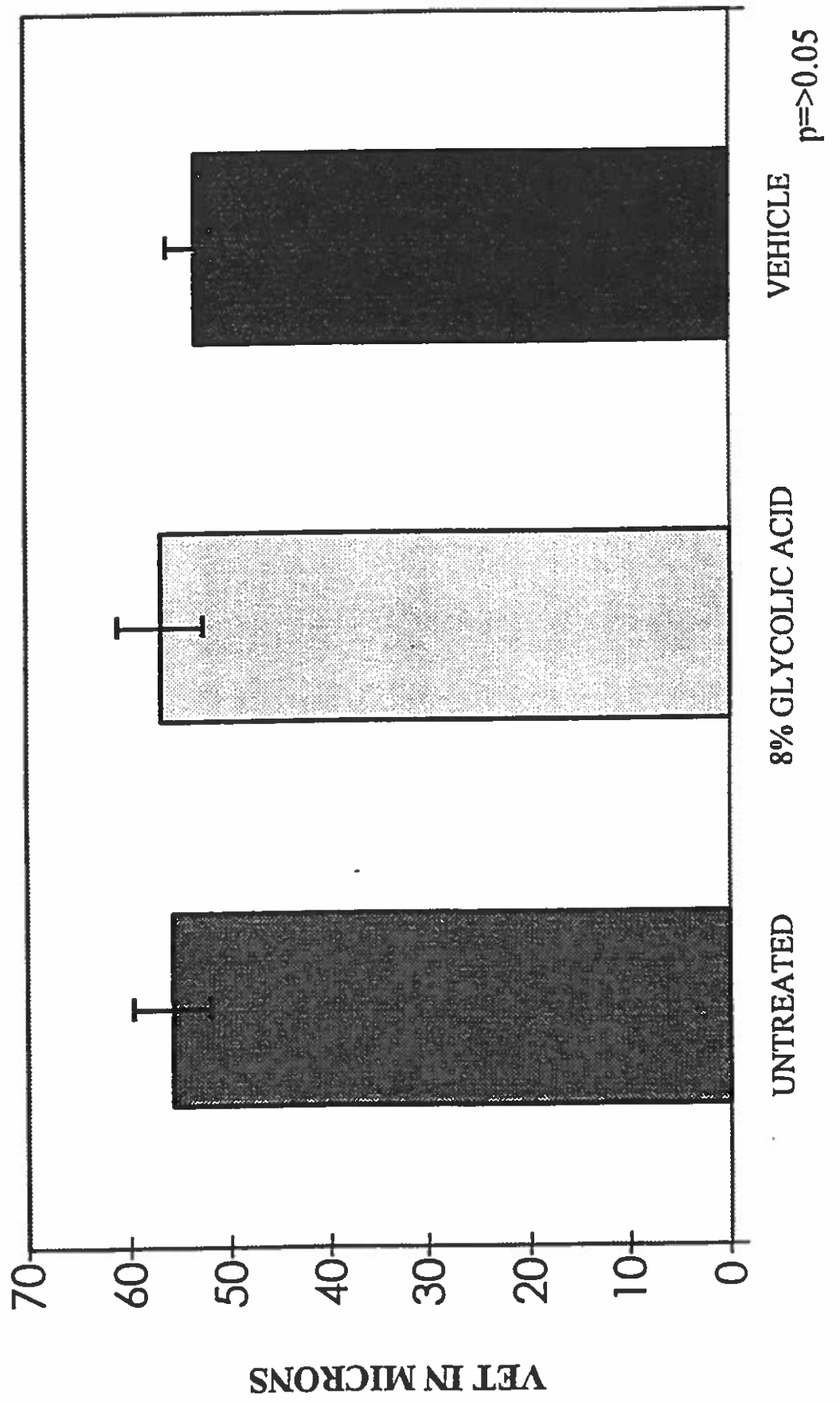


METHODOLOGY

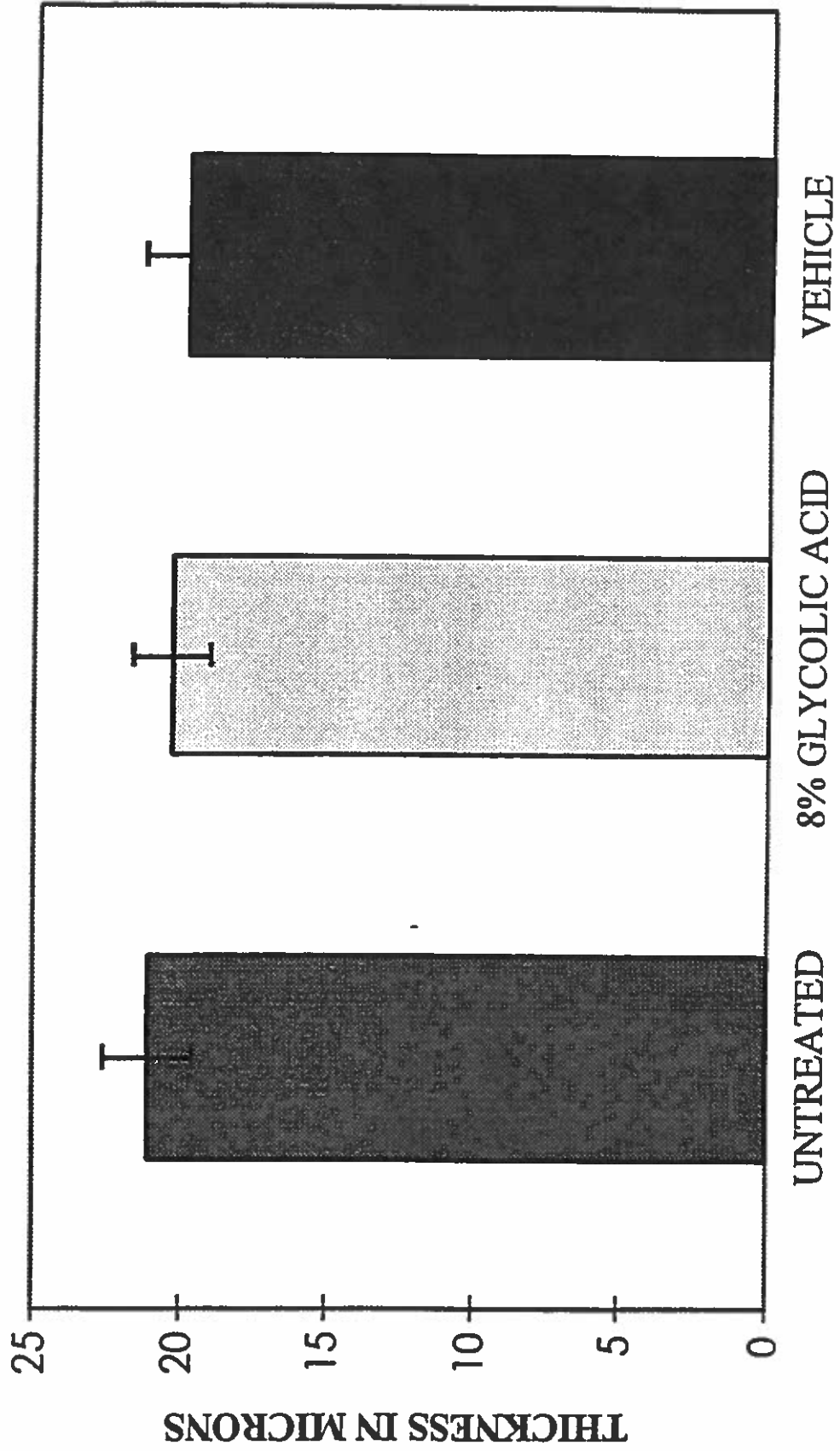
- 8% GLYCOLIC ACID (pH 3.9) IN STANDARD COSMETIC CREAM
- 10 SUBJECTS/LOWER BACK
- SUPERVISED APPLICATION 2x/DAY FOR 28 DAYS
- ADJACENT CONTROL SITES RECEIVED VEHICLE AND NO TREATMENT
- SHAVE BIOPSIES TAKEN AT END OF STUDY FOR HISTOLOGICAL EVALUATION

(LEYDEN, LAVKER & GROVE, 1994, UNPUBLISHED DATA)

VIABLE EPIDERMAL THICKNESS AFTER 1 MONTH OF TREATMENT



STRATUM CORNEUM THICKNESS AFTER 1 MONTH OF TREATMENT



$p \geq 0.05$

EFFECTS OF AHA'S ON **PERCUTANEOUS** **ABSORPTION**

SUMMARY - EFFECTS OF **AHA'S ON SKIN BARRIER** **PROPERTIES**

- AHA'S DO NOT COMPROMISE STRATUM CORNEUM BARRIER FUNCTION
- LONG-TERM APPLICATION DOES NOT AFFECT STRUCTURE OF THE SKIN BARRIER
- REPEATED USE PRODUCES MINIMAL CHANGES IN TEWL

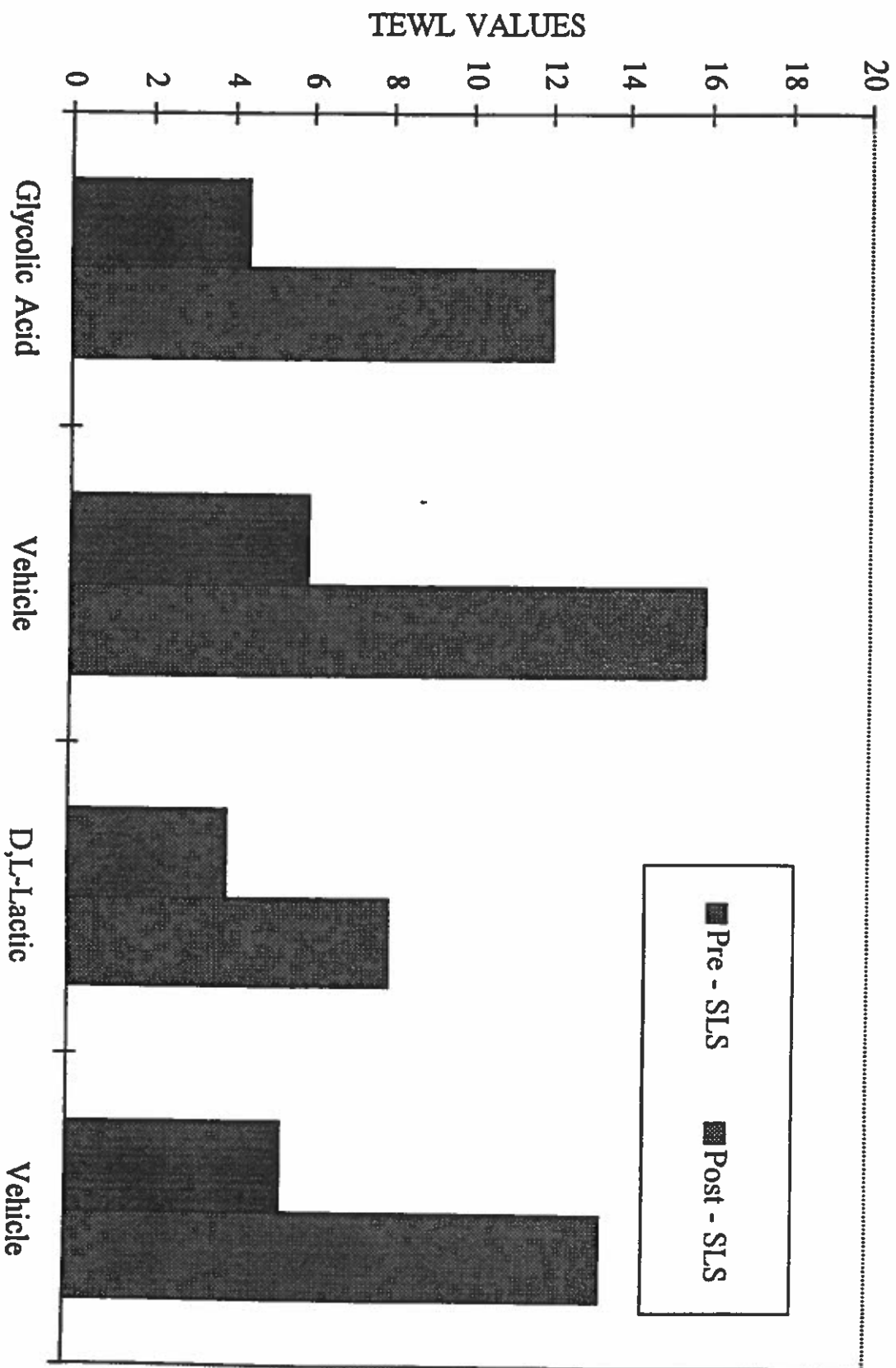
METHODOLOGY

2 SEPARATE STUDIES

- 4% GLYCOLIC ACID OR LACTIC ACID (pH 4.0) IN AQUEOUS SOLUTION
- APPLICATION 2x/DAY FOR 28 DAYS/VOLAR FOREARM
- VEHICLE APPLIED TO CONTRALATERAL FOREARM
- AFTER 28 DAYS, 0.25% SLS IN WATER APPLIED UNDER OCCLUSIVE PATCH FOR 24 HOURS
- TEWL MEASUREMENTS TAKEN BEFORE AND AFTER SLS PATCH

(RAWLINGS, 1995, UNPUBLISHED DATA)

SLS CHALLENGE: AFTER 4 WEEKS OF TREATMENT



FACTORS AFFECTING **PENETRATION THROUGH** **STRATUM CORNEUM**

- STRUCTURAL INTEGRITY
- SKIN SITE
- DEGREE OF HYDRATION
- PHYSICO-CHEMICAL PROPERTIES OF PENETRANT
 - POLARITY
 - MOLECULAR SIZE
 - OIL/WATER PARTITION COEFFICIENT

THE APPLICATION TO
SKIN OF VARIOUS
MATERIALS CAN AFFECT
THE PERCUTANEOUS
ABSORPTION OF OTHER
MATERIALS

SKIN HYDRATION CAN AFFECT PERCUTANEOUS ABSORPTION

EXAMPLES FROM THE PHARMACEUTICAL LITERATURE

- PENETRATION OF SALICYLIC ACID INCREASED ~ 4 FOLD IN TRANS-6-OCTADECENOIC ACID VS. CIS-9-OCTADECENOIC ACID (GOLDEN ET. AL., 1987)
- SLS INCREASED NAPROXEN PERMEATION >8 FOLD (CHOWAN & PRITCHARD, 1978)
- ACETONE HAD NO INFLUENCE ON IBUPROFEN PENETRATION WHILE N-METHYL-2-PYRROLIDONE INCREASED PERMEATION 16 FOLD VS. ACETONE (AKHTER & BARRY, 1985)
- DMSO ENHANCED SCOPOLAMINE PENETRATION BY ORDERS OF MAGNITUDE (CHANDRASEKARAN ET. AL., 1977)

AHA'S HAVE NOT INCREASED ALLERGIC REACTIONS

28 SEPARATE STUDIES

- EXAGGERATED CONDITIONS (OCCLUSIVE OR SEMI-OCCLUSIVE PATCH) .
- FIVE DIFFERENT AHA'S AT CONCENTRATIONS UP TO 10% (pH 3.6 - 7.0)
- TYPICAL COSMETIC PRESERVATIVES & LEVELS
- NO CONTACT DERMATITIS

EXAMPLES FROM THE LITERATURE

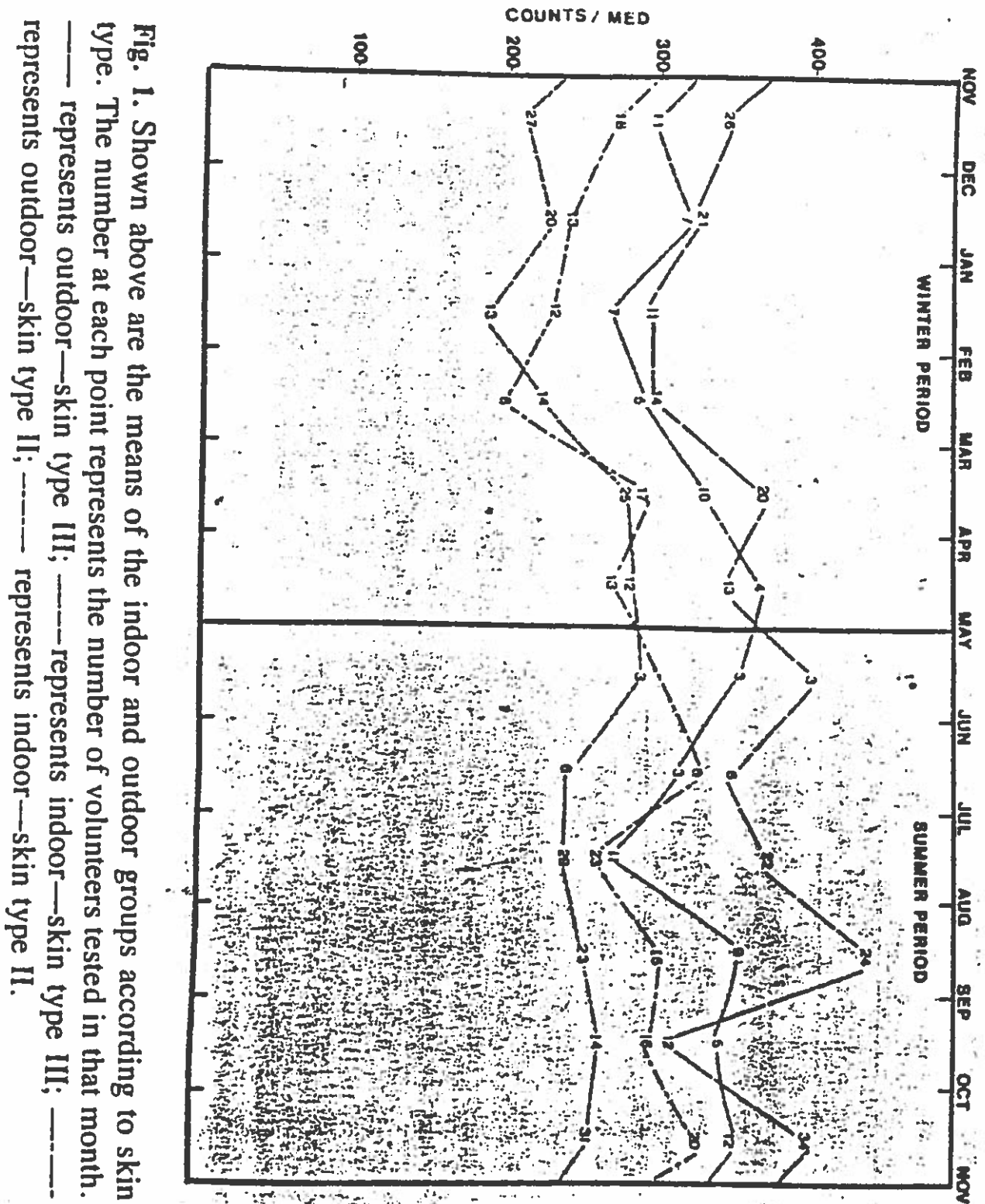
- NITROGLYCERIN FLUX INCREASED WITH INCREASED SKIN WATER CONTENT
(ZATZ, 1993)

- PETROLATUM VEHICLES INCREASED THE ABSORPTION OF HYDROCORTISONE-17-VALERATE
(WANG, ET. AL., 1988)

HUMAN CLINICAL TESTS

10 SEPARATE STUDIES

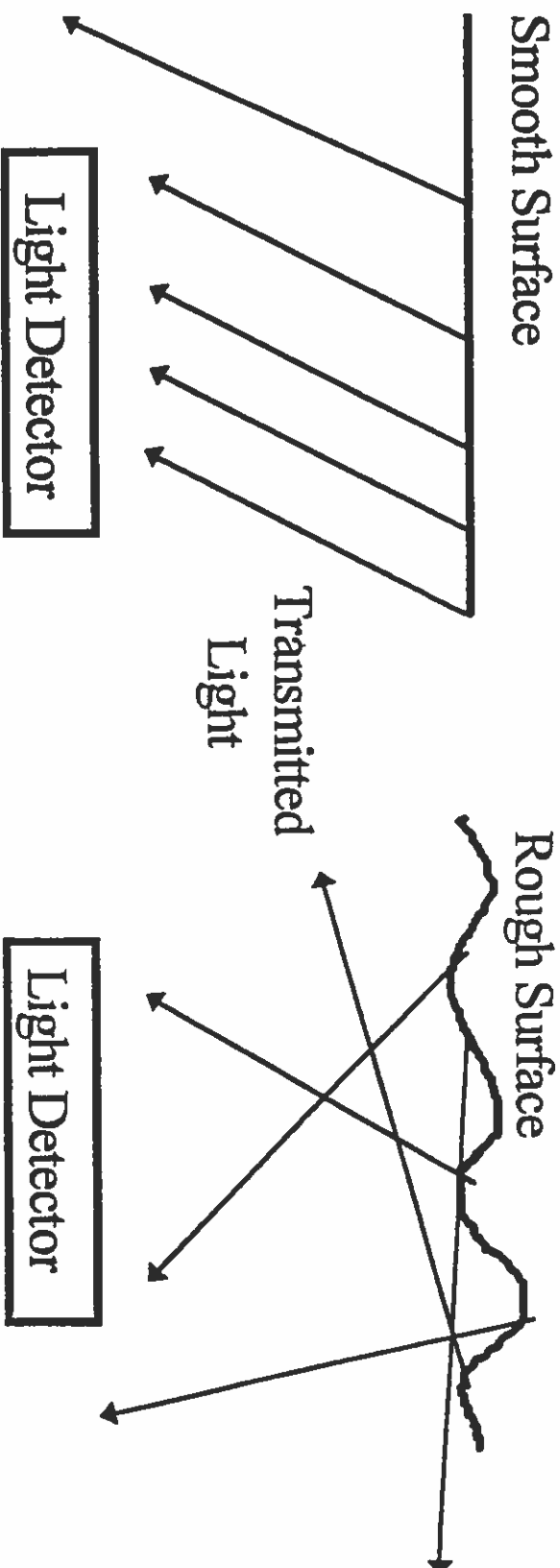
- **459 SUBJECTS**
- **DAILY APPLICATION OF COSMETIC PRODUCTS CONTAINING GLYCOLIC WITH OR WITHOUT LACTIC ACID AT LEVELS UP TO 10% (pH 3.6 - 4.2)**
- **EXTENDED TREATMENT PERIODS OF UP TO 12 MONTHS**
- **CLOSELY MONITORED, OFTEN DERMATOLOGIST SUPERVISED**
- **TYPICAL COSMETIC PRESERVATIVES AND LEVELS**
- **NO CONTACT DERMATITIS**



- PRIMARY CAUSE OF SKIN ROUGHNESS IS STRATUM CORNEUM CELLS
- TOP LAYER OF STRATUM CORNEUM IS ALWAYS IN THE PROCESS OF BEING SHED.
- EXCESSIVE AMOUNTS OF FLAKING OR PARTIALLY SHED CELLS MAKE SKIN SURFACE APPEAR DULL

SOME BASIC PHYSICS

Depth of Light Transmission Due to Surface



MORE LIGHT PENETRATES INTO A SMOOTH SURFACE

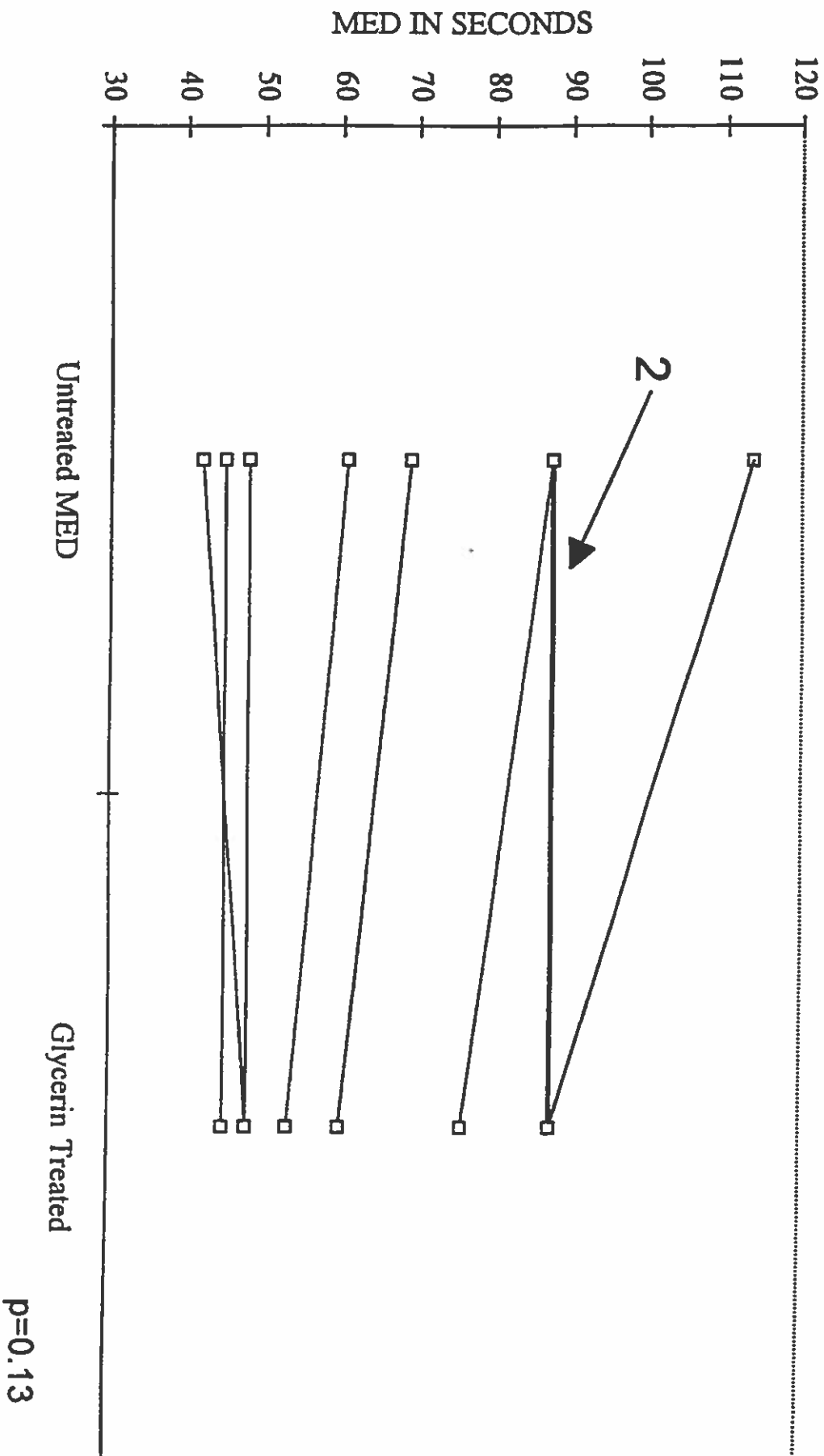
EFFECT ON MED OF TOPICAL APPLICATION OF MOISTURIZERS

- 32 SUBJECTS TOTAL
- TEST PRODUCT APPLIED TO ONE SITE ON LOWER BACK;
ADJACENT SITE SERVED AS UNTREATED CONTROL
- TEST PRODUCTS:
 - LEADING MOISTURE LOTION CONTAINING ~ 10% MINERAL OIL
 - PROTOTYPE COSMETIC LOTION WITH 10% GLYCERIN
- THIRTY MINUTES AFTER APPLICATION, SITES IRRADIATED WITH
GRADED DOSES OF UV
- MED DETERMINED 20-24 HOURS POST-IRRADIATION

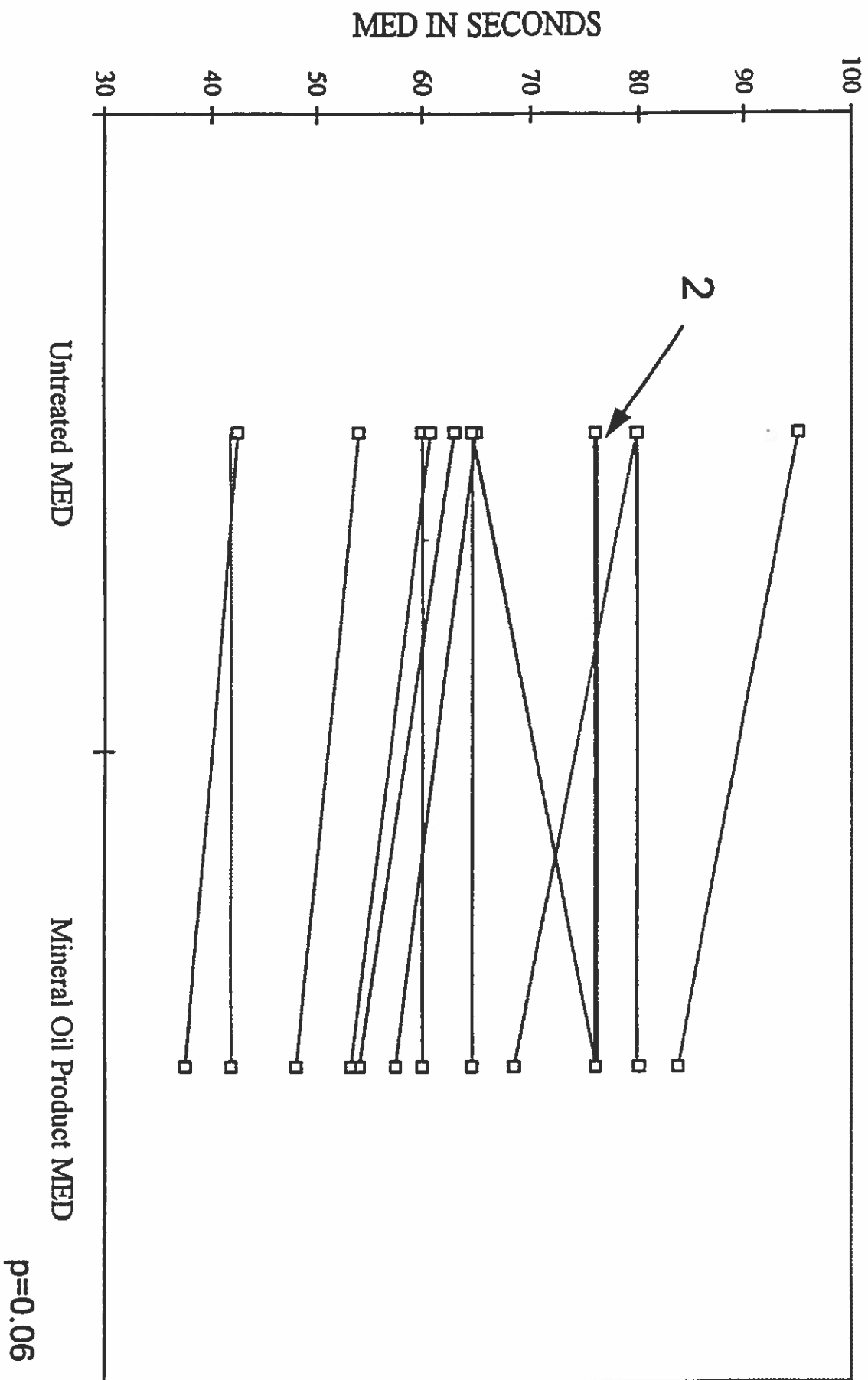
(TKL RESEARCH, 1995, UNPUBLISHED DATA)

SKIN TREATMENTS CAN ALTER MED

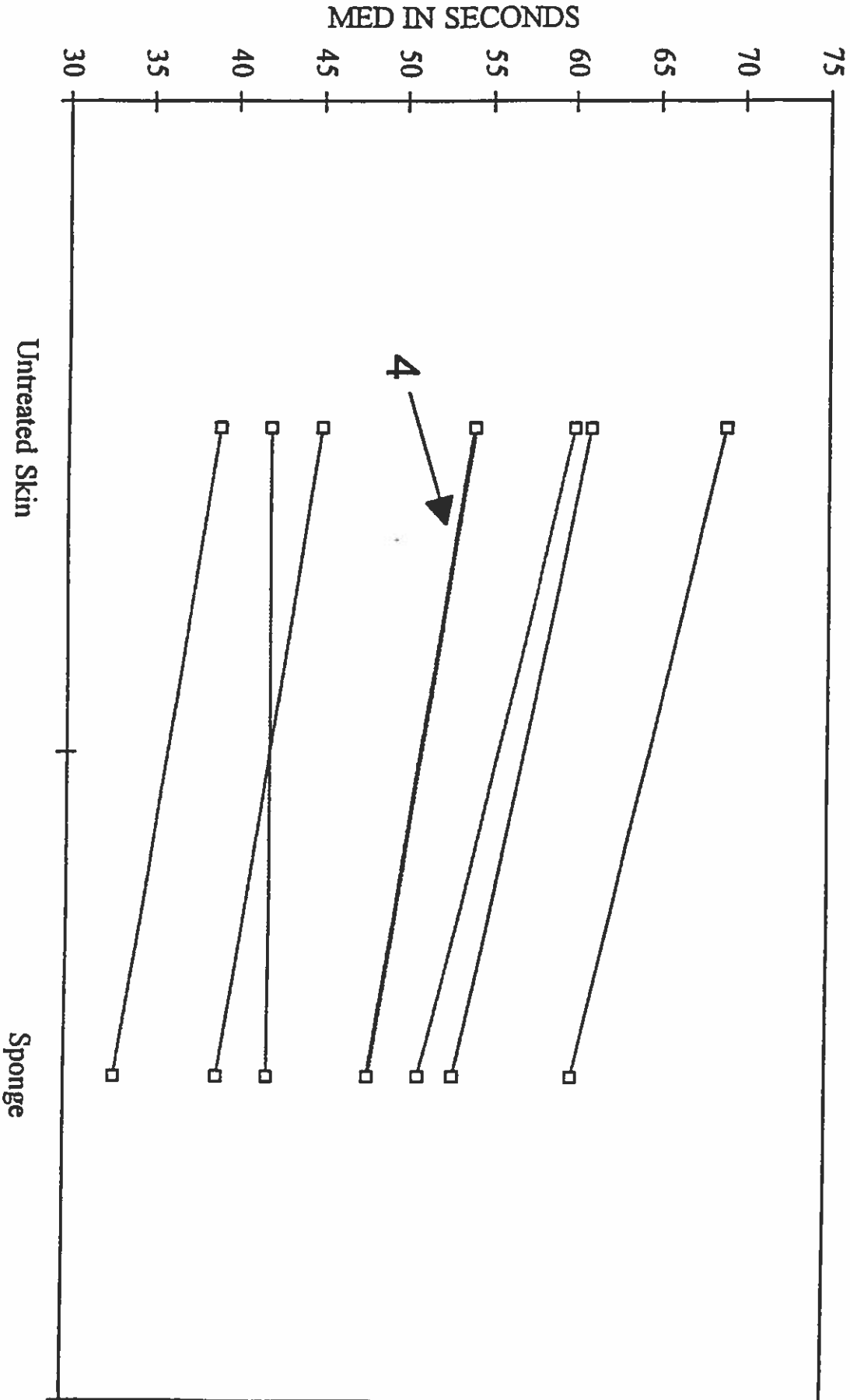
MEDS WITH AND WITHOUT 10% GLYCERIN PRODUCT



MEDS WITH AND WITHOUT 10% MINERAL OIL PRODUCT



UNTREATED MED VS. MED OF SKIN WASHED WITH EXFOLIATING SPONGE



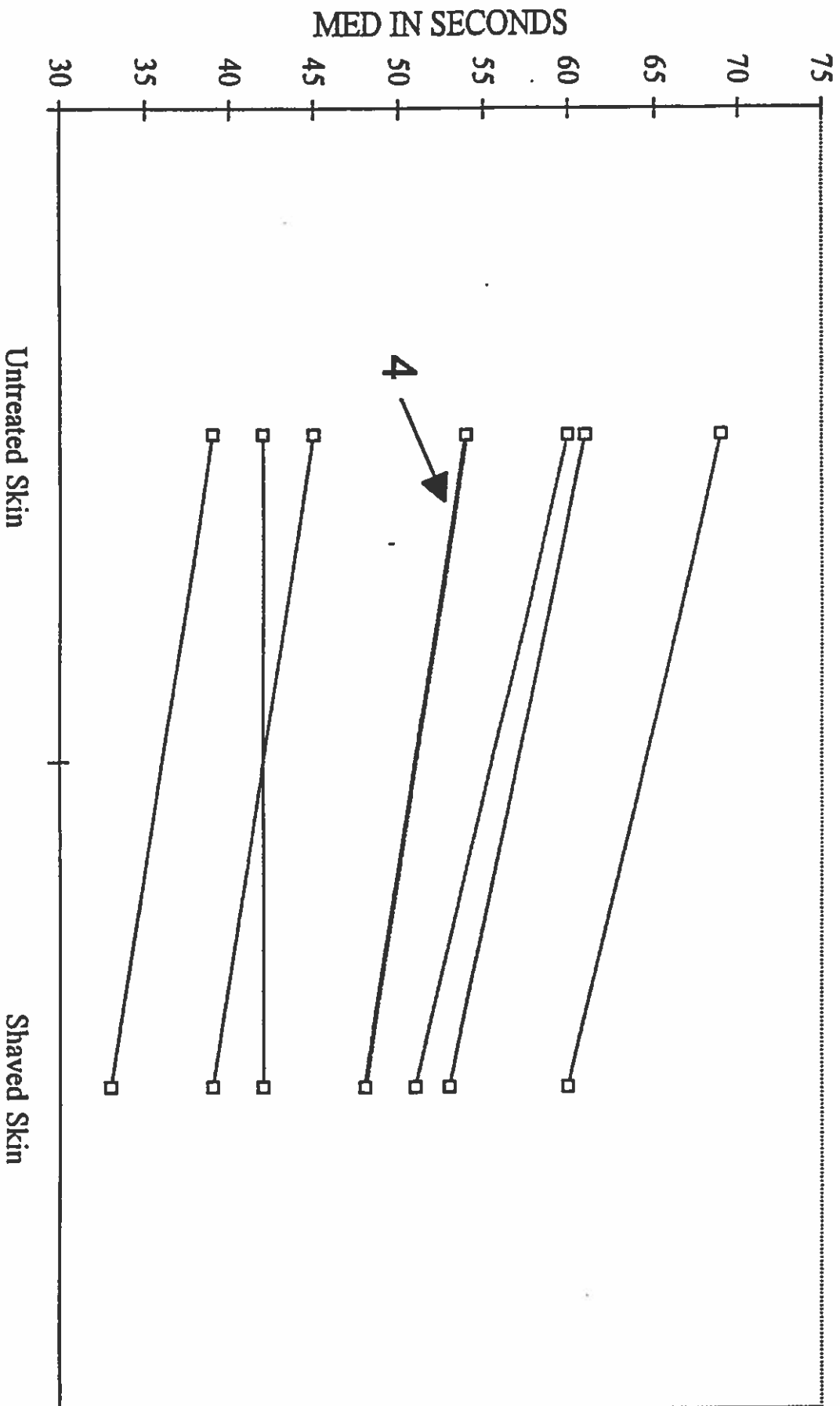
EFFECT OF MED OF REMOVAL OF PARTIALLY SHED CELLS BY MECHANICAL EXFOLIATION

- 10 SUBJECTS
- THREE TEST SITES ON LOWER BACK:
 - RUBBED FOR 15 SECONDS WITH COSMETIC EXFOLIATING SPONGE
 - SHAVED WITH LEADING SHAVING CREAM AND DISPOSABLE RAZOR
 - UNTREATED CONTROL
- THIRTY MINUTES AFTER TREATMENT, SITES IRRADIATED WITH GRADED DOSES OF UV
- MED DETERMINED 16 - 24 HOURS POST-IRRADIATION

(TKL RESEARCH, 1995, UNPUBLISHED DATA)

EFFECTS OF SEASONAL/CLIMATIC CHANGES ON MILD

MEDS WITH AND WITHOUT SHAVING



VARIATIONS IN MIED BETWEEN JANUARY & APRIL

- 16 SUBJECTS
- MIED MEASURED IN JANUARY &
APRIL

(KAIDBEY, 1995, UNPUBLISHED DATA)

ROUTINE SCREENING OF PANELISTS FOR MIED

- DATA FROM 1, 141 TESTS INVOLVING 292 SUBJECTS
- CONDUCTED FROM 2/79 TO 3/80
- STANDARD MED DETERMINATION

(SAYRE, ET. AL., 1981)

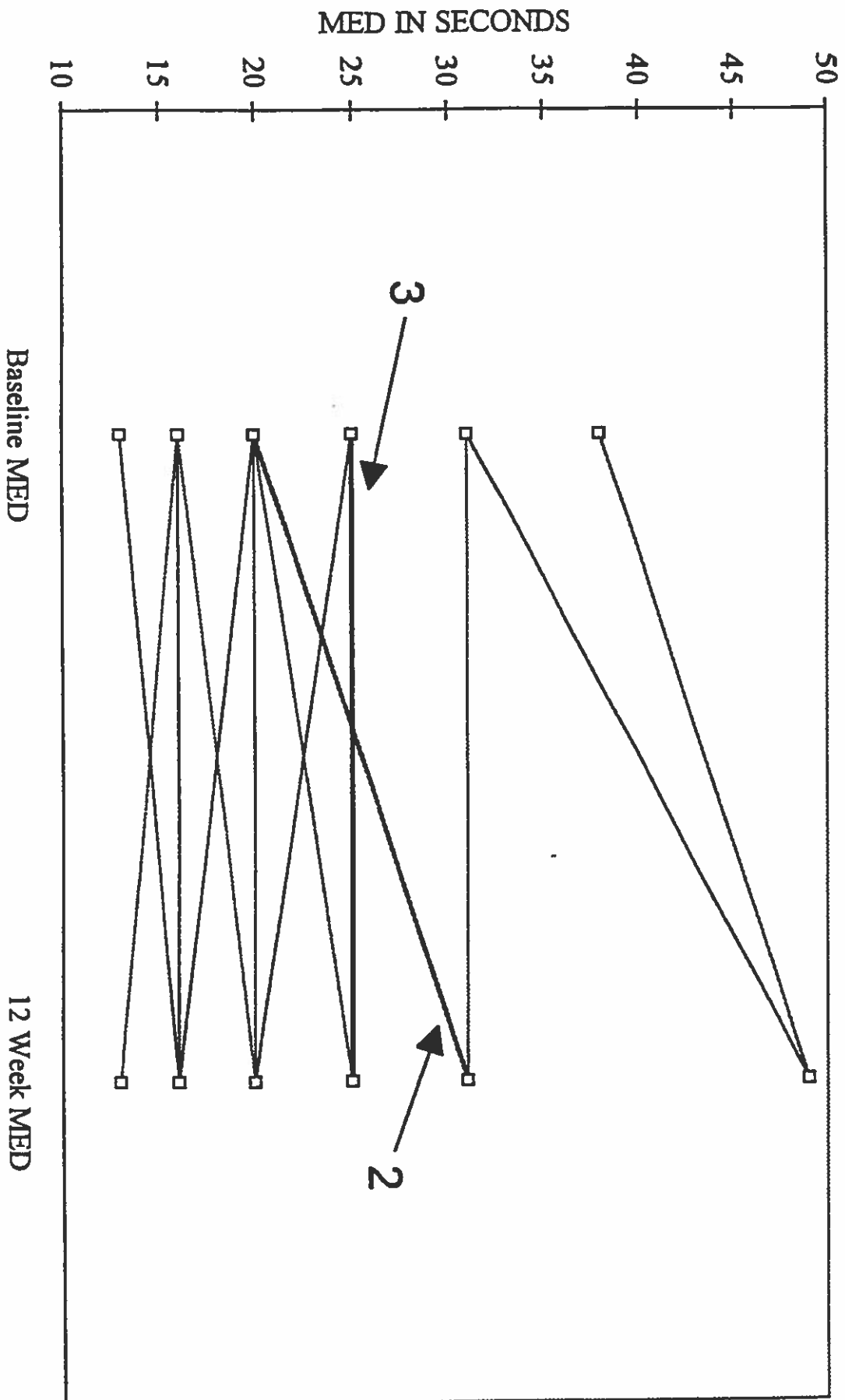
EFFECT OF REPEATED AHA APPLICATION ON

MED

- 19 SUBJECTS/LOWER BACK
- APPLICATION FOR 2X/DAY FOR 3 MONTHS OF 4% GLYCOLIC ACID (pH 3.8)
- ADJACENT UNTREATED SITE SERVED AS CONTROL
- MED'S MEASURED AT END OF TREATMENT PERIOD

(KAIDBEY, 1995, UNPUBLISHED DATA)

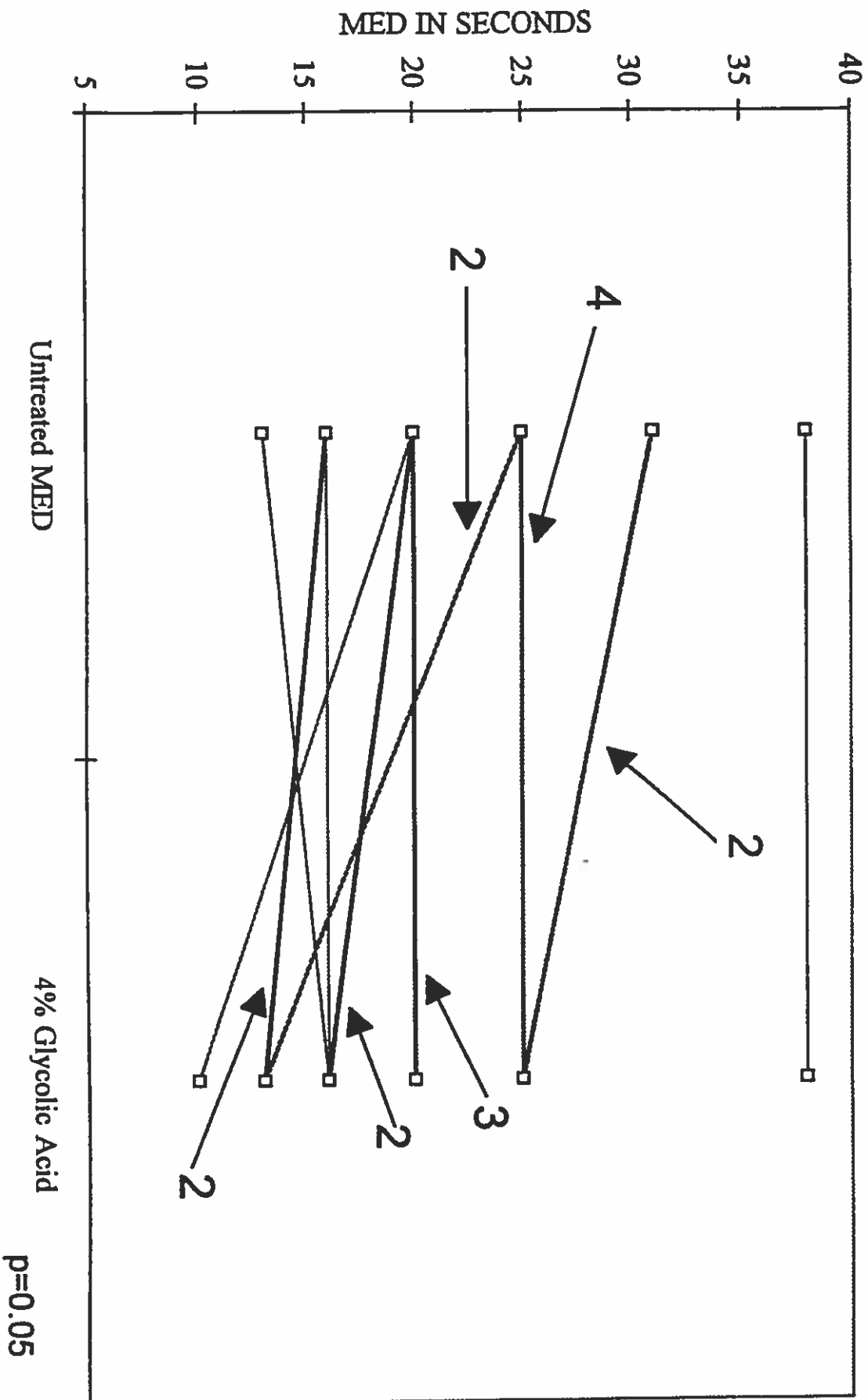
SEASONAL VARIATION: INITIAL MEDS AND MEDS 12 WEEKS LATER



SUMMARY - EFFECTS OF REPEATED APPLICATIONS OF AHA'S ON MED

<u>Parameter</u>	<u>% Change in MED</u>
Seasonal Variation (3 months)	14.1%
10% Mineral Oil Product	- 5.0%
10% Glycerin Product	- 7.6%
Shaving	- 11.6%
Exfoliating Sponge	- 11.6%
4% Glycolic Acid (3 months)	- 13.2%

MEDS UNTREATED AND SKIN TREATED WITH 4% GLYCOLIC ACID FOR 12 WEEKS



OVERALL SUMMARY

- COSMETIC LEVELS OF AHA'S ARE SAFE FOR USE
- AHA'S DO NOT COMPROMISE STRATUM CORNEUM BARRIER FUNCTION

FIFTY-EIGHTH MEETING

OF THE

EXPERT PANEL

March 4-5, 1996

LOEWS L'ENFANT PLAZA HOTEL

Washington, D.C.

Expert Panel Members

Wilma F. Bergfeld, M.D., Chairman

Donald V. Belsito, M.D.

William W. Carlton, D.V.M., Ph.D.

Curtis D. Klaassen, Ph.D.

Arnold L. Schroeter, M.D.

Ronald C. Shank, Ph.D.

Thomas J. Slaga, Ph.D.

CIR Staff

F. Alan Andersen, Ph.D.

Director/Scientific Coordinator

Liaison Representatives

Consumer

Mary Ellen Fise, Esq.

Industry

Gerald N. McEwen, Jr., Ph.D.

FDA Contact Person

John Bailey, Ph.D.

Adopted _____
(Date)

Wilma F. Bergfeld, M.D.

Others Present At Meeting

Kim Boozer	Unilever Research
Susan Carpenter	CIR
Jay R. Dickerson	Herald Pharmacal/Allergan, Inc.
William Dressler	Clairol
Paul Dykstra	American Beauty Association
H. J. Eiermann	
Monice Fiume	CIR
L. Gans	Medicis
Steve Gettings	CTFA
Donald Havery	FDA
Takeshi Hirose	Ajinomoto USA
Akiko Jacobson	Shiseido
Rebecca Johnson	CIR
Tony Johnson	Chesebrough-Pond's USA
Wilbur Johnson	CIR
Matthew Jonasse	Bausch and Lomb
Kays Kaidbey	Ivy Labs
Mark Lees	American Beauty Association
Ken Margnos	Estee Lauder
Kathy Merrell	Allure
Jill Merrill	Gillette

cosmetic products. However, subsequent to the issuance of this conclusion, new data were received and the Panel voted unanimously in favor of issuing a Tentative Report with a new conclusion at the August 1995 Panel meeting. At today's meeting, this Tentative conclusion was approved as a Final conclusion.

ADMINISTRATIVE DISCUSSION

AMMONIUM, SODIUM, AND POTASSIUM PERSULFATE

The Panel voted in favor of issuing a Final Report, with an insufficient data conclusion, on the Persulfates at the December 1995 Panel meeting. It was determined that the following data are needed in order to complete the safety assessment of these ingredients: (1) Human delayed-type hypersensitivity data, i.e. allergic contact dermatitis, at use concentrations and conditions and (2) Human immediate contact urticaria reactions at use concentration and conditions. However, because an offer by industry to develop and provide these data was accidentally overlooked at this meeting, the decision not to issue the Final Report was subsequently made by Dr. Andersen and Dr. Bergfeld.

At the present meeting, based on the commitment to provide data, the Panel voted unanimously in favor of rescinding its previous decision and tabling the report on Persulfates pending data.

SPECIAL PRESENTATIONS

SKIN PENETRATION STUDIES USING CADAVEROUS SKIN

Industry presentations on the use of *in vitro* skin penetration studies were made by Dr. Bill Dressler, with Clairol, Inc. and Dr. Ken Walters, with the University of Wales at Cardiff. The following conclusions were drawn: Provided that the experimentation is performed using suitably designed protocols and the *in vivo* in use conditions are followed as closely as possible, viable and realistic data for risk assessment can be obtained using human skin *in vitro*. Concerning the percutaneous absorption of hair dye materials, the human data are most relevant [e.g. For three hair dyes, the values for absorption through guinea pig skin seemed to underestimate human dermal absorption by a factor of 2].

At the conclusion of the industry presentations, Dr. Robert Bronaugh stated that, for regulatory purposes, human data are the most accurate. In other words, there is no good animal model for human skin.

ALPHA HYDROXY ACIDS

Dr. John Bailey presented FDA's position on the Alpha Hydroxy Acids. He discussed portions of the FDA report on these ingredients that was prepared under contract by KRA Corporation as well as adverse reactions data and chemical analysis data on AHA products. The following remarks were made at the conclusion of this presentation: The

widespread use of chemical exfoliants is really a new phenomenon in the cosmetics industry. While there clearly is insufficient data in some areas relative to the review of AHAs, there is adequate data on which to draw some conclusion about the safety of AHAs.

Regarding FDA's ongoing testing program on AHAs, Dr. Bailey said the following: (1) Skin penetration enhancement studies will be conducted. (2) Dr. Bronaugh recently completed a study on two different vehicles that were tested with the same level of AHA - This research is based on the assumption that different surfactants may have different effects on skin penetration. All studies will be made available to CIR upon completion.

Concerning the proposed skin penetration enhancement study, Dr. Havery said that excised skin from guinea pigs dosed with a 10% AHA emulsion will be used. Using the epithelial cells *in vitro*, the penetration of hydroquinone will be compared with that of a polar compound and a fragrance compound such as xylol (lipophilic chemical).

With respect to the testing of AHAs using different vehicles, Dr. Bronaugh said that the results indicate that different surfactants can cause different effects on the skin penetration of Glycolic Acid.

Following Dr. Bailey's presentation, Dr. McEwen stated that industry has proposed a human study to evaluate the effects of AHA products on the skin, to determine whether or not there is a significant alteration of the potential for photodamage. The endpoint will be the production of sunburn cells.

Presentations by representatives of the American Beauty Association addressed the following three areas of concern: (1) Manufacturing issues, which involve the concentration and pH level of AHAs, (2) The distribution channel - how AHA products are distributed to professional estheticians and cosmetologists as well as their availability to consumers, and (3) Professional use, which deals with the training and background of professional estheticians and cosmetologists.

REPORTS ADVANCING TO THE NEXT LEVEL

GLYCOLIC AND LACTIC ACID, THEIR COMMON SALTS AND SIMPLE ESTERS

At the Panel meeting, Dr. Andersen received input from industry and FDA indicating that the proposed studies mentioned in the preceding section should be completed prior to the December 16-17, 1996 Panel meeting. Therefore, this meeting is being targeted for issuance of a Tentative Report on AHAs. Dr. Andersen reminded the audience that the Panel needs to receive the completed studies one month in advance of the Panel meeting.

molecules during the percutaneous penetration process in viable epidermis. Dr. Bronaugh said that it is legitimately wise to use cadaver skin because it does have a more accurate barrier.

Dr. Klaassen asked why human skin is so different from that of other species.

Dr. Bronaugh said that this is due to the lipid content of human skin. Additionally, human stratum corneum has more layers. Another difference relates to hair follicles. Animal skin is very hairy in comparison with human skin

Dr. Bronaugh said that FDA has conducted studies using approximately ten compounds, in which viable versus nonviable skin was compared. For a chemical such as benzocaine, it was found that if one applies radioactive benzocaine to the skin, approximately 80% of the amount that is absorbed is acetylated. Acetyl transferase is a very active enzyme in the skin. However, if one looks at viable versus nonviable skin, the amount of radioactivity that passes through is approximately the same. This has been observed for the majority of the compounds that FDA has studied. Dr. Bronaugh said that, clearly, animal skin overestimates human percutaneous absorption. From a regulatory standpoint, this would probably prove to be unsatisfactory.

REPORTS ADVANCING TO THE NEXT LEVEL

Glycolic and Lactic Acid, their common salts and simple esters

Dr. Bergfeld announced that Dr. John Bailey would be presenting FDA's position on the Alpha Hydroxy Acids. It was noted that Dr. Bailey would be using several cosmetic products containing Alpha Hydroxy Acids as display items. Dr. Bailey's

comments are summarized as follows:

Dr. Bailey: FDA has completed a report on the Alpha Hydroxy Acids (AHAs), and this report has been circulated to the CIR Expert Panel and others. This review was prepared under contract by KRA Corporation. The actual review was prepared by Dr. Randall Wickett at the University of Cincinnati School of Pharmacy. Dr. Wickett is the Associate Professor of Pharmaceutics and Cosmetic Science, where he is responsible for the graduate program at the University of Cincinnati, and has conducted extensive research on skin pharmaceutics and cosmetic science. The report that was generated was not prepared specifically for the CIR Expert Panel. This effort was part of an in-house ongoing review of AHAs.

One of the documents that was provided to the Panel consists of adverse reactions information and chemical analysis data. It was FDA's intention to provide "real life" information concerning adverse reactions that had been reported for products. There has not been an overwhelming number of adverse reports (97 were confirmed). FDA has been advised that one of the 97 is on a product that does not contain AHAs. The number of adverse reactions reports (97) is a small number. However, it has been FDA's experience that consumers are not aware of how to report adverse reactions or to whom they should be reported. Based on certain adverse reactions data that have been received by FDA, the agency has determined that the company will receive 50 to 100 adverse reactions reports for each one that is received by FDA. Furthermore, consumers are told that products containing AHAs will sting.

A few of the observations are for products that are used in beauty salons. As one

would expect, most of the reactions are irritation reactions. It is interesting to note that there is a report relating to some sensitivity in the area where the AHA was applied to an individual. The adverse reactions data largely represent acute reactions, individuals who experience immediate reactions to the product. These data do not provide any information that addresses concerns relative to long-term use.

The analytical data are for products that FDA has surveyed over the last few years, and these data have been broken down into two categories, professional use and marketed. To illustrate some of the data that have been collected, data on twelve products that were purchased within the last month was distributed [Attachment B]. It was noted that two of the products have relatively high concentrations of AHAs at a very low pH. One product contains 8.8% Lactic Acid (pH 2.68) and the other contains 13.6% Glycolic Acid (pH 3.26). Additionally, there is a product on the market that is purported to contain 50% Glycolic Acid. FDA has been unable to obtain this product; however, product samples (three vials) were obtained. The pHs for the three vials were 3.56, 3.55, and 3.53, respectively.

Looking at the data (published and unpublished) included in the full report on AHAs submitted by FDA, it was somewhat frustrating to note that pH values are absent from the studies. Clearly, pH is important in the safety assessment of AHAs, because there seems to be a very close association between pH and effect.

Looking at the AHAs as moisturizers, clearly, this effect is evident and pH does not seem to be important in this process. The salts of AHAs are known to be hygroscopic, and this may explain the moisturizing effects.

Clearly, the AHAs have medicinal effects. AHAs are claimed to be effective against acne, and regular AHA use is supposed to improve the acne condition. However, there aren't any good, solid studies that support this.

While there is some evidence that AHAs can reduce the appearance of fine lines and wrinkles, this is actually a case where there are no well-controlled studies that address this issue and define the conditions under which fine lines and wrinkles may be treated.

In spite of all of the work that has been done and the volumes of data that have been provided, there is really not much information on the mechanism of action, the way AHAs work. *In vitro* data on keratinocytes indicate that there may be, in effect, direct stimulation of cell division in one study. In another study, the results are contradictory; there was no observed effect on cell proliferation.

AHA treatments have been shown to affect skin histology and have been related to wounding effects. This is very significant because AHAs are, under some conditions, chemical irritants, and, as such, one would expect them to have effects on irritation. AHAs have also been shown to reduce the thickness of stratum corneum under some conditions, and could affect barrier properties.

Regarding skin penetration, conflicting data exist. FDA has attempted to provide more up-to-date results from its laboratories to show that there is significant penetration. The studies that are included in the report on the Alpha Hydroxy Acids provided by FDA use water mostly as the vehicle, and this will have an effect on impeding skin penetration. Until this work has been completed, there is no information

in the literature that constitutes a well-documented case. There is also some data in the FDA report that suggests that AHAs may have significant effects on the penetration of other compounds.

Regarding human studies, there are clearly pH and concentration effects. Cumulative irritation testing showed that 32% Glycolic Acid (pH 4.4) was less irritating than 8% Glycolic Acid (pH 3.25). There does not seem to be too much evidence that AHAs are photoallergenic or phototoxic. However, they could have an effect by altering the skin penetration and absorption of other compounds; they could have an indirect effect in this regard.

The most significant information from the FDA review of AHAs relates to increased sun sensitivity in some individuals. Two studies tend to contradict one another. Perricone and DiNardo reported a protective effect. However, it is important to review this study in great detail; only five subjects were studied and there is a significant question regarding skin type. The subjects may have had disease conditions to begin with and the AHA treatments may return these to normal (repair of impaired skin). This could account for the observed protective effect, the increase in SPF values of the skin. The more relevant studies were those that were presented at the last Panel meeting, where 4% Glycolic Acid was used for twelve weeks and a 15% reduction in the MED was reported. This was possibly related to physical effects in the skin (transmission and skin smoothness). However, it is extremely important to note that of the 19 that were in the test, three experienced a significant reduction (50%) of the MED. These results require further study and clarification.

In looking at the possible physical effects accounting for the reduction in MED, FDA performed a statistical analysis of skin smoothness and the moisture content of the skin. A significant correlation between the two was not found. Even with other types of skin smoothing (using sponge or shaving), the greatest reduction in MED was 15%. There was no evidence that as low as 50% reduction was observed in some individuals. It is important to keep in mind that this study was conducted with fairly low levels of AHAs (4% Glycolic Acid). Clearly, if there is a significant lowering of MED by the user, then this has fairly serious consequences. It is well-known that long-term sun exposure can accelerate the photoaging process. It can even place the individual at increased risk for skin cancer. The use of sunscreens by individuals already using AHAs becomes an extremely critical situation. The public is informed through marketing that individuals should begin using AHA products at a young age and use them continually (once or twice per day). Therefore, long-term considerations are important.

Another key safety question has to do with irritation. The FDA report examines repeated insult patch tests (RIPT) versus the cumulative irritation tests. It was determined that the RIPT did not reveal any problems. However, the cumulative irritation test resulted in significant irritation that was caused by some products. It is important to look even further at the way in which the human patch test is conducted, because one has considerations of 14 days versus 21 days. A report concerning new data was forwarded to FDA by CIR. These data (14-day study) show a strong correlation between irritation and pH.

Regarding the long-term adverse effects, the longest-duration study in the data that FDA has is six months, and the products were tested at fairly low concentrations (at relatively high pH). Long-term safety remains a significant question. Products containing AHAs were purchased for display at this Panel meeting because FDA is seeing higher concentration and lower pH products on the market, and this will probably be a trend. There are effects on skin structure and physiology, and few studies suggest that there may be a wounding process that is taking place. Therefore, more data may be needed in this area.

FDA has additional material that can be provided relative to the vehicle used. Dr. Bronaugh recently completed a study on two different vehicles that were tested with the same level of AHA. The purpose of this study was that of accounting for the difference in vehicle. It was also thought that, perhaps, ionic surfactants may cause the skin to be more susceptible (i.e. may have an irritation effect). These data will be made available to CIR also.

In closing, Dr. Bailey suggested that the widespread use of chemical exfoliants is really a new phenomenon in the cosmetics industry. While there clearly is insufficient data in some areas relative to the review of AHAs, there is adequate data on which to draw some conclusion about the safety of AHAs.

Dr. Bailey announced that Donald Havery, from FDA's analytical laboratory, was present at the meeting and would answer any questions regarding the analytical data that were presented.

Dr. Bergfeld asked if what is being referred to as a wounding effect of AHAs has

been compared with studies on topical tretinoin. She noted that the effects of both treatments are similar and that the effect of topical tretinoin was not considered wounding by dermatologists in the published literature.

Dr. Bailey said that, with respect to the studies presented today, FDA has not made such comparisons.

Dr. Bergfeld and the Panel expressed concern over the possible enhanced skin penetration of other ingredients due to the presence of AHAs. She said that it was her understanding that FDA would be studying this, and wanted to know if this study is the same as the vehicle study that was recently completed.

Dr. Bailey said that additional studies will be conducted in which animals will be treated with AHAs and skin penetration measurements will be taken before and after treatment.

Dr. Belsito wanted to know the specific chemicals that would be applied in skin penetration enhancement studies.

Dr. Havery, investigator with FDA analytical laboratory, said that guinea pigs will be dosed with a 10% AHA emulsion. This will be done for at least 30 days or until an increase in turnover of the stratum corneum is observed. Following a significant effect of this 10% solution, the skin will be removed. Using the epithelial cells *in vitro*, the penetration of hydroquinone will be compared with that of a polar compound and, probably, a fragrance compound such as xylol (a lipophilic chemical).

Concerning FDA's consumer adverse reports, Dr. Belsito wanted to know if there had been any attempts on the part of FDA to verify that the adverse reports were in any

way related to the product. He also wanted to know whether the report was simply a consumer statement.

Dr. Bailey said that, frequently, the adverse report is a consumer statement. In some cases, there may be follow-up (particularly in FDA field offices) to the direct phone calls. Some of the reports are received as direct phone calls, and there is an opportunity to interview the consumer.

Dr. Bergfeld wanted to know if a summary statement would be made by FDA to the effect that FDA's major concern may be increased sun sensitivity and, possibly, increased irritation.

Dr. Bailey indicated that these are the two major concerns.

Dr. Bergfeld said that the long-term effects of the increased sun sensitivity and irritation is increased susceptibility to skin damage (cancer) over time.

Dr. Bailey agreed.

With respect to the skin penetration enhancement studies on AHAs to be performed by FDA, Dr. Slaga said that he hoped that the chemicals selected would be representative of a range encompassing highly water soluble to highly lipid soluble. In so doing, one would have a good idea as to whether AHAs are affecting any of a broad class of compounds.

Dr. Bailey asked Dr. Bronaugh to address the Panel with respect to any vehicle effects that have been observed in the testing of AHAs.

Dr. Bronaugh: In looking at the data (in some cases), it was found that for formulations with identical Glycolic Acid concentrations and identical pH values, there

are marked differences with respect to the irritation that is induced. One reason for this is probably the vehicle formulations, and, possibly, the surfactants. Surfactants are known to be chemicals that can alter penetration.

In an *in vitro* skin penetration study in which two formulations (pH 3 for both) containing 5% Glycolic Acid were compared; viable human skin was used. The percentage of applied Formulation A (contains two nonionic surfactants) that was absorbed was approximately 25% over a 24 h period. Some of the formulation was detected in the receptor fluid and substantial amounts were found in the various layers of the skin. The percentage of applied Formulation B (contains two surfactants, one of which is different and stronger than either of the two in Formulation A) that was absorbed was approximately 35%. These results illustrate the fact that different surfactants can cause different effects on skin penetration. **[The results of this comparison and other results generated by FDA are included in Attachment C]**

Dr. McEwen thanked Dr. Bailey and FDA for participating today and taking an active role in the review of AHAs. Concerning the adverse reactions data that were presented, he noted that there is not a single product on the market for which no adverse reactions have been reported. He also said that the cosmetics industry had provided the Panel with information indicating how the adverse reactions to AHA products could be placed in perspective. In this effort, companies that produce AHA products were asked to provide information on their rate of adverse reactions to these products compared to that of traditional moisturizers. This means that each company involved was comparing the rate of reaction for AHA products with that of traditional

moisturizers within that company. The results of such comparisons did not reveal much variation between the two types of products. The difference was slight, on the order of 1 reaction per million for traditional moisturizers and 1.5 per million for AHA products. Dr. McEwen said that this is not an unexpected result because AHA products are getting publicity. Thus, it is expected that more adverse reactions would be associated with the AHA products.

Dr. McEwen noted that Dr. Bailey had also mentioned claims. According to Dr. McEwen, claims do not constitute a concern that should be addressed by the Panel, unless the claims lead to a question regarding safety.

Dr. McEwen stated that industry is in favor of FDA's efforts with respect to studying the skin penetration of AHAs.

On the subject of increased sun sensitivity, Dr. McEwen recalled Dr. Bailey's comments to the effect that one study indicates that AHA's caused an increase in the MED (i.e., increase in sun protection). Dr. McEwen said that this study is not to be interpreted as meaning that AHAs should be used in lieu of sunscreens. Furthermore, the increase in MED was very small. The study was provided by industry to illustrate the existence of a marketable formulation with no effect. Dr. McEwen also recalled Dr. Bailey's comments relative to the 50% change in the MED that was noted in another study. According to Dr. McEwen, this change is equivalent to an SPF of 2. He said that a 50% decrease in three of 19 subjects in the test is not a biologically significant factor.

Dr. McEwen said that it is important to keep in mind that there is a question

concerning sun sensitivity. He noted that industry has been in the process of developing a test to address this question.

Relative to Dr. Bailey's comments on the cumulative irritation that was induced by AHAs and the absence of reactions in repeated insult patch tests (RIPT), Dr. McEwen said that, obviously, more irritation would result from patch testing every day (cumulative irritation test) when compared to patch testing three days per week (RIPT). The purpose of the cumulative irritation test is to overestimate skin irritation.

Dr. McEwen said that industry has proposed a study to evaluate the effects of AHA products on the skin, to determine whether or not there is a significant alteration of the potential for photodamage. The protocol is in draft form. Dr. McEwen informed the Panel that the author of the protocol and a consultant to industry were present at the meeting to address any questions. The principal investigator is Dr. Kays Kaidbey, of Ivy Laboratories, and the proposal is to study the effects of AHA treatment and compare those to what would be more normal under conditions that would also be expected to exfoliate the skin. More normal is intended to mean that which most individuals face all of the time. An acute study will be conducted to compare a number of the conventional activities and will involve the following: wet shaving prior to UV irradiation, a conventional moisturizer like mineral oil or glycerol, washing with soap, and an untreated control. The daily routine that would be tested in the long-term study would be daily application of two AHA products (one at 1 dose, and 1 at a higher dose). This would provide information as to any differential that may exist and what it means in terms of concentration. The pH used would probably be one that would be considered

low enough that it would encompass other pHs above it. The results of the long-term study would be compared with an exfoliation procedure using a buff puff. The procedure for the long-term study will be carried out over a period of 12 weeks, and 15 human subjects will be tested per group. The duration of the study (12 weeks) is believed to be a suitable multiple of the life of the organ system (skin) that is being studied.

Dr. Bergfeld wanted to know which endpoints would be evaluated in this study.

Dr. McEwen said that the endpoint will be the evaluation of sunburn cells, with each subject serving as his/her own control. These were chosen for the human because, compared to any other method, there is much more information on various effects correlating to sunburn cell evaluation. The sunburn cell has been recognized as a good surrogate for photodamage, for thymine dimer build-up without repair.

Given the duration of the long-term study (12 weeks), Dr. Bergfeld reminded Dr. McEwen that the Panel anticipates that its review of AHAs will be completed this year.

Dr. McEwen said that industry would prefer some indication from the Panel as to whether or not the proposed study is acceptable. He said that given the process that is generally associated with conducting a study, the time period from initiation to availability of the report will likely be seven months.

Dr. Andersen wanted to know how many MEDs would be delivered.

Dr. McEwen said that a UVB source (fluorescent bank) has been proposed. He asked Dr. Kaidbey, principal investigator, to review the exposure regimen for the Panel.

Dr. Kaidbey said that the plan is to use a bank of exposing bulbs only because, in

his opinion, there would be more uniformity at skin level with the bank than would be obtained with a solar stimulator. The variability within the radius inside of the solar stimulator can be up to 60 or 80%. So, this would result in a very big difference in terms of the production of sunburn cells. The UVB fluorescent bank has often been used (uniformity within $\pm 20\%$ is attainable), and this covers the action spectrum for sunburn cell production.

Dr. Belsito asked if the light source will be filtered to insure that the light is strictly in the UVB range.

Dr. Kaidbey said that a celluloseacetate foam can be used to eliminate the UVC component, such that there is only UVB. He also said that he is planning to use a single MED dose. This should produce a few sunburn cells.

Dr. Bergfeld wanted to know if this method has been validated.

Dr. Kaidbey said that there is quite a bit of literature on sunburn cell production. Sunburn cells are considered to be markers of DNA damage by UV light. In his opinion, this is a more specific endpoint than using MED or erythema because inflammation is a nonspecific endpoint.

Dr. Belsito asked Dr. Kaidbey if he has the capabilities of measuring reflectance from the skin.

Dr. Kaidbey said that he does not have the capabilities for measuring reflectance. He said that he is looking for direct UV damage, and this should be addressed by a spectrum because, in the acute experiment, the optics of the skin are being manipulated by applying a moisturizer or formulation. UV penetration is being

enhanced.

Dr. McEwen said that a comparative efficacy study is not being done. The proposed study concerns the use of a model product and the determination of whether or not AHAs can be safely used.

Dr. Belsito said that the controls are being done to put into perspective that even if it turns out that AHAs enhance UVB penetration, one sees the same type of enhancement when one shaves or uses a buff puff. Therefore, the ideal control will be to match reflectance. However, Dr. Belsito acknowledged that the fact that Dr. Kaidbey does not have the capability for measuring reflectance is really not a major concern.

Dr. Belsito also suggested that the test population in the proposed study be skewed to skin types 1 and 2 and away from skin types 4 and higher, such that the data can be easily evaluated. Furthermore, he said that because the Panel will be concerned about acute and chronic effects of AHAs on the skin, Dr. Kaidbey may want to sample at various times during the 12 weeks of treatment. This should be done because there will be individuals who intermittently use the product once per week as well as those who use the product twice a day, and the effects may be quite different with acute use in UVB versus chronic use (where the skin has become adapted to the product). Dr. Belsito suggested that Dr. Kaidbey consider irradiating at two days into treatment, a week into treatment etc., rather than just treating for 12 weeks and doing one irradiation and one evaluation.

Dr. McEwen said that he appreciated Dr. Belsito's recommendation of multiple sampling, given the problem of biopsy.

Finally, Dr. Belsito said that the Panel frequently sets concentration limits for cosmetic ingredients. With this in mind, he suggested that concentration and pH ranges in the proposed test be stretched to the limit.

Dr. Slaga recalled that it had been said that there is a good correlation between the number of sunburn cells and the level of damage. He wanted to know if damage is expressed in terms of photoproducts.

Dr. Kaidbey said that one can show that sunscreens, for example, prevent the formation of photoproducts.

Dr. Shank asked if the proposed study is a dose-response study.

Dr. McEwen said that two concentrations will be used and that he was not certain as to whether more than one pH will be used. One MED of light will also be used. Each subject in the study is his or her own control. One is determining the effect of a dose of light on an area of the back that has been treated with AHAs versus an untreated area on the back. The concept is that as long as that dose of light produces an effect, then it is the level of the effect that is comparable. There is no reason to expect that changing the dose of AHA is going to cause a change in the relative amount, just in terms of the absolute amount.

Dr. Bergfeld said that the back heals very poorly and always has hypertrophic scarring, and recommended that a forearm volar surface would be a better choice for a test site.

Dr. Belsito said that the problem with using the forearm is that it is an area of potential sun damage, unrelated to the study. He added that for the purpose of getting

sunburn cells, suction blisters could be done. For a certain skin type, the suction blisters will heal without any significant scarring.

In response to Dr. Carlton's question, Dr. McEwen anticipated that 15 subjects would be used in the proposed study.

Dr. Schroeter said that the inner aspect of the arm, which is well-protected and heals well, is also a potential test site. Any scarring at this site would not be that perceivable because of the location. He also asked why UVB light only had been selected for the study.

Dr. McEwen said that the endpoint that is being looked at is sunburn cells.

Dr. Schroeter said that there are changes in the dermis that also are of concern. Therefore, how much UVA as well as UVB is allowed to be penetrated or increased by the AHAs is of concern.

Dr. McEwen said that the question is will the experiment serve as a reasonable surrogate for sun damage, and can it be done in a reasonable amount of time to address the question of safety. He then said that it is anticipated that once the proposed experiment has been completed, there will be a very good approximation of any changes in UVA. If there is a significant diminution of the barrier, then this will be seen in the sunburn cells. There is not going to be zero change in the epidermis and, yet, a significant risk from UVA exposure.

Dr. Carlton asked if sunburn cells will be used in the acute study.

Dr. McEwen said that in the acute study, the subjects will shave and then the site will be irradiated one-half hour later. Sunburn cells will be used as markers. The

question here is what effect does skin that has been shaved have on the sunburn cells, versus skin that has not been shaved.

Dr. Slaga said that since histology is being done, the sunburn cells have a reasonable correlation, but there are other things that can be examined. There are even antibodies that can be examined histoimmunologically to determine if there is photoproduct damage.

Dr. McEwen said that Dr. Slaga's suggestion had already been considered. However, it was determined that the use of sunburn cells would adequately address the question of increased photodamage, because there is so much data in the literature that correlates with it.

Dr. Bergfeld announced that Paul Dykstra, Executive Director of the American Beauty Association and others had asked to address the Panel relative to the Alpha Hydroxy Acids. The three areas of focus in today's presentation are as follows: (1) Manufacturing issues, which will involve the concentration and pH level, (2) The distribution channel - how these products are distributed to professional estheticians and cosmetologists as well as their availability to consumers, and (3) Professional use, which deals with the training and background of professional estheticians and cosmetologists. Some of the scientific information that was discovered over the past several weeks will precede these three topics. Dr. Jay Dickerson, also a member of the American Beauty Association, will be the first presenter:

Dr. Dickerson: Results from a study designed to address safety concerns relative to the use of rinse-off products (salon use only) were distributed. [See

Attachment D] Often, some of the beauty treatments are within the level and pH studied to be cosmetic in nature. The study, conducted by Dr. Gary Grove, is two-fold; transepidermal water loss barrier function measurements were taken and barrier function was also addressed in terms of histology using twelve subjects. In the study, 30% Glycolic Acid (at pHs of 2.5, 3.0, and 3.5) was applied to the right and left upper thighs of female subjects. Each product was applied randomly to eight sites on each subject. Exaggerated conditions were used (20 min application period; three applications in six days); applications were made on days 0, 3, and 6. The normal recommended application time is 10 min and there are normally one to two applications per week. Transepidermal water loss was measured at 15 min and 3 h after each application, and on day 13 (7 days after the final application). Superficial shave biopsies were taken at days 0, 6, and 15 [Histological results are not available, but should be available within the next few weeks.]. The results indicated a minimal effect on transepidermal water loss after the first chemical wash. After the second and third chemical washes (at 15 min reading point) there was a dose-dependent response, whereby the lower pH gave the higher values of water loss. However, at 3 h, transepidermal water loss was stabilized down to its 10 to 20% increase; there was no specific pH pattern. One week after the final application, the barrier function had actually slightly increased, compared to the initial reading; the higher pH products gave better results. The relative transepidermal water loss readings for this experiment varied from approximately 4.2 to 6.6 g/m²/h, and a recent article in the Journal of the Society of Cosmetic Chemists (1995) indicates that the exaggerated use of soaps and

detergents gave readings in the value range of 5.5 to 14.1.

Paul Premo (with Murad Skin Research): I would like to submit to the Panel some suggested guidelines that have been assembled, on behalf of the beauty industry, for the training protocol of cosmetologists and estheticians regarding AHAs **[Attachment 5]**. The Esthetic Manufacturers and Distributors Alliance has developed professional guidelines for AHA cosmetic chemicals exfoliation procedures for cosmetologists and/or estheticians. These guidelines are intended to insure procedural consistency in the use of professional rinse-off pulse applications of AHAs, namely Glycolic and Lactic Acids, for which product safety has been substantiated. These guidelines exclude all other chemical exfoliation peeling procedures and substances including, but not limited to, trichloroacetic acid, carbolic acid, phenol, resorcinol, or combinations thereof.

Cosmetic chemical exfoliation procedures utilizing AHAs facilitate stratum corneum desquamation, improving the esthetic appearance and quality of skin. These procedures are not intended to elicit viable epidermal and/or dermal wounding injury or destruction, and, therefore, are different from chemical peeling procedures administered by physicians. The guidelines cover professional use only AHA products, with a concentration not exceeding 30% (pH 3), through applications, precautions, and post-procedural care. Recommended professional qualifications (i.e. These products* and procedures are not intended for consumer resale or use) are also covered. Manufacturer and structural requirements include the curriculum that should be covered and the training (estimated to be 4 to 5 h) of these procedures. We go through

the recommended application procedure, and most importantly, a predisposition patch testing 24 h prior to these procedures. We also recommend a client consultation. Suggested questions for the client consultation include the following: the prehistory of sun exposure and tanning bed use; the history of cosmetic-related irritant or allergic contact dermatitis currently under a physician's supervision; history of medication, including tretinoin and isotretinoin, predisposition to HSV (herpes simplex virus); previous facial plastic reconstructive surgery; previous chemical peel procedures - types and results; previous cosmetic chemical exfoliating procedures - types and results; and current skin care regimen. We also recommend that these procedures are not recommended when a client is under the supervision of a physician for skin-related disorders, and a physician's approval is recommended before administering these procedures.

We recommend a client skin evaluation and inspection prior to the administration of the treatment and a post-care procedure for the client, including the use of an SPF 15 UVA/UVB block. We also take note that a manufacturer's directions can vary. Therefore, one should always read and follow directions according to manufacturer's specifications.

Finally, we have the following disclaimer: Compliance with these guidelines does not guarantee the practitioner a successful procedure, and consideration should be given to each client and procedure as an individual case.

The suggested guidelines that have been assembled are recommended to all manufacturers, especially the members of The Esthetic Manufacturers and Distributors

Alliance (EMDA). We are getting wide acceptance of these guidelines and feel that when they are followed and there is consistency in the procedure, consumer safety is assured.

Paul Dykstra added that EMDA and the American Beauty Association have both been approached by the National Interstate Council of State Boards of Cosmetology, and their board of directors has been seeking specific information on standardization for esthetician and cosmetology licensing.

Dr. Mark Lees (member, EMDA board of directors): We have worked on clarifying some of our guidelines and we have several new things that have been added to the list. We have defined professional use products as AHA products developed and intended for application by a licensed esthetician or cosmetologist. As was indicated in our last protocol that was submitted, professional use products should not exceed a 30% concentration of AHAs, nor should the products have a pH below 3.0. Manufacturers are being asked not to use the word peel or peeling in describing the AHA salon use exfoliation products. It is our opinion that the word peel implies removal of live tissue and the word exfoliation implies the removal of dead surface skin cells.

Manufacturers should not sell AHA professional products to estheticians or cosmetologists who have not been properly trained in the use of AHA exfoliation products. Manufacturers and distributors should require that estheticians purchasing professional use AHA products have hands on instruction relative to use of the product.

Professional AHA products should not be sold to consumers. Manufacturers have

agreed to use the following warning statement under salon use AHA products:

Warning - This product is for professional use only by licensed estheticians or cosmetologists who have specialized skin care training in the use of AHA products, and is not intended for consumer resale or home use. Use of this product by untrained, unlicensed persons may result in skin irritation. A sunscreen with a minimum SPF of 15 should be used after the use of this product, and should be used routinely by individuals using AHA products. We are also requesting that all of our member companies provide ingredient labeling on their products and instructions for use designed for the licensed professional.

Dr. Bergfeld thanked the presenters for the information provided and indicated that much progress has been made since the last Panel meeting.

With reference to the guidelines discussed, Dr. Bergfeld noted that no exclusionary groups had been mentioned. She wanted to know whether there are any at risk or high risk groups.

Dr. Lees said that the following recommendation has been made: It is not recommended that cosmetic chemicals exfoliation procedures be administered to skin exhibiting open sores (apparent skin irritation, such as chemical burns, or sensitivity predetermined by a 24-hour predisposition test or case history). Photodocumentation is also recommended.

Dr. Bailey asked if there is any recommendation regarding the number of treatments a customer should have (e.g. maximum number within a certain period of time).

Dr. Lees said that most manufacturers recommended that AHA application procedures be performed on a given client not more than once per week over a period of six weeks, with not more than 10 min per application. There are also some recommendations of twice per week, depending on the condition of the skin.

Dr. Bailey asked how often might a client receive the regimen described in the preceding paragraph.

Dr. Lees said that if the assessment of the condition of the skin is good and the client is satisfied, a recommendation of twice per year may be made.

Realizing that the procedures outlined thus far are only recommendations, Dr. Bailey asked if there are any follow-up activities for determining what percentage of the salons are actually following the recommendations.

Dr. Lees said that the industry is hoping to set some precedents, such that the state boards of cosmetology will follow the guidelines that have been recommended. He stated that he is currently on the state AHA task force for the state board of cosmetology and barbering in California, along with physicians, helping to establish guidelines within the state of California for these cosmetic procedures. In so doing, it is anticipated that rules and regulations as to what cosmetologists and estheticians should and should not do will become official requirements. Dr. Lees said that the only question that needs to be answered relates to specific limitations on the concentration and pH of AHAs.

Dr. Belsito wanted to know approximately how many states would be interested in regulating AHA products, as their boards of cosmetology are set up at this point.

Dr. Lees said that a large number of sates would have this level of interest.

Dr. Bergfeld indicated that the next order of business is the Expert Panel's discussion of AHAs. She said that the Panel's discussion on Glycolic and Lactic acids, their salts and simple esters will not lead to any conclusion on the safety of these ingredients at this Panel meeting. Data that have been promised are forthcoming and new information that was made available at the present meeting needs to be interpreted and deliberated upon.

Dr. Belsito congratulated industry on its rapid response to the Panel's data requests. He then confirmed with the beauty industry representatives at the meeting that AHA salon products consist primarily of Glycolic Acid. With this in mind, Dr. Belsito noted that the Panel should not expect any data on rinse-off products that contain a relatively high concentration of Lactic Acid.

Dr. Belsito said that the Panel is still awaiting the following information: clarification of the Lactic Acid impurities data that was promised at the last Panel meeting, the DuPont clarification on the company's technical grade of Glycolic Acid, and clarification of the units for a formaldehyde impurity in Glycolic Acid that is mentioned in the current CIR Report on AHAs. In addition to these minor data needs, Dr. Belsito noted that the following major data needs were mentioned during today's discussion: (1) What is the effect of acute and chronic use of AHAs on the penetration of sunlight into the skin - [This will be answered by the studies that Dr. McEwen has suggested will be performed.] and (2) What is the effect of AHAs on the penetration of other chemicals into the skin - [This will be investigated by the studies that Dr.

Bronaugh and FDA will be doing.]

It was also noted by Dr. Belsito that the DiNardo studies have allowed the Panel to look at the issue of irritation in a concentration and pH-dependent way, such that if the other studies validate safety, the Panel can at least arrive at some conclusion as to where limits should be set, particularly relative to leave-on products. Dr. Belsito concluded that data on the effects of AHAs on light penetration and on the penetration of other chemicals through the skin are still needed.

Dr. Schroeter said that the Panel has an overwhelming amount of data and is still integrating these data and trying to determine how they should be relevant to safety. He concurred with Dr. Belsito's assessment of the Panel's data needs; however, he noted that two specific concerns were not mentioned. Dr. Schroeter recalled that the Panel is concerned about photocarcinogenicity (photoproducts, thymine dimers, and adducts produced upon application of AHAs).

Dr. Belsito wanted to know if Dr. Schroeter is requesting photocarcinogenicity data in addition to the sunburn cell data.

Dr. Schroeter noted that the photocarcinogenicity data had been requested originally.

Dr. Slaga said that if the Panel receives all of the data stating that the sunburn cells are going to be good indicators as a surrogate, the Panel can then make a final decision with respect to the need for photocarcinogenicity data.

Dr. Andersen said that there is current information on the correlation between DNA photoproduct damage and sunburn cells.

Dr. Slaga said that there are simple histoimmunological procedures for looking at photoproducts in the skin. With this in mind, a joint study incorporating this may be performed.

Dr. Bergfeld said that it is her understanding that, most likely, the skin samples in the proposed study will be saved under frozen conditions. She said that hematoxylin and eosin slides of skin samples can be made in order to identify sunburn cells, and frozen skin samples can be maintained for the photoactivated antibody experiments.

Dr. McEwen expressed reservations about additions to the proposed experimentation at this point.

Dr. Bergfeld said that, for the time being, the proposed study should proceed as planned.

Dr. Belsito reiterated that in designing studies both for chemical penetration and light penetration, the Panel will potentially be using these studies to establish concentration limits. With this in mind, he advised industry to literally "push the limits" in this study.

Dr. Bergfeld said that the Panel intends to complete its review of AHAs this year, and asked Dr. Andersen how this might be accomplished, given the timelines that the Panel is looking at in the best of circumstances.

Dr. Andersen noted that the September 19-20, 1996 Panel meeting is approximately seven months away, and projected that the results of studies initiated after the present meeting could be made available at that time. This would allow CIR to guarantee consideration of a tentative report on AHAs this year. He also said that the

December 16-17, 1996 Panel meeting would be the last opportunity for the Expert Panel to reach a tentative conclusion this year.

Dr. McEwen said that it would be more realistic for CIR to consider issuing a Tentative Report on AHAs at the December 1996 Panel meeting.

Dr. Andersen asked Drs. Bailey and Bronaugh for the projected time to completion of FDA's skin penetration studies on AHAs relative to the December 1996 Panel meeting.

Dr. Bronaugh said that the projected completion of studies by December is practical.

Having received input from industry and FDA, Dr. Andersen said that the target for issuance of a Tentative Report on AHAs will be the December 16-17, 1996 Panel meeting. He reminded the audience that the Panel needs to receive the completed studies one month in advance of the Panel meeting. This would allow for an adequate amount of time for effectively reviewing all meeting materials.

Dr. Bergfeld said that AHAs should also be included on the agenda for the September Panel meeting, such that the document can be revised appropriately prior to the incorporation of additional information that is to be received before the December Panel meeting.

PCA and Sodium PCA

Dr. Schroeter noted that PCA is the abbreviation for 2-Pyrrolidone-5-Carboxylic Acid, and that an Insufficient Data Announcement on PCA and Sodium PCA was issued

ATTACHMENT B

March 4, 1996

John,

The pH of the twelve AHA products provided by you have been determined. Products were prepared by diluting them 1 to 9 with water. The pH meter was calibrated before and after the analyses with pH 1 and 4 buffers. The results of the determinations are shown in Table 1. In addition two products were selected to determine the effect of the dilution factor on pH. These products were diluted with several different volumes of water and the pH was determined. The results of this experiment are shown in Table 2.

Table 1. PH of Cosmetic Products Containing α -Hydroxy Acids

Product	Manuf./Dist	AHAs (%)	pH
Eucerin	Beiersdorf Inc.		7.11
Formula 405 AHA Facial Day Cream	Dermatologics	8.8 (lactic)	2.68
Vaseline Intensive Care Lotion	Chesebrough-Ponds		8.19
Sally Hansen Skin Recovery	Sally Hansen		4.26
Pond's Age Defying System	Chesebrough-Ponds		3.83
Camocare Gold - Camomile Face Lift	Abkit Inc.		3.76
Plentitude Clarify A ³	Cosmair		5.38
Aloe Hydroxy Lotion	Fruit of the Earth		3.73
Pond's Age Defying Lotion; Delicate Skin	Chesebrough-Ponds		3.73
LactiCare Lotion	Stiefel Labs. Inc		5.65
Plentitude Excell A ³	Cosmair		3.81
Healthy Skin Face Lotion	Neutrogena Corp.	13.6 (glycolic)	3.26

Table 2. PH as a Function of Dilution of Two α -Hydroxy Acid Products

Product	Dilution	pH
Formula 405 AHA Facial Day Cream (96-3371)	1:1	2.35
	1:3	2.39
	1:5	2.41
	1:7	2.41
Camocare Gold - Camomile Face Lift (96-3375)	1:0	3.62
	1:1	3.64
	1:2	3.65
	1:3	3.66
	1:4	3.66

Three samples of Estee Lauder's Fruition were analyzed for pH. The following data was obtained:

PH of Fruition			
Sample Number	Purchase Date	pH (Initial)	pH (Check)
93-3165	3/17/93	3.9	3.7
94-3269	5/2/94	3.5	3.7
96-3382	2/26/96	3.82	

The check analyses were in agreement with the results previously obtained.

Another AHA-containing product, Natura Bissé Glycoline, purported to contain 50% glycolic acid was analyzed for pH and composition. The product contained 10 separate vials of the same product. Three were randomly selected pH for analysis. The pH of this product was found to be 3.56, 3.55, and 3.53. Glycolic acid was present at 30%.

ATTACHMENT C



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

Date March 3, 1996

From Chief, Skin Absorption and Metabolism Section, HFS-128

Subject Summary of Glycolic Acid Studies

To Acting Director, Office of Cosmetics and Colors (HFS-100)

The percutaneous absorption of glycolic acid is dependent on the pH of the formulation since the ionized molecule is more polar and therefore less readily absorbed. The effect of pH on ionization of glycolic acid can be calculated from the Henderson-Hasselbalch equation (Figure 1). We have evaluated glycolic acid absorption from oil in water (O/W) emulsions adjusted to pH 3.0, to simulate the acidic pH of most cosmetic products, and pH 7.0.

The percutaneous absorption and metabolism of glycolic acid was measured over a 24 hour period through viable human skin using flow-through diffusion cell techniques. Glycolic acid (with a tracer dose of C^{14} -glycolic acid) was formulated in two O/W emulsion vehicles at a concentration of 5%. Relatively high surfactant concentrations must be used to emulsify the large amounts of glycolic acid and other alpha hydroxy acids (AHAs) in cosmetic products.

Formulation A was prepared using a mixture of two non-ionic surfactants to incorporate the glycolic acid: polyethylene glycol (PEG) 100 stearate (2%) and PEG-4 lauryl ether (Laureth-4) (1%). Total skin absorption of glycolic acid from this formulation was 21.6% at pH 3.0 and only 1.9% at pH 7.0 (Table 1). Some of the absorbed glycolic acid was found in the receptor fluid beneath the skin but the majority had accumulated in the viable skin layers where it might cause effects on skin structure.

A second O/W emulsion (Formulation B) was prepared in order to study the effects of surfactants on the percutaneous absorption of glycolic acid. This formulation contained 1% ammonium laureth sulfate (ALS) instead of 1% laureth-4. ALS is an ionic surfactant but milder than sodium lauryl sulfate, and is contained in some AHA rinse-off formulations. Again, a 5% glycolic acid emulsion was prepared at pH 3.0 and 7.0.

Greater total glycolic acid absorption was obtained with Formulation B at pH 3.0 (Table 2). Skin levels were similar to those obtained with Formulation A but receptor fluid levels were almost four times higher. Total absorption at pH 7.0 was small and

similar to the corresponding value with Formulation A, but the receptor fluid level had also increased. It appears that ALS facilitates the absorption of glycolic acid.

Total glycolic acid absorption (pH 3.0) from Formulation B varied from 24.3% to 44.6% with an average value of 34.8% (Table 2). The data reflects the normal variability in skin permeation found in the human population. The skin from each donor was pretested with a standard compound (H^3 -water) and the differences in barrier properties assessed by this method correlated well ($r^2 = 0.92$) with glycolic acid absorption values obtained from the different donors (Figure 2). The differences in the skin barrier in the population is another variable in assessing glycolic acid absorption.

Since differences in glycolic acid absorption were obtained with Formulations A and B, it seemed that ingredients in the emulsions (such as the surfactants) might be affecting the integrity of the skin barrier. These two emulsions and several marketed cosmetic products were compared for their effects on the barrier properties of hairless guinea pig skin. Steady-state 3H -water absorption was measured through skin following 24 hr exposure to the emulsions, and a permeability constant (K_p) was calculated. The average of K_p values for all formulations was higher than the control (no emulsion) value (Table 3). However, a one-way analysis of variance (Sigma Stat Ver.1, Jandel Scientific) showed that none of the formulations were significantly different from each other. Use of Formulation B gave greater absorption of glycolic acid through human skin than Formulation A. However, its effects on water permeation through hairless guinea pig skin were small and not greater than any other vehicle. Surfactants may have other actions such as facilitating the partitioning of glycolic acid from the O/W emulsion into the skin.

Our glycolic acid absorption values are substantially higher than values previously reported by industry using 10% aqueous solutions adjusted to pH 3.7-3.8. This may be because the aqueous vehicles rapidly evaporate, which could limit partitioning into the skin and also affect pH.

Although glycolic acid is metabolized extensively to oxalic acid following systemic administration, no metabolites of glycolic acid were detected in either skin or receptor fluid samples.

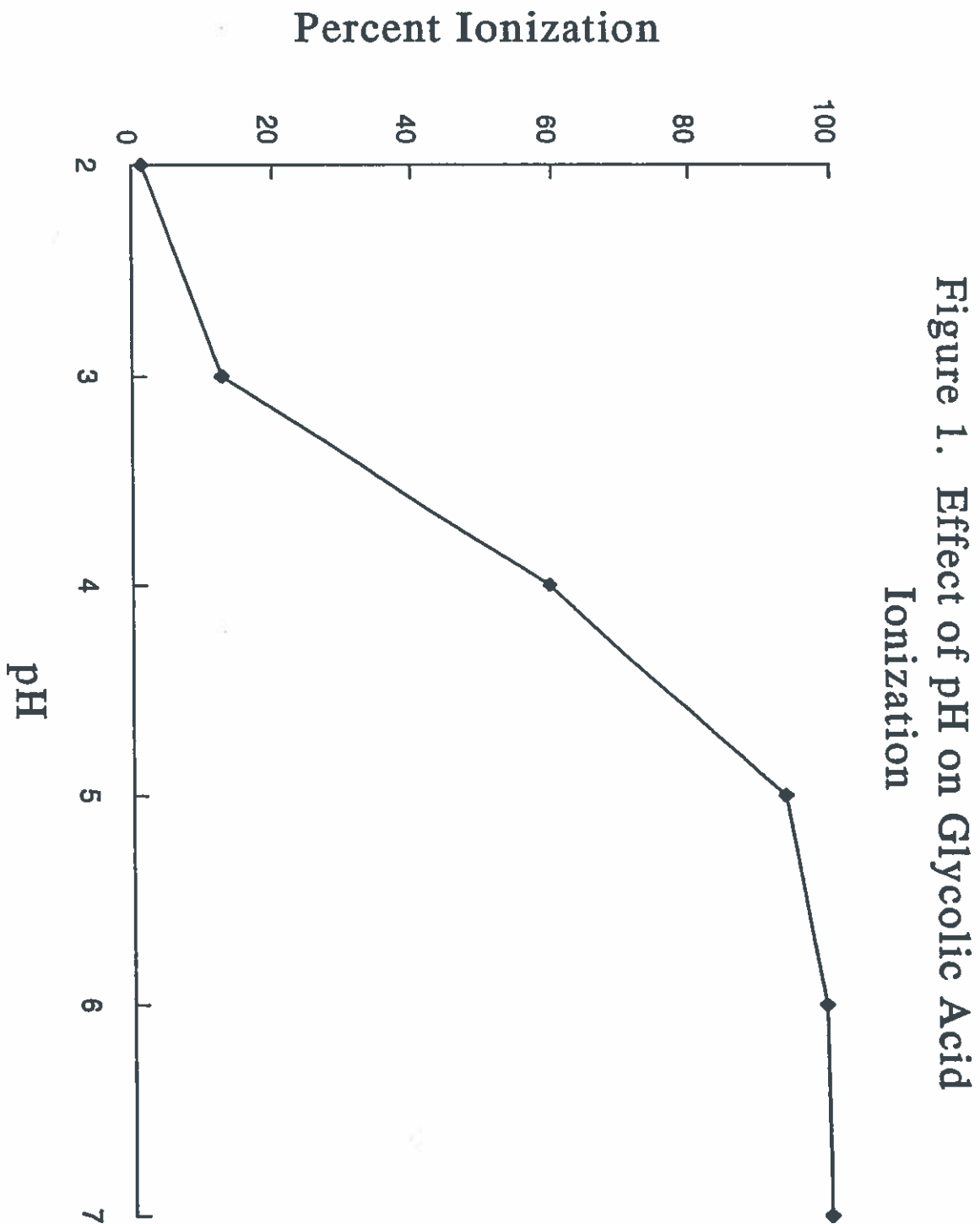

Robert L. Bronaugh, Ph.D.

CC:

HFS-125 (Dennis)

HFS-127 (Havery)

HFS-128 (Kornhauser, Bronaugh)



**Figure 2. Human Skin Variability in Glycolic Acid Absorption:
Correlation with Tritiated Water Barrier Integrity Test**

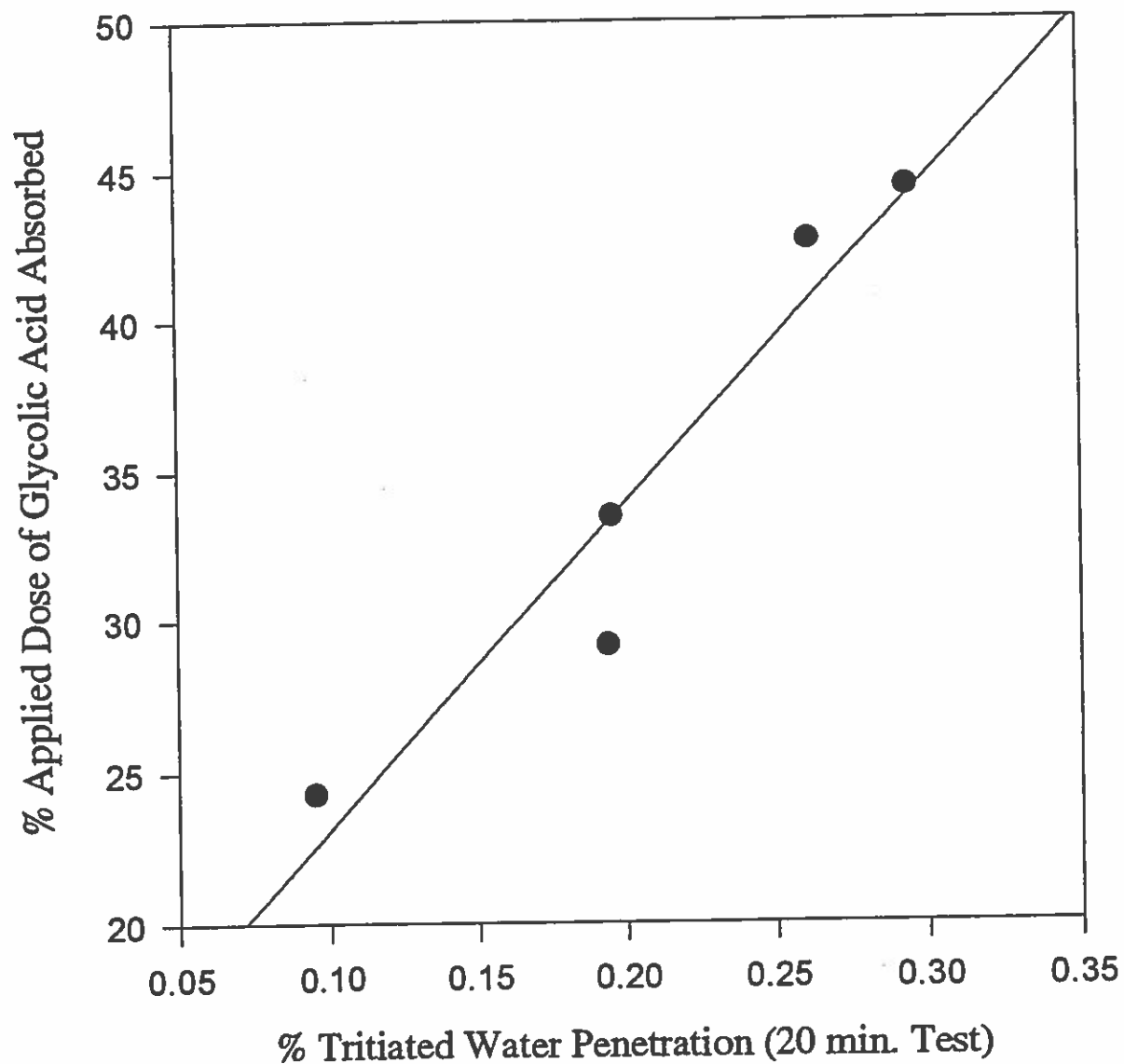


Table 1

Glycolic Acid Absorption from Formulation A		
Location	Percent Applied Dose Absorbed	
	pH 3.0	pH 7.0
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

Values are the mean ± S.E. from 2 donors.

Table 2

Glycolic Acid Absorption from Formulation B		
Location	Percent Applied Dose Absorped	
	pH 3.0	pH 7.0
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

Values are the mean ± S.E. from 5 donors (pH 3.0) and 3 donors (pH 7.0).

Table 3

Effect of Cosmetic Formulations on Hairless Guinea Pig Skin Barrier Properties: Evaluation by the Tritiated Water Permeability Constant (Kp)			
Test Formulation	Gly Acid % Conc.	pH	Kp Value x 10 ⁻⁴
Untreated Controls			4.64 ± 0.54
Formulation A ^a	5	3	8.51 ± 0.77
Formulation A	5	7	6.36 ± 0.72
Formulation B	5	3	8.27 ^b
Aloe Exfoliant Lotion	5	2.54	7.35 ± 1.58
Ponds Age Defying Complex	10	3.52	7.08 ± 1.06

^aThere is no significant difference (p(0.5) between Formulation A, pH 3 and all the other cosmetic formulations.

^bOnly one data set available to date.



ATTACHMENT D

The Effects of 30% Glycolic Acid Chemical Wash at Various pH Levels Under Exaggerated Conditions of Use on Stratum Corneum Integrity

J. C. DiNardo, M.S.¹; G. L. Grove, Ph.D.²

Introduction: AHAs especially at high concentrations, are known to act as exfoliants and some concern has been expressed that the removal of dead skin surface cells may adversely affect barrier function of the stratum corneum. In order to examine this issue with formulations intended for rinse-off salon use, we monitored changes in transepidermal water loss rates using a Servo Med Evaporimeter. Normally, the stratum corneum acts as a very effective barrier and water loss rates are low. If the barrier is disturbed, there will be a corresponding increase in water loss rates. The objective of this investigation was to study the effects of Experimental Glycolic Acid Chemical Washes on the skin at various pH levels with regard to whether or not the stratum corneum is adversely affected by monitoring barrier function in a non invasive fashion with a Servo Med Evaporimeter. In addition, biopsies were taken for histological studies that will be covered in a separate report.

Method & Materials: Twelve healthy females, between the ages of 27 and 55 (mean age of 41.2 years), free of any underlining dermatitis participate in the study. Three experimental 30% glycolic acid chemical washes (partially neutralized with ammonium hydroxide to achieve pH levels of 2.5, 3.0 and 3.5) were applied to either the left or right upper thigh using a random design that allowed each product to be applied to eight different test sites. Prior to product application, the test sites were cleansed with a prepping solution, in a similar manner as recommended by various manufacturers. In order to enhance any potential of the products to disturb the barrier function of the stratum corneum, the products were left in contact with the skin for 20 minutes and were applied 3 times within a 6 day period of time (days 1, 3, and 6). This represented a 2 fold exaggeration of the generally recommended application time as well as a 1 1/2 to 3 fold exaggeration of the number of applications recommended by manufactures. Transepidermal water loss measurements were made at baseline, 15 minutes and 3 hours after each chemical wash, and at 1 week after the last chemical wash (day 13). Superficial shave biopsies were taken on day 0 (prior to chemical washing), day 6 (15 minutes after the last chemical wash), and on day 13 (1 week after the last chemical wash). Tissue samples were paraffin embedded, cut into 5 micron sections, stained with Hale's Stain, and evaluated using a computerized image analysis technique (designed by Dr. Lavker) as well as microscopically. This procedure allows the integrity of the stratum corneum to be assessed colorimetrically, via image analysis, based on the amount of stain in the tissue as well as structurally through microscopic inspection.

*1) Independent Research Consultant, Raleigh, NC; 2) Skin Study Center, Broomall, PA;
This study was Funded by a grant from the Esthetics Manufacturers & Distributors Alliance of the American Beauty Association and its Members.*

Results: As depicted in Figures 1 and 2, a minimal effect appears to be observed after the first chemical wash. The wash with a pH of 2.5 maintained a water loss rate of 4% at both the 15 minute and 3 hour readings. A moderate increase (21%) in water loss was observed at the 15 minute interval for the pH 3.0 wash which dropped to a 6% decrease in water loss after 3 hours. Additionally, the pH 3.5 wash also demonstrated a slight increase (4%) at 15 minutes which dropped to a 8% decrease in water loss after 3 hours. The data observed 15 minutes after the second and third chemical washes, appears to demonstrate a dose response effect, whereby, the lower the pH value the higher the water loss. However, 3 hours after insult it appears that water loss is stabilized by the stratum corneum and settles down around 11% to 20%, but does not reflect a specific dose response pattern. Transepidermal water loss values obtained for the 1 week after the last wash, implies a trend that the stratum corneum has rebounded from any potential impairment and appears to have better barrier function capabilities, whereby, the higher the pH value the better the barrier function, 13%, 17%, and 19% for pH levels of 2.5, 3.0 and 3.5 respectively. Additionally, it should be noted that no clinical irritation (erythema and/or edema) was noted during the course of testing for any of the pH levels, under the conditions tested.

Figure 1

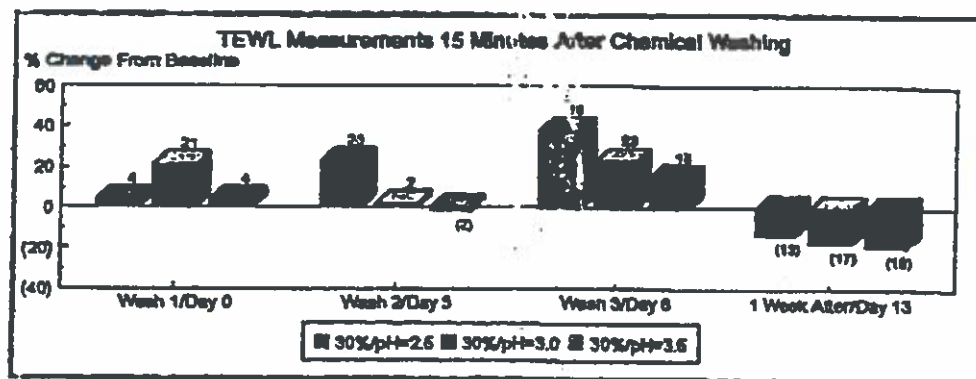
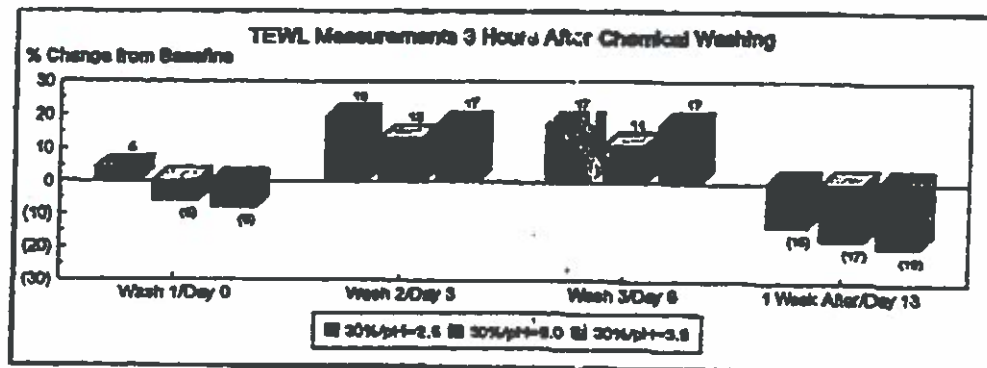


Figure 2



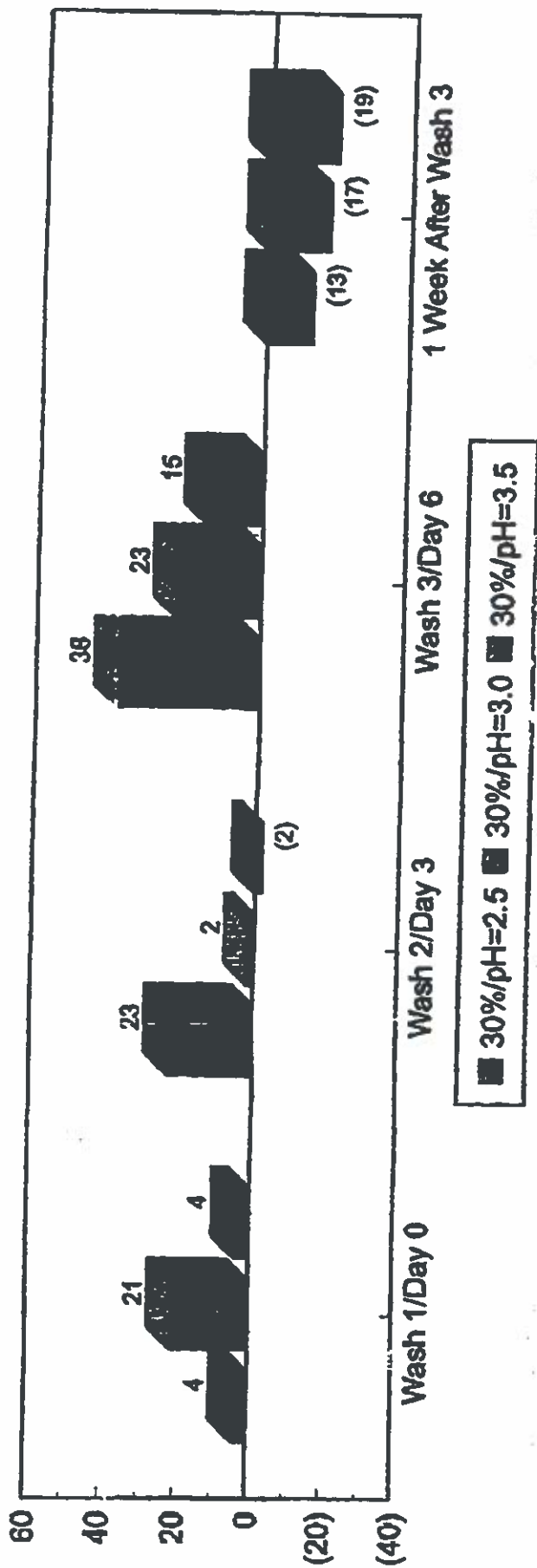
Discussion: The data obtained for the various pH levels appears to suggest that under exaggerated conditions, which based on the various manufactures use directions would be considered "abusive", the products have a potential to increase transepidermal water loss implying some disruption of barrier function. However, it should be noted that the values obtained for these products (4.2 ± 1.4 to 6.6 ± 1.9 ; refer to table 1) represent slight changes in the fluctuation of the amounts of water loss expressed in $\text{gm/m}^2/\text{hr}$ and for the purpose of comparison reflect ranges that have been reported for conventional soap based and synthetic-detergent based cleansers (which are used by millions of people daily) ranging from 5.5 ± 0.4 to $14.9 \pm 1.3 \text{ gm/m}^2/\text{hr}$, under exaggerated use conditions (Nicoli, et al; J Soc. Cosmet. Chem. 46, 129-140; 1995). It should also be noted that the dose response trends observed after the second and third washes for the 15 minute values may imply that with continued application, with little time for the skin to recover from insult, a cumulative irritation effect may be evoked. This would coincided with the data previously submitted by DiNardo on the cumulative irritation potential of glycolic acid at various concentrations and pH levels, which suggest that irritation potential is pH dependant not concentration dependant. Lastly, it is interesting to note that a trend appears implying that the higher the pH the better the efficacy, or in this case improvement of barrier function, 1 week after treatment. This trend was also noted in the data submitted by DiNardo, Grove, and Moy when evaluating the efficacy of glycolic acid at various concentrations and pH levels.

Table 1: TEWL Raw Data

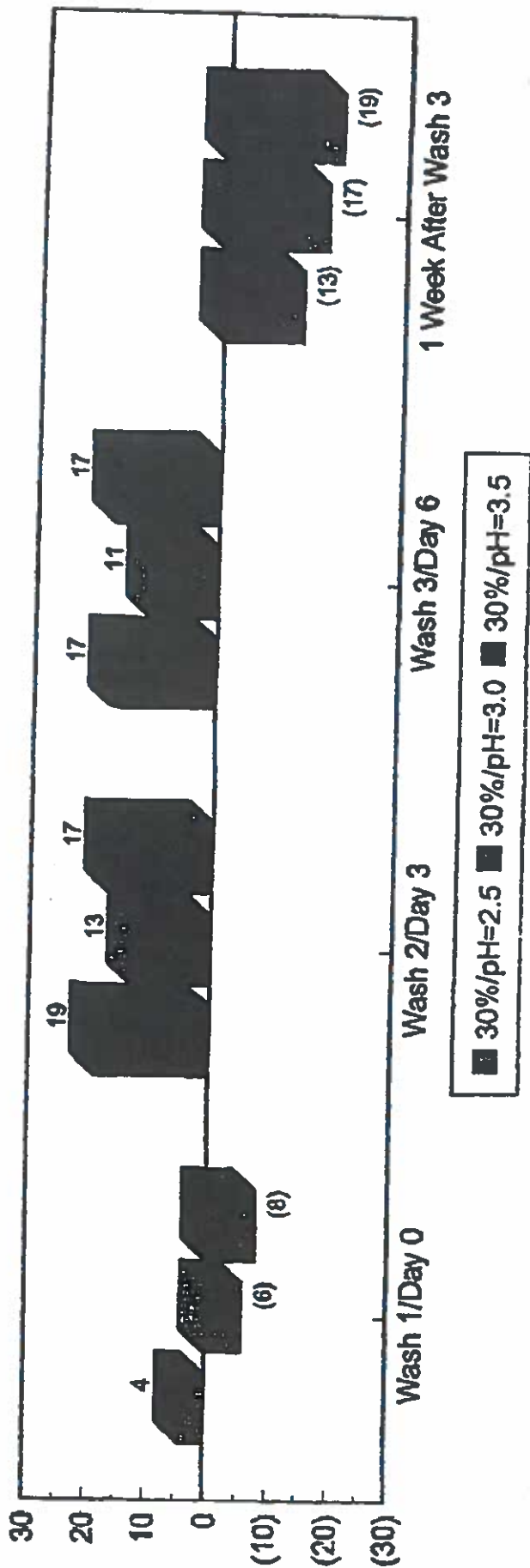
Time	pH 2.5	pH 3.0	pH 3.5
Baseline	4.8 ± 0.9	4.7 ± 0.8	5.3 ± 1.2
Day 0 + 15 Minutes	5.0 ± 1.4	5.7 ± 1.3	5.1 ± 1.5
Day 0 + 3 Hours	5.0 ± 1.3	4.4 ± 1.4	4.9 ± 1.3
Day 3 + 15 Minutes	5.9 ± 1.6	4.8 ± 1.3	5.2 ± 1.7
Day 3 + 3 Hours	5.7 ± 1.1	5.3 ± 1.3	6.2 ± 2.1
Day 6 + 15 Minutes	6.6 ± 1.9	5.8 ± 1.3	6.1 ± 1.8
Day 6 + 3 Hours	5.6 ± 1.4	5.2 ± 1.0	6.2 ± 1.6
Day 13	4.2 ± 1.4	3.9 ± 1.2	4.3 ± 1.2

Conclusion: Based on the data obtained under the conditions of the experimental design used, it would appear that a 30% glycolic acid chemical wash, partially neutralized, can be used safely with minimal damage occurring to the stratum corneum integrity with regards to impairment of barrier function as measured as transepidermal water. However, one may be considered prudent in determining an appropriate pH, in light of the research reviewed on irritation potential, to select a higher pH (3.0 or higher) to allow for an additional margin of safety for use in the general public. Additional data is currently being prepared which will evaluate the histological effects of the above noted products, which should add additional incite to the potential of these agents to effect stratum corneum integrity.

TEWL Measurements 15 Minutes After Chemical Washing



TEWL Measurements 3 Hours After Chemical Washing



Formula Compositions

Glycolic Acid Chemical Wash:

Water

Glycolic Acid

Ammonium Glycolate

Hydroxyethylcellulose

Prepping Solution:

Water

SD Alcohol 40-B

Glycolic Acid

Ammonium Glycolate

FD&C Green No. 3



SKIN STUDY CENTER

390 REED ROAD, 1st FLOOR, BROOMALL, PA 19008-4008 USA
TELEPHONE: (610) 544-1715 FAX: (610) 544-6305

FINAL REPORT
TO
HERALD PHARMACAL / ALLERGAN, INC.
ON
STRATUM CORNEUM INTEGRITY STUDY

KGL #3736

MARCH 1, 1996

Submitted by,

G. Grove
Gary L. Grove, Ph.D.

3/1/96
Date

The name of Skin Study Center, Ivy Laboratories, KGL, Inc., any officer, employee or collaborating scientist are not to be used for any advertising, promotional or sales purposes without the written consent of Skin Study Center, Ivy Laboratories, or KGL, Inc.

Quality Assurance Officer: P.F. Alfano 3-1-96
Patricia F. Alfano Date

CONFIDENTIAL

TABLE OF CONTENTS

I. BACKGROUND

II. OBJECTIVE

III. EXPERIMENTAL DESIGN

- A. General Considerations**
- B. Panelist Selection**
- C. Test Sites & Treatments**
- D. Water Loss Rate Measurements**
- E. Superficial Shave Biopsies**
- F. Data Processing Procedures**

IV. RESULTS

- A. Panelist Accountability**
- B. Change in Water Loss Rates Over Time**

V. CONCLUSIONS

VI. RECORD RETENTION

Appendix A: Calendar of Events

Appendix B: Weather Information

Appendix C: Sample Consent Form

Appendix D: Treatment Schedule

Appendix E: Demographic Data

Appendix F: Water Loss Data

KGL #9730

Glycolic Acid Study

2

AHA's, especially at higher concentrations, are known to act as exfoliants and some concern has been expressed that the removal of dead skin surface cells may adversely affect the barrier function of the stratum corneum. In order to examine this issue with formulations intended for rinse-off salon use, we monitored changes in transepidermal water loss rates using the Servo Med Evaporimeter. Normally, the stratum corneum acts as a very effective barrier and water loss rates are low. If the barrier is disturbed, there will be a corresponding increase in water loss rates.

The objective of this investigation was to study the effects of 30% Glycolic Acid chemical wash on the skin at various pH levels with regard to whether or not the stratum corneum is adversely affected by monitoring barrier function in a non invasive fashion with a Servo Med Evaporimeter. In addition biopsies were taken for histological studies that will be covered in a separate report.

A. General Considerations

This project was conducted under the supervision of Gary Grove, Ph.D., at the Skin Study Center located in Broomall, Pennsylvania. The conduction period ran from February 13, 1996 through February 26, 1996. In conducting this study, we followed Good Clinical Practices (GCP) and Good Laboratory Practices (GLP) guidelines. A calendar of events outlining the schedule of treatments and evaluative procedures followed is attached as Appendix A. Pertinent weather information as extracted from daily newspaper reports is attached as Appendix B. A more detailed account issued by the US Weather Bureau will be provided when it is issued by them.

Pertinent details of the study and brief explanations of the fundamentals of the instrumentation will be provided in the sections that follow.

B. Panelist Selection

The volunteers for this project were recruited from a pool of healthy white women. All panelists were interviewed to ascertain that they were neither pregnant nor breast feeding, had no medical problems, were not using concomitant medications that might interfere with the study results and had no known sensitivities to cosmetics, moisturizers, adhesive dressings, etc. Twelve females in general good health, free from any underlying dermatitis were selected.

Each panelist was informed of the nature, risks and purpose of the study and an informed consent describing the purpose and relevant information was obtained from each volunteer prior to initiation of the study. A sample of the consent form is attached as Appendix C. Copies of all signed consent forms are kept on file at the Skin Study Center (KGL, Inc.).

C. Test Sites & Treatments

The following materials were furnished by the Sponsor:

M.D. Formulations Aesthetics Training Manual & Video Tape

Glycolic Acid Chemical wash 30%, pH 2.5 R&D 02-50A 1/18/96

Glycolic Acid Chemical wash 30%, pH 3.0 R&D 02-50B 1/18/96

Glycolic Acid Chemical wash 30%, pH 3.5 R&D 02-50C 1/18/96

Pretreatment Cleansing Solution 5%, pH 4.0 R&D 02-50D 1/18/96

Mrs. Lynda Johnson served as the Treatment Team Leader for this study. Mrs. Sheri Gimbel assisted her in administering the treatments on Day 0, Day 3 and Day 6. At these times, the upper right and left thighs were first cleansed with a cotton ball saturated with the sponsor's cleansing solution. The sites were then patted dry with a tissue after which the designated chemical wash was applied with a cotton tip swab to the site indicated in the treatment schedule attached as Appendix D. After 20 minutes, the treatments were rinsed off with water using cotton balls and patted dry with a Bounty paper towel. Please note that this represents an exaggerated use of these products because the manufacturer's instructions recommend only a 10 minute exposure and that no more than 2 applications should be done in one week with at least 3 days between.

D. Water Loss Rate Measurements

Evaporative water loss was measured by Ms. Denise Milligan with the assistance of Mrs. Marsha Damia at Baseline and at various times after treatment. This was done 15 minutes and 3 hours after each of the treatments was rinsed off on Day 0, Day 3 and Day 6 as well as on Day 13 which was 1 week after the last treatment.

These measurements provide an instrumental assessment of skin barrier function. These measurements were made using recently calibrated Servo Med instruments as designed by Nilsson and described by Pinnagoda [Pinnagoda, J., R.A. Tupker, T. Anger and J. Serup. Guidelines for transepidermal water loss (TEWL) measurement. In: Contact Dermatitis 1990: 22:164-178]. The panelists were measured with Unit #231/Probe #146 and Unit #233/Probe #270. Each of these instruments is comprised of a hand held probe which is attached by a cable to a portable electronic display unit. Each probe consists of an open cylinder, 15.5mm long, with a mean diameter of 12.5mm. Two sensors within each probe measure the temperature and relative humidity at two fixed points approximately 4mm apart, along the axis normal to the skin surface. This arrangement is such that the device can electronically derive a value that corresponds to evaporative water loss in $g/m^2/hr$.

The data from the evaporimeter was collected by a data collection system utilizing a Dia-Stron A/D conversion board and associated software. The extracted value refers to the average evaporative water loss rate collected over a twenty second interval once steady state conditions had been achieved.

Such measures provide a noninvasive method for determining the barrier function of the stratum corneum. Damage leads to a disruption of the barrier which is accompanied by elevated water loss rates. On the other hand water loss rates will also be slightly elevated when the skin surface is more moisturized.

E. Superficial Shave Biopsies

Skin specimens (biopsies) were taken by Kays Kaidbey, M.D., from the sites on Day 0, Day 6 and Day 13.

All collected specimens were forwarded to Dr. Robert Lavker for analysis. The results and discussion from this part of the study will be covered by Dr. Lavker in a separate report.

F. Data Processing Procedures

Dr. Grove was responsible for devising a decoding and sorting template that was based on Enable spreadsheet software and implemented on the IBM-XT clone desktop computer. The decoded and sorted data for each parameter was tabulated and arranged in order of panelist number for every point of evaluation. In creating these tables, column averages were computed in every case, but only to give a preliminary look at the findings.

Dr. Grove was also responsible for evaluating the findings. Due to the small number of panelists within each group, we did not undertake a formal statistical analysis of the data. Instead, a series of time course plots were constructed and general trends in the data noted when observed.

IV. RESULTS

A. Panelist Accountability

All twelve panelists were able to successfully complete the entire course of the treatments without any problems. There were no missed visits during the course of the study. Moreover, we have no reason to believe that the panelists were not fully compliant with the study requirements.

Appendix E contains a listing of the selected panelists along with the age and skin classification using the Fitzpatrick Skin Classification Scale (Fitzpatrick, T.B.: The validity and practicality of sun-reactive skin types I through VI. Arch. Dermatol. 124:867-871, 1988).

B. Change in Water Loss Rates Over Time

Appendix F tabulates the water loss values obtained at various times during this study. To facilitate comparisons, we have summarized the means for each of the 3 treatment groups over time in the table that follows:

Time	pH 2.5	pH 3.0	pH 3.5
Baseline	4.8 ± 0.9	4.7 ± 0.8	5.3 ± 1.2
Day 0 + 15 M	5.0 ± 1.4	5.7 ± 1.3	5.1 ± 1.5
Day 0 + 3 H	5.0 ± 1.3	4.4 ± 1.4	4.9 ± 1.3
Day 3 + 15 M	5.9 ± 1.6	4.8 ± 1.3	5.2 ± 1.7
Day 3 + 3 H	5.7 ± 1.1	5.3 ± 1.3	6.2 ± 2.1
Day 6 + 15 M	6.6 ± 1.9	5.8 ± 1.3	6.1 ± 1.8
Day 6 + 3 H	5.6 ± 1.4	5.2 ± 1.0	6.2 ± 1.6
Day 13	4.2 ± 1.4	3.9 ± 1.2	4.3 ± 1.2

Our results clearly show that water loss rates do not change dramatically during the course of treatment. All of the values are well within the normal range of values obtained from the thighs of the general population and there is nothing to suggest that any of these formulations may have adversely affected the stratum corneum leading to elevated water loss rates.

KGL #3736

Glycolic Acid Study

7

V. CONCLUSIONS

On the basis of the information obtained during the course of this study, it seems reasonable to conclude that the stratum corneum barrier function was not adversely affected by this series of treatments even though they were done in an exaggerated manner.

VI. RECORD RETENTION

Please be advised that the records for this study will remain on file at KGL, Inc. (or a remote storage site) for a period of 5 years from the issue date of the final report and then destroyed unless we are notified otherwise by the Sponsor using the form accompanying this report.

ATTACHMENT E

2/2/20

2/2/20

2/2/20

GUIDELINES

Esthetic Manufacturers / Distributors Alliance (EMDA)

Professional Guidelines for Alpha Hydroxy Acid (AHA) Cosmetic Chemical Exfoliation Procedure

Guideline Committee: Joseph A. Lewis, Director, Research and Development, Allegran Inc., Herald Pharmacal; Paul Scott Premo, Director, Corporate Communications / Technical Service, Murad, Inc.

Review Committee: Mark Lees Ph.D., Howard Murad, M.D., Paul Dykstra, Executive Director, American Beauty Association (ABA)

I. Introduction

The Esthetic Manufacturers / Distributors Alliance (EMDA) has developed professional guidelines for Alpha Hydroxy Acid (AHA) Cosmetic Chemical Exfoliation procedures for cosmetologists and/or estheticians. The guidelines are intended to ensure procedural consistency in the use of professional rinse off, pulse applications of Alpha Hydroxy Acids (Glycolic & Lactic) for which product safety has been substantiated. These guidelines exclude all other chemical exfoliation / peeling procedures and substances including, but not limited to Trichloroacetic Acid (TCA), Carboic Acid (phenol), Resorcinol or combinations thereof.

II. What is Cosmetic Chemical Exfoliation Procedure?

Cosmetic Chemical Exfoliation procedures utilizing Alpha Hydroxy Acids facilitate stratum corneum desquamation improving the aesthetic appearance and quality of the skin. Cosmetic Chemical Exfoliation procedures are not intended to elicit viable epidermal and/or dermal wounding, injury or destruction, and therefore differ from chemical peeling procedures administered by physicians. These guidelines cover "professional use only" AHA products with a concentration not exceeding 30%, pH 3.0, their application, precautions and post procedural care.

III. Professional Use Qualifications

Cosmetic Chemical Exfoliation procedures are intended for "professional use only" by licensed cosmetologists and/or estheticians in a state approved, licensed cosmetology establishment. A licensee must comply with the rules and regulations established by their respective State Board of Cosmetology regarding Cosmetic Chemical Exfoliating procedures. These products and procedures are not intended for consumer resale or use.

IV. Manufacturer Instructional Requirements

Manufacturers marketing and distributing AHA Cosmetic Exfoliating products for professional use according to the guidelines and specifications established within this document, should provide instructional procedural and product use training to each licensed cosmetologist / esthetician. Manufacturer sponsored training programs are exclusive of training requirements established by individual State Boards of Cosmetology. It is the responsibility of the manufacturer to provide procedural demonstrations, practical training, video and/or written instructional materials with the initial purchase of their product. It is extremely important that licensed practitioners of Cosmetic Chemical Exfoliation procedures be well trained to ensure consumer safety. Manufacturer instructional training should cover theoretical and practical application of Alpha Hydroxy Acid Cosmetic Exfoliating Procedures and products.

The following training program guidelines are recommended:

1. Scientific overview of Alpha Hydroxy Acids
2. Clinical indications vs Cosmetic applications
3. Client general history, skin evaluation, realistic expectations
4. Contraindications / Precautions
5. Predisposition patch testing
6. Client pre-application care
7. Application procedure
8. Post application care
9. Client follow-up

V. Recommended Alpha Hydroxy Acid (AHA) Cosmetic Chemical Exfoliating Procedure:

1. Appropriate disinfection and sanitation as established by respective state board of cosmetology.
2. Client preparation and protection as established by respective state board of cosmetology.
3. **Predisposition Patch Testing**

The Federal Law mandates under the Food, Drug and Cosmetic Act of 1938 provides that a skin test designed to determine an individual's sensitivity. Sensitivity to chemical exfoliating products can only be determined by administering a Predisposition Patch Test. This is recommended to be done 24 hours prior to the application of Alpha Hydroxy Acid (AHA) Cosmetic Chemical Exfoliating Procedures.

4. Client Consultation

A thorough skin evaluation and consultation should be conducted on each client to determine if the procedure is appropriate.

Suggested questions during the client consultation:

- History of sun exposure and/or tanning bed use
- History of cosmetic related irritant / allergic contact dermatitis
- Currently under physicians supervision
- History of medication i.e. tretinoin (Retin-A, Renova), isotretinoin (Accutane) etc.
- HSV (herpes simplex virus) predisposition
- Previous facial plastic / reconstructive surgery
- Previous chemical peel procedure - type and results
- Previous cosmetic chemical exfoliating procedure - type and results
- Current skincare regimen including Alpha Hydroxy Acids

Precaution:

Cosmetic Chemical Exfoliating Procedures are not recommended when a client is under the supervision of a physician for skin related disorders. Physician approval is recommended before administering these procedures.

5. Client Skin Evaluation and Inspection:

- A. Thoroughly evaluate facial skin
- B. Check for degree of sebaceous activity (skin oiliness), acne, telangiectasias (broken capillaries)
- C. Check for open cuts, sores, lesions or apparent skin irritation or sensitivity
- D. Outline realistic expectations with client

It is not recommended to administer cosmetic chemical exfoliating procedures to skin exhibiting open cuts, sores, sunburn, chemical or thermal burns, apparent skin irritation or sensitivity. Twenty-four hours prior to the procedure, a predisposition patch test is also recommended. Client photodocumentation is also recommended at baseline and upon conclusion of each procedure.

6. Administering the Cosmetic Chemical Exfoliating Procedure:

- Thoroughly wash and disinfect hands. The use of sterile latex gloves are recommended during the procedure.
- Drape and protect client appropriately according to established state board of cosmetology rules and regulations.
- Conduct client skin evaluation and inspection
- Cleanse clients skin according to manufacturers directions.
- Apply protective eye pads to eye area.
- Apply cosmetic chemical exfoliation preparation according to the recommended procedure of the manufacturer.

*** Please note, manufacturers directions can vary, always read carefully and follow complete directions.**

- Always follow manufacturers directions regarding exposure time.
- Remove preparation after the appropriate exposure time with cool, damp gauze or cotton pads.
- Conclude procedure with manufacturers skincare procedure including the use of a sunscreen or sunblock SPF 15.
- Instruct client on any appropriate post care.
- Have client report to you any adverse reaction. Seek medical assistance if necessary.

VI. Disclaimer

Compliance with these guidelines do not guarantee the practitioner a successful procedure and consideration should be given to each client and procedure as an individual case.

EMDA GUIDELINES FOR
Alphahydroxy Profesional Use Only Product
Manufacturing and Distribution

The following guidelines have been established for the safe manufacturing of Alphahydroxy professional use products. "Professional Use Products" are defined as alphahydroxy acid products developed and intended for application by a licensed esthetician or cosmetologist.

1) Salon use professional products should not exceed 30% concentration of alphahydroxy acids, nor should the products have a pH below 3.0.

2) Manufacturers should not use the word "peel" or "peeling" in description of AHA salon use exfoliation products. It is the opinion of EMDA that the word "peel" implies removal of live tissue, and the word "exfoliation" implies the removal of dead surface skin cells.

3) Manufacturers should not sell AHA professional products to estheticians or cosmetologists who have not been properly trained in the use of AHA exfoliation products. Manufacturers/Distributors should require that estheticians purchasing professional use AHA products have hands-on instruction in the use of their product.

4) Professional Use AHA products should not be sold to consumers. Manufacturers agree to use the following warning statement on their salon-use AHA products:

"WARNING: This product is for professional use only by licensed estheticians or cosmetologists who have specialized skin care training in the use of alphahydroxy acid products, and not intended for consumer resale or home use. Use of this product by untrained, unlicensed persons may result in skin irritation.

A sunscreen with a minimum SPF of 15 should be used after use of this product, and should be routinely used by persons using alphahydroxy acid products."

Manufacturers should also provide ingredient labeling for professional products, and instructions for use, designed for the licensed professional.

COSMETIC INGREDIENT REVIEW

FIFTY-NINTH MEETING

OF THE

EXPERT PANEL

June 3-4, 1996

ANA HOTEL

Washington, D.C.



Expert Panel Members

Wilma F. Bergfeld, M.D., Chairman

Donald V. Belsito, M.D.

William W. Carlton, D.V.M., Ph.D.

Curtis D. Klaassen, Ph.D.

Arnold L. Schroeter, M.D.

Ronald C. Shank, Ph.D.

Thomas J. Slaga, Ph.D.

Liaison Representatives

Consumer

Mary Ellen Fise, Esq.

Industry

Gerald N. McEwen, Jr., Ph.D.

FDA Contact Person

John Bailey, Ph.D.

CIR Staff

F. Alan Andersen, Ph.D.

Director/Scientific Coordinator

Adopted _____
(Date)

Wilma F. Bergfeld, M.D.

Others Present At Meeting

Susan Carpenter	CIR
John Corbett	Clairol, Inc.
Paul Dykstra	American Beauty Association
H. J. Eiermann	
Monice Fiume	CIR
Donald Havery	FDA
Akiko Jacobson	Shiseido
Rebecca Johnson	CIR
Wilbur Johnson	CIR
Steve Margolia	Shiseido
Dave McGregor	Stepan Company
Bindu Nair	CIR
Kate Rawson	"The Rose Sheet"
John Tedeschi	Cosmair
Jeffrey Yourick	FDA

June 1996

Dr. Belsito also noted that information on methods of manufacture and a UV spectral analysis were received after the Tentative Report was announced, and that these data do not warrant substantively changing the Panel's conclusion.

The Expert Panel voted unanimously in favor of issuing a Final Report on Iodopropynyl Butylcarbamate with the conclusion stated on the preceding page.

Alpha Hydroxy Acids (AHA) Update

Dr. Andersen said that this update is being presented because the Panel was provided with another draft of the AHA report, which contains the following new data: stratum corneum integrity (Glycolic Acid), professional salon use of AHAs, data received from FDA at the last Panel meeting, developmental toxicity data, and a recent study on the bioavailability of AHA topical formulations (publication by Van Scott). Additionally, although not added to the report, CIR has resolved questions that were outstanding at past Panel meetings concerning the concentration of formaldehyde that may be present as an impurity. CIR has also received clarification on the ways in which distribution or use of technical grade Glycolic Acid is restricted by the supplier of that ingredient to the formulators. This information will be incorporated into the next report draft.

Dr. Andersen noted that the studies on AHAs that have been targeted for consideration at the December 16-17, 1996 Panel meeting are as follows: The evaluation of sunburn cells as a surrogate assay for UV radiation damage (to be provided by industry) and studies underway at FDA to assess the potential for AHAs to

increase/enhance the skin penetration of other compounds. These studies have been identified by the Panel as being very important in reaching a final conclusion on the safety of AHAs.

Dr. Bergfeld asked if the studies will be completed prior to the December Panel meeting.

Dr. McEwen said that industry has begun testing to determine the effects of Glycolic Acid on the skin's barrier to UV radiation, and that there should be no problem with meeting the deadline.

Dr. Bergfeld asked Dr. Bronaugh to comment on the studies being conducted by FDA.

Dr. Bronaugh said that FDA is conducting pilot studies to look at the response in hairless guinea pig skin to different concentrations and pH of formulations of Glycolic Acid. Results thus far indicate that the hairless guinea pig skin is more sensitive (more of an irritant response) than human skin. Thus, different concentrations are being tested with the intention of finding a concentration that can be tolerated by the guinea pigs during daily application for one month.

REPORTS ADVANCING TO THE NEXT LEVEL

Urocanic Acid

Dr. Bergfeld noted that CIR received two submissions on Urocanic Acid (published CIR Final Report) from Beiersdorf AG, and asked Dr. Schroeter to comment on this.

Cosmetic Ingredient Review

*Commitment . . . Credibility
Since 1976*

SIXTY-FIRST MEETING

OF THE

EXPERT PANEL

December 16-17, 1996

EMBASSY ROW HOTEL

Washington, D.C.



Expert Panel Members

Wilma F. Bergfeld, M.D., Chairman

Donald V. Belsito, M.D.

William W. Carlton, D.V.M., Ph.D.

Curtis D. Klaassen, Ph.D.

Arnold L. Schroeter, M.D.

Ronald C. Shank, Ph.D.

Thomas J. Slaga, Ph.D.

Liaison Representatives

Consumer

Mary Ellen Fise, Esq.

Industry

Gerald N. McEwen, Jr., Ph.D.

FDA Contact Person

John Bailey, Ph.D.

CIR Staff

F. Alan Andersen, Ph.D.

Director/Scientific Coordinator

Adopted _____
(Date)

Wilma F. Bergfeld, M.D.

Dec 1996

Cosmetic Ingredient Dictionary (PPG-2-Buteth-2) are acceptable and could provide a basis for expanding this family of ingredients to include all of the PPG Buteths.

The preceding data requests will be included in the report discussion.

Dr. Andersen noted that because the conclusion reached at the present meeting is substantially different from the one included in the Tentative Report, the current document will be re-issued as a Tentative Report with the new conclusion that was approved today. Announcement of the Tentative Report will be followed by a 90-day comment period. The Panel had previously issued a tentative insufficient data conclusion on PPG-12-Buteth-16, PPG-9-Buteth-12, PPG-26-Buteth-26, and PPG-28-Buteth-35.

REPORTS ADVANCING TO THE NEXT LEVEL

Alpha Hydroxy Acids

Dr. Bergfeld made the following introductory remarks relative to the Panel's review of AHAs:

In 1994, the Panel became aware of the fact that there was increased use of AHAs in the cosmetics arena and that dermatologists were being asked about the safety of these ingredients. During the Panel's annual discussion of cosmetic ingredient priorities in 1994, it was determined that AHAs should be moved up on the priority list for consideration. In April of 1995, the Scientific Literature Review on AHAs (containing hundreds of studies) was made available for review, and, since that time, the published literature has been monitored continuously for pertinent information.

Approximately one year ago, two questions arose regarding the safety of AHAs. These questions have now been answered by a variety of studies that were done by both the cosmetics industry and the FDA. The questions were as follows: (1) Do AHAs enhance the skin penetration of other ingredients? and (2) Do AHAs increase the potential for UV light damage?

At the conclusion of her introductory remarks, Dr. Bergfeld introduced Dr. John Bailey, noting the Panel's appreciation that FDA had volunteered to conduct skin penetration studies:

Dr. Bailey noted that approximately one week ago, the results of skin penetration enhancement studies conducted at FDA laboratories by Dr. Robert Bronaugh were made available. He then asked Dr. Bronaugh to present the results of these studies.

The text of Dr. Bronaugh's presentation appears below **[Slides used in this presentation are inserted at the end of the minutes]**:

Actually, two studies on AHAs were promised for this Panel meeting. The results of these two studies will be summarized. I would like to acknowledge the expert work of Margaret Kraeling and Harolyn Hood, who actually conducted these studies.

Initially, we examined the percutaneous absorption of a homologous series of Alpha Hydroxy Acids (AHAs). Basically, we conducted a series of studies on the penetration of a series of AHAs and increasing molecular weight. These studies were done using excised human skin that was obtained using abdominoplasty surgical procedures. The skin was dermatomed to approximately 250 microns and assembled in a flow through diffusion cell (**Slide 1**). The viability of the skin in the cell was

maintained by perfusing underneath the skin with a physiological buffer. Very importantly, we applied these formulations to the surface of the skin to try as closely as possible to simulate exposure conditions. A very thin layer (approximately 3 mg/cm²) of each oil-in-water emulsion was applied.

This cross section of the skin (**Slide 2**) simulates the appearance of the skin in the diffusion cell. We thought it important to actually measure the levels in all three layers of the skin (stratum corneum, viable epidermis, and papillary epidermis), because the actual sites of AHA action in the skin are still really not known. There is some feeling that AHAs may act on the intracellular cement in the stratum corneum to facilitate the sloughing off of stratum corneum cells. However, in many studies, we see a hyperproliferation in the viable epidermal layer, which indicates that there may be some effects on the epidermis. Finally, even in the dermis, chronic AHA treatment has resulted in changes in collagen synthesis and effects on glycosaminoglycan levels. So, because of the uncertainty of the mechanism of action of AHAs, we thought it important to look at the AHAs in all three levels of skin, as well as the amount in the receptor fluid.

We looked at AHAs in an oil-in-water formulation (**Slide 3**) and also in the study involving hairless guinea pigs, where we looked at the effect of chronic dosing on penetration. We used a simple oil-in-water emulsion with poloxyethylene (100) glycerol stearate and laureth-4 as nonionic surfactants.

I want to briefly talk about pH, which is very important with regard to the penetration of AHAs through the skin. It is known that at a very low pH (pH of

approximately 2 or 3), the most favorable absorption is observed, because essentially most of the material is not ionized. At higher pHs, material is ionized and very polar and does not penetrate very well. Many of the cosmetic formulations on the market have a pH of approximately 3.8, which is the pK_a of Glycolic Acid and Lactic Acid. But, there are products that are fairly acidic, as low as pH 3 or even lower. So, in our studies, we looked at penetration at pH 3 and pH 7.

I think that it is interesting to try and extrapolate from the data that I am going to show (Slide 4): At pH 3, approximately 88% of the Glycolic acid is not ionized, and, at pH 4, approximately 44% is not ionized. These are calculations based on the Henderson-Hasselbach equation at the different pH values. So, one can extrapolate, maybe roughly, to say that since there is half as much ionized material at pH 4, approximately half as much of this material will be absorbed at pH 4 than what would be absorbed at pH 3.

Glycolic Acid absorption was determined in an oil-in-water emulsion at a concentration of 5% (Slide 5). Basically, all of our results were obtained from three different donor samples of human skin and presented as the mean \pm the standard error. The studies were done over a period of 24 h. The stratum corneum was removed by cellophane tape stripping, and the viable epidermis was then separated from the dermis using heat separation techniques. One can see that for Glycolic Acid at pH 3, there is a small amount in the receptor fluid, and fairly significant amounts in the various skin layers. Total in skin + the receptor fluid constitutes the total absorption of this material. There are substantial differences, as one might expect, between Glycolic

Acid at pH 3 and pH 7.

For Lactic Acid absorption (**Slide 6**), the values were very similar when compared to Glycolic Acid absorption, both at pH 3 and pH 7.

For 2-hydroxyhexanoic acid absorption (**Slide 7**), surprisingly, we start to see more material coming completely through the skin and into the receptor fluid at the end of the 24 h experiment. Skin levels now, with these more lipophilic materials, are becoming less when compared to what was observed with Glycolic Acid and Lactic Acid. So, maybe, we seem to be seeing the opposite of what one might expect. We are not seeing reservoir formation with these more lipophilic materials, and, again, we see the pH effect.

This slide (**Slide 8**) shows an analysis of variance between these lower molecular weight AHAs at a concentration of 5% and pH 3. One sees a significant difference in the receptor fluid with the 2-hydroxyhexanoic acid. However, in the dermis and in the total skin, there are significantly lower values of 2-hydroxyhexanoic acid. So, the net effect is that there is not that much of a difference in total absorption, but substantial differences in the layers of skin.

This slide (**Slide 9**) shows the study results for 2-hydroxyoctanoic and 2-hydroxydecanoic acids (the more lipophilic materials). This absorption study was done using a lower concentration, 0.5%, because these materials are not that soluble in water and because this more closely simulates the concentration in cosmetic products. 2-hydroxyhexanoic acid absorption was also evaluated at this lower concentration (0.5%). One can see that with these more lipophilic materials, larger percentages of

the material penetrated through the skin and into the receptor fluid. The levels of 2-hydroxyoctanoic acid and 2-hydroxydecanoic acid in the skin are significantly less than the levels of 2-hydroxyhexanoic acid in the skin. We also see, maybe, a little less absorption with these longer chain acids.

The next two slides (**Slides 10 and 11**) summarize the absorption study that was done with this homologous series of compounds. **Slide 10** shows the absorption profile of AHAs, the % of the applied dose absorbed in each of these 6 h fractions that were collected in the 24 h studies. Small amounts of Glycolic Acid and Lactic Acid appeared in the receptor fluid. However, the absorption profiles for 2-hydroxyhexanoic acid, 2-hydroxyoctanoic acid, and 2-hydroxydecanoic acid are different; there was rapid and more extensive penetration through the skin.

In **Slide 11**, the effect of AHA chain length on skin levels is evaluated. For Glycolic and Lactic Acids, between 80 and 90% of the absorbed material is still in the skin at the end of the 24 h studies. However, for the longer chain-length AHAs, there is a trend toward decreasing reservoir formation in the skin. For 2-hydroxydecanoic acid, only 50% of what was absorbed is still in the skin at the end of 24 h. Basically, what I think is happening is that these materials, although they are lipophilic (these longer chain AHAs), they are really not that lipophilic when compared to fragrance ingredients and other compounds that have log P values of 3 or 4. The octanol-water partition coefficient of 2-hydroxydecanoic acid is only 75 when it is not ionized. More importantly, I think that once these materials leave the formulations and get into the stratum corneum and start diffusing through the skin, they start to ionize, they are polar

molecules and they don't tend to form reservoirs in the skin.

We have seen before in clinical studies that chronic treatment with AHAs has significant effects on the viable epidermal layer, the thickness of this layer. They are also known to reduce the stratum corneum thickness of the skin. Thus, we thought that it would be possible that chronic treatment with AHAs might have an effect on the barrier properties of skin. So, we tried to develop an animal model for looking at this using the hairless guinea pig. We thought that looking at stratum corneum turnover was one relatively easy way to assess how effective we were in causing changes in the structure of the skin that might reproduce changes seen in clinical studies.

So, initially, we evaluated 5 and 10% Glycolic Acid formulations (pH of 3 for both formulations) in the same oil-in-water emulsion that was used for the previous penetration studies in human skin (Slide 12). Initially, we treated the hairless guinea pigs twice a day with these formulations; however, we found that they were not able to tolerate this. They were more sensitive to these products, compared to human skin. Redness appeared and scratching was also reported, rendering the skin unsuitable for looking at effects on barrier properties. So, treatment was reduced to dosing once a day, and this was well-tolerated. A little bit of redness sometimes occurred, but the guinea pigs were not scratching. After approximately ten days, a little bit of flaking of the stratum corneum was observed.

The animals were dosed daily for two weeks, and dansyl chloride in 5% petrolatum (on occlusive patch) was then applied for 24 h. The skin was rinsed after patch removal and dosing with the formulations (5 and 10% Glycolic Acid formulations)

was continued until the dansyl chloride disappeared, which is a measure of the stratum corneum turnover time. Areas of skin (8 cm x 5 cm rectangle on each side of hairless guinea pig) were marked off using a black marking pen (**Slide 13**). A very thin layer of the emulsions was then applied. One formulation was applied on one side and, another formulation, on the other side. Stratum corneum turnover was measured using a UV lamp, and observations were made daily until the dansyl chloride disappeared.

The results of the stratum corneum turnover studies are shown in **Slide 14**. With untreated skin, the complete stratum corneum turnover of hairless guinea pig skin was noted at approximately 26 days. Treatment of the skin with vaseline intensive care lotion (control lotion - does not contain AHAs), resulted in a reduction in the turnover time to approximately 15 or 16 days. It is possible that the vaseline intensive care lotion has some effect on stratum corneum turnover. But, more likely, what is happening is the manipulation of daily application of an emulsion to the skin and then, at the end of 24 h, washing it off and reapplying an emulsion. This tends to remove surface layers of the stratum corneum. However, the effects of treatment with 5 and 10% Glycolic Acid (turnover times) were compared with the control value. There was a significant increase in turnover time of approximately 35 to 40% with the Glycolic Acid formulations. This compares favorably to some reported values for the effects of chronic AHA use in clinical studies. So, we felt that we had established conditions that would affect the structure of the skin.

Initially, we tried applying the pH 3 formulation itself (without the AHAs), and found that we got almost the same effect that was observed with the two Glycolic Acid

formulations. This is not shown on any of the slides. So, applying an acidic formulation may not be a very good control, because the acid pH plays a large role in the turnover of the stratum corneum. Thus, we thought that vaseline intensive care (pH of approximately 7.7) would be a more logical control to run as a control moisturizing agent.

After establishing the conditions for dosing, we applied these formulations to the hairless guinea pigs (two at a time) for three weeks (**Slide 15**). Guinea pig #1 was dosed with 5% Glycolic Acid on one side and vaseline intensive care lotion on the other side. Guinea pig #2 was dosed with 10% Glycolic Acid on one side and vaseline intensive care lotion on the other side. When the animals were sacrificed at the end of three weeks, we took untreated skin from areas on both of the hairless guinea pigs. This two-guinea pig experiment was repeated twice; so, there was a total of three replicates of this experiment. At the end of three weeks, we sacrificed the guinea pigs and set up diffusion cells with the dermatomed skin (dermatomed to a thickness of 250 microns). Diffusion cells were set up for untreated skin, vaseline intensive care, 5% Glycolic Acid, and 10% Glycolic Acid (both Glycolic Acid formulations at pH 3).

Prior to testing our model compounds, hydroquinone (polar model compound) and musk xylol (nonpolar model compound), we did a 20 min test with tritiated water (**Slide 16**). A small amount of tritiated water was applied to the skin for 20 min. At the end of that time, the unabsorbed material was washed off, and a small amount of tritiated water in the receptor fluid was collected during the 1 h collection period. The % of the applied dose that was absorbed was determined. A trend for an increase in the

absorption of tritiated water through skin treated with the 5 and 10% Glycolic Acid formulations was observed. However, an analysis of variance indicated no significant difference between the Glycolic Acid-treated skin and the control- treated skin with regard to water permeation.

The hydroquinone absorption study was done using the same diffusion cells (Slide 17). Hydroquinone was applied in an oil-in-water emulsion. Several antioxidants were added to prevent the oxidation of hydroquinone during the study. The percentage of the applied dose absorbed was determined using radiolabeled material, in order to facilitate the quantitation of absorption. If one looks at the % of the applied dose absorbed that was found (in the receptor fluid, in the skin, and the total absorption) at the end of these 24 h studies, one sees is a very similar pattern of absorption of hydroquinone through the Glycolic Acid and control skin, with regard to the receptor fluid skin or total absorption.

In the musk xylol (very lipophilic material) absorption studies, musk xylol was applied in a very thin oil-in-water emulsion, and the study was conducted for 24 h (Slide 18). We found that there was fairly good absorption through the skin into the receptor fluid and into the skin. But, if one compares the values for % of the applied dose of musk xylol found in the receptor fluid, the skin, and the total absorption, there was no significant difference in the penetration of musk xylol with respect to any of these pretreatment conditions.

Finally, if one looks at the thickness of the epidermis of the treated hairless guinea pigs, we have not yet measured the actual thickness (in microns) of the

epidermal layer (Slide 19). However, we have counted the epidermal cell layers in the slides made from skin with standard H & E sections. What we have seen is that in the untreated skin and also in the vaseline intensive care-treated skin, the epidermal layers are approximately 5 cell layers thick. With 5% Glycolic Acid, we see approximately a two-fold increase in thickness of the viable epidermal layer. With 10% Glycolic Acid, we see a little bit less, but not significantly less, of an increase in thickness of the viable epidermal layer.

It appears that under the conditions of our test, we don't see significant effects on the skin barrier layer in hairless guinea pig skin treated with 5% and 10% Glycolic Acid formulations.

Additional studies are ongoing. We want to look at stratum corneum layers, because the stratum corneum is probably the most important in terms of the barrier properties of the skin. In order to explain our results more completely, we are going to be studying frozen sections of skin (following chronic treatment of the skin with AHAs) in order to evaluate the appearance of the stratum corneum **[End of Dr. Bronaugh's presentation]**.

Dr. Slaga asked Dr. Bronaugh if he had conducted any studies using labeled compounds (e.g. bromodeoxyuridine incorporation), to determine how the cells are labeled as well as the actual turnover rate.

Dr. Bronaugh said that these types of studies have not been done.

Dr. Bailey made the following comments on AHAs: Alpha Hydroxy Acids are products that are formulated using organic acids, and these are acids in the true

sense. The alpha hydroxy nature makes them stronger acids; this is one of the reasons why they are used. FDA views these as relatively new products; they are being used as chemical exfoliants, not to simply adjust pH. AHA ingredients have been in existence for many years, but their introduction into the marketplace to the extent that they have been over the last few years is really a relatively new phenomenon. Furthermore, unlike most other cosmetic ingredients, we don't have a history of use of these chemicals. Lipsticks, lotions, and other types of products have been in existence for a long time, and we have a good sense of their relative safety.

Because AHAs are chemical acids, they have the potential for causing skin irritation, and it is no surprise that certain safety questions are raised. In addressing these safety of AHA ingredients, the following three areas of concern have been identified: (1) irritation, (2) effect on barrier properties of the skin, and (3) possible increase in sun sensitivity. These concerns have been communicated and discussed extensively over the last three or four years. FDA has committed significant resources over this period of time to address these concerns. These efforts include conducting a thorough review of the available data, which was completed in February, 1996, and included the unpublished data that were provided to CIR and FDA by the cosmetics industry. This was a comprehensive, critical review that has been released as a public document.

FDA has also been monitoring consumer adverse reactions, as well as conducting chemical analyses of products to help define what is in the marketplace. One of the issues that the Panel has frequently raised and that is also of concern to

FDA (along with the issue of pH) relates to current use levels of AHAs in cosmetic ingredients.

One of the things that FDA intends to do is to request a separate meeting with industry for discussion of the details of these studies as well as the issues and perspectives that will result from this discussion. Dr. Bailey concluded by noting that FDA is in the process of convening government experts within the various centers of FDA, the National Center for Toxicological Research and other agencies, to review the science that is associated with the ongoing studies and to decide what course of action would be appropriate within FDA's responsibilities.

Dr. Bergfeld wanted to know why FDA is in the process of convening experts in relation to its study of AHAs. She recalled that 69 adverse reactions to AHAs were reported a year ago, and wanted to know whether this effort is in any way based on FDA's monitoring of adverse effects.

Dr. Bailey said that it is quite normal for FDA to monitor for adverse reactions, and, in this case, the AHAs were targeted as separate products because they are chemical acids and have the potential for causing irritation. He said that FDA was interested in obtaining information indicating the types of reactions that have been reported.

Dr. McEwen remarked that industry is appreciative of the data on AHAs that was provided by FDA.

Dr. Bergfeld complimented industry on its response to the Panel's requests for data on AHAs and FDA for its involvement in the CIR review process at a higher level

than usual in relation to the present review of AHAs. She noted that FDA performed the skin penetration studies on AHAs that were reviewed by the Panel.

Dr. Bergfeld asked Dr. Belsito to elaborate on the Panel's deliberations thus far relative to the review of AHAs.

Dr. Belsito said that during the Panel's review of the report on AHAs, the following three areas of concentration were noted: (1) Irritation, and the effect of concentration and pH on that phenomenon, (2) Skin penetration, and (3) The potential for these chemicals, by virtue of their action on the stratum corneum and other layers of skin, to cause changes in the sensitivity of the skin to sunlight. Dr. Belsito noted that the data presented by FDA indicated that AHAs did not enhance the penetration of other chemicals through the skin. He also noted that the data submitted by industry indicated a slight, but significant, increase in skin sensitivity to sunlight associated with the use of AHAs. Based on these data and the skin irritation data that were reviewed, Dr. Belsito said that the Panel determined that a conclusion on the safety of AHAs in cosmetics could be made. He emphasized that the Panel's proposed conclusion does not apply to the use of AHAs by physicians; however, a conclusion relating to the use of AHAs by a cosmetologist was also proposed.

Dr. Belsito read the following two conclusions on the safety of AHAs that were proposed by the Panel: (1) Based on the available information included in this report, the CIR Expert Panel concludes that Glycolic and Lactic Acids, their common salts, and their simple esters are safe for use in cosmetic products at concentrations $\leq 10\%$ at final formulation pHs ≥ 3.5 , when formulated to avoid increasing the skin sensitivity to

sun, or when directions for use include the daily use of sun protection. (2) For the cosmetologist, Glycolic and Lactic Acids, their common salts, and their simple esters are safe for use at concentrations of $\leq 30\%$ at final formulation pHs ≥ 3 in products designed for brief, discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals and when applications are accompanied by directions for the daily use of sun protection.

The following comments were made by Dr. Bailey in response to the proposed conclusions:

The issue of increased sun sensitivity is important. The details of the sunburn cell test conducted by industry were not discussed today, as we have discussed the details of our work on skin penetration enhancement. There are really two studies that address the issue of increased sun sensitivity. The study on the effects of AHA treatment on MEDs (reviewed thoroughly in the FDA report provided in February) found that there was an increase in average sun sensitivity at 13.0% overall. However, in looking at the actual results, there were three of 19 subjects (skin types 1, 2, and, maybe, 3) in that study for which a 50% decrease in the MED was reported, a 100.0% increase in sun sensitivity. When these results are combined with the sunburn cell test, together they are significant in considering whether there are changes in sensitivity to sunlight.

I think that it is also worth pointing out that in the earlier discussions of sun sensitivity in the MED study that was reported, arguments concerning underlying "mechanical" mechanisms (whether the optics of the skin play a role) were raised. I

think that with the addition of the second study (sun burn cell test), optics is no longer an issue. Other possibilities need to be considered in terms of what is going on.

I think that it is worth keeping in mind that in the future, it may still be determined that increased sun sensitivity is not a problem. But, I have to say that the sunburn cell test data do not demonstrate that this is not a problem, and I think that this is the salient point.

Dr. Belsito said that, in principle, he agrees with the preceding comments made by Dr. Bailey. He also said that in reviewing the data, it was noted that the application of very mild concentrations of SLS (0.1%) to the skin seemed to create an enhancement of the MED. Furthermore, the enhancement induced by SLS seemed to have been greater than that induced by 10% Glycolic Acid.

Dr. Belsito noted that there were data on the use of mechanical abrasives and sun sensitivity. He recalled that the mechanical puff that was rubbed over the skin in one of the studies also seemed to increase the MED, and that this increase was not statistically different from that induced by the AHAs.

Dr. Belsito said that because of the issue of increased sun sensitivity and the data previously provided by FDA, the caveat relating to the formulation of products containing AHAs to avoid increasing the skin sensitivity to the sun, or the incorporation of the need for daily use of sun protection into directions for product use appears in the Panel's proposed conclusions on AHAs that were read.

Regarding industry's study on AHAs and sunburn cell formation, Dr. Bailey said that it is a bit misleading to rely only on averages, and that looking at the individual

responses within the group of test subjects points to some other areas that may be of concern. He noted that there is tremendous variation within the sunburn cell test in terms of responses, and this may have significance.

Dr. McEwen said that there were a number of other MED tests submitted by industry that indicated protective effects of products containing Glycolic Acid. He also said that, unquestionably, formulation is an issue with this ingredient as it is with all ingredients. That is, certain consumers will respond differently to one formulation than they will to another formulation. Dr. McEwen added that the statistics used in the sunburn cell tests are the most advanced and complete with respect to finding any type of response.

In explaining why industry did not make a presentation on AHAs at the present meeting, Dr. McEwen noted that around 150 unpublished studies were presented to the Panel and that it was not possible to present all of them. He also noted that the Panel's ability to review these data was sufficient.

Dr. Carlton said that in addition to the statements on AHAs and sun sensitivity in the report conclusion, additional comments relating to this area of concern should be included in the report discussion.

Dr. Bergfeld said that specific comments on AHAs and sun sensitivity for the report discussion will be discussed after the Panel's vote on the proposed conclusion on AHA's.

Ms. Fise made the following comments regarding the Panel's proposed conclusions on AHAs (See pp 29-30 for conclusion):

I think that probably the most important word in the conclusion is when. These are products that are safe when, followed by the caveat. I find this extremely troubling, and am concerned about the finding of safety. What the Panel is really doing is putting the onus on the consumer, because manufacturers could choose not to include in the formulation something that will provide protection from the sun, and, instead, leave this up to the consumer. I am concerned because of some of the studies indicating that consumers don't use sunscreens (40% or less in one study). I honestly believe that the burden should be on the industry to produce the formulation in a manner that results in safe use by the consumer at home.

With regard to the products for home use with AHA concentrations greater than 10%, I think that what the Panel's conclusion really means for consumer is that they should not be using these products, because the Panel cannot say that these products are safe. I want to remind you that these products are being sold with AHA concentrations as high as 30%.

With regard to professional use (the salon use of AHAs at concentrations of 30% with a pH of 3.0 or higher), there is reason for concern because this level of use relies on adequate protection from the sun, again, placing the burden on the consumer. I am very troubled and concerned about the prospective compliance by salon professionals, and whether the information relating to adequate sun protection is going to be communicated.

Whether it is home use or salon use of the AHAs, an additional concern that I have is with consumers taking prescription medications or OTC drugs that increase

their photosensitivity. They should not be using these products at all, or, if they do, should understand the risks that they are taking in doing so.

I am also reminded that there are still three products on the market that contain urocanic acid, and, in the past, these have been used in sunscreens. I would be particularly concerned about consumers using a sunscreen that contains urocanic acid while using AHAs.

Ms. Fise went on to say that the CFA is very pleased that FDA will be continuing its investigation and is looking forward to its guidance.

Dr. Slaga said that the effect of Glycolic Acid in bringing about a sustained hyperplastic effect in guinea pig skin should be discussed, because the potential for more turnover of the skin could lead to further sun damage if one is exposed.

Dr. Schroeter said that, perhaps, as the Panel instructs the consumer, consumers should be advised that it would possibly be injurious for them to be using other photosensitizing drugs that are being used for medication.

Ms. Fise said that consumers could continue taking their prescription medication and not use AHAs.

Dr. Belsito said that it is the duty of the physician and his staff to instruct a patient when that patient is taking a photosensitizing drug.

Dr. Bergfeld asked the Panel to vote on the conclusion on AHAs that was proposed.

The Panel voted unanimously in favor of issuing a Tentative Report on AHAs with the following conclusions:

Based on the available information included in this report, the CIR Expert Panel concludes that Glycolic and Lactic Acids, their common salts, and their simple esters are safe for use in cosmetic products at concentrations $\leq 10\%$ at final formulation pHs ≥ 3.5 when formulated to avoid increasing the skin sensitivity to sun, or when directions for use include the daily use of sun protection.

For cosmetologists, Glycolic and Lactic Acids, their common salts, and their simple esters are safe for use at concentrations of $\leq 30\%$ at final formulation pHs ≥ 3 in products designed for brief, discontinuous use followed by thorough rinsing from the skin when applied by trained professionals and when applications are accompanied by directions for the daily use of sun protection.

Dr. McEwen recalled that Ms. Fise had mentioned products containing urocanic acid in comments made earlier. He said that if there is a product with urocanic acid in it, it is not a product made by anyone in the United States, but one that is manufactured outside of the United States. He also said that FDA is taking action against that product.

Dr. Bailey said that it is important to keep in mind that in reviewing the Consumer Federation of America petition on urocanic acid, FDA has considered all of the data that were available and reached a conclusion based on these data. He added that the information that was developed as part of the CIR review process was relevant to FDA's review. Dr. Bailey noted that when FDA takes action and considers an appropriate response, the information in total is the basis for that response.

With respect to development of the report discussion, Dr. Belsito said that the

following main points should be made: (1) Irritation potential - On the basis of irritation, there was probably justification for a higher concentration allowable for Glycolic Acid, perhaps as high as 20.0%, and the limitation on Lactic Acid should remain at 10.0% . (2) The skin penetration data were "fairly clean" and did not influence a restriction. (3) The Panel's restriction is based on results of the sunburn cell studies, because they were done at a highest concentration of 10.0%, and not because there were significant data that were of concern at higher concentrations. Using the fact that there was a slight (but statistically significant) increase in sunburn cell formation, the Panel felt that it could rule on the safety of that. Furthermore, Dr. Belsito said that it should be stressed in the report discussion that the changes that were noted in the MED were not different from changes that one would expect with an abrasive or with a simple soap solution (as low as 0.1% SLS).

Dr. Belsito questioned how much the one particular outlier (with abnormal MEDs or elevated MEDs, even on skin that was untreated) in the sunburn cell study that seemed to skew the statistics should be discussed. He said that such data support Dr. Bailey's point that there is inherent variability in the population. Dr. Belsito noted that the Panel's recommendation to the manufacturers that products containing AHAs should be formulated so as either not to increase sun sensitivity or that there should be directions to use a daily sunscreen would, in effect, cover those outliers that may exist in the population.

Dr. Schroeter said that the decreased SPF that is seen in the skin should also be discussed. He noted that the effect of AHAs on the epidermis and cornified layer

has been well documented. Dr. Schroeter also said that points should be made in the discussion that the stinging and burning that occurs with product application should be reduced, and that there should be protection against ocular irritation. Additionally, he said that there should also be a paragraph in the discussion defining professional use.

Dr. McEwen noted that it had been mentioned that something should be said concerning the increased thickness of the epidermis that was observed in the FDA study. He said that it would be valuable to note in the discussion that the pH of the test compound was 3 in that study, which is below what the Panel has said would be reasonable for at home use or multiple applications.

Dr. McEwen also recalled that it had been mentioned earlier that the skin turnover rate with the vehicle control at pH 3 was the same as that noted for Glycolic Acid. Thus, he said that one may be seeing a pH phenomenon or an irritant response, rather than any effect of the AHA.

Dr. Bronaugh said that the pH 3 vehicle effects were noted initially in one or two animals, and an original decision was made to use vaseline intensive care lotion as a control. He noted that there were not enough data to perform a statistical analysis of this finding, which is the reason why this type of analysis is not presented in the report. Dr. Bronaugh said that it is important to note that pH is important in terms of causing this type of proliferation, and that it is important to choose a vehicle as a control that does not have the same pH as the AHA product that is being tested.

Dr. McEwen said that if pH causes the hyperproliferation, how can it be said that the AHA is causing the hyperproliferation.

Dr. Bronaugh said that he does not think that anyone understands the mechanism that is responsible for the hyperproliferation.

Dr. Klaassen wanted to know if hyperproliferation was observed in humans in the sunburn cell study.

Dr. McEwen said that this was not remarked upon by the investigators. He also said that the slides are available.

Regarding the study on sunburn cell formation in humans, Dr. Shank said that he would not refer to the subjects who responded significantly differently from the mean as outliers, and that they should not be referred to as such in the report discussion. He said that there was a lot of variation in the responses that were observed. Some subjects had an increase in MED, that is, they were less sensitive to light; some did not change appreciably; and some changed considerably. Furthermore, he said that the variation noted in this study is a strong reason why the Panel wanted some kind of sun protection mode, protection against an increase in sun sensitivity.

Additionally, Dr. Shank recalled that Ms. Fise had mentioned urocanic acid in comments that were made earlier. He confirmed that the Panel had issued an insufficient data conclusion on this ingredient, and wanted to know whether it is necessary for the Panel to state in the AHA report discussion that urocanic acid should not be used as a sunscreen with AHAs.

Dr. Andersen noted that as recently as two Panel meetings ago, the Panel reaffirmed its conclusions on urocanic acid, stating that there are insufficient data to support safety.

In response to Dr. Shank's question on the use of urocanic acid, Dr. McEwen said that urocanic is used in a product that was imported into the United States.

Dr. Bailey said that there are three products containing urocanic acid that are registered (valid registrations) in FDA's voluntary program. He also noted that the products are from a foreign manufacturer, and, presumably, are imported into the United States.

Dr. Bergfeld noted that a recommendation had been made that the report discussion contain a statement indicating that photosensitizing drugs should not be used with AHAs. She said that it is possible to add one chemical (urocanic acid) to this statement, if this is deemed necessary by the Panel.

Dr. McEwen clarified that urocanic acid was not used as a sunscreen in the United States, but that it was being used in Europe as a sunscreen at concentrations higher than those in the United States. He also noted that manufacturers in the United States discontinued use of the product before the Panel's conclusion was finalized.

Dr. Bailey said that urocanic acid is not an approved sunscreen in the United States; however, at one time, it was added to products and its functionality could be debated. He also said that it is understood that urocanic acid has sunscreen properties.

Ms. Fise said that it would be very helpful to include information on urocanic acid as a cross-reference to the CIR Final Report on Urocanic Acid in the AHA report discussion.

All of the Panel members concurred with Ms. Fise's proposal to mention urocanic

acid in the AHA report discussion, as stated in the preceding paragraph.

Dr. Bergfeld called for discussion of the possible inclusion of the American Academy of Dermatology's (AAD) recommendation for sun protection in the AHA report discussion. The AAD's recommendation was stated by Dr. Bergfeld as follows: The sun avoidance between the hours of 10:00 a.m. and 4:00 p.m., a reduced exposure, the use of sunscreens with SPF of 15 (the broad spectrum), and use of protective clothing and hats.

Dr. Bergfeld noted that the AAD's recommendation is applicable to the Panel's discussion of sun sensitivity and sun protection.

Ms. Fise recalled that both of the Panel's conclusions on AHAs refer to daily use of sun protection.

The Panel agreed that the AAD's recommendation for sun protection should be included in the AHA report discussion.

Dr. Belsito said that another issue that should be addressed in the report discussion is the absorption of AHAs across the skin. He noted that because of the complete lack of any other significant toxicological data, the absorption of AHAs through and across the skin was not considered problematic for the chemicals and concentrations discussed by the Panel. Dr. Belsito requested that the preceding statement be included in the discussion.

Dr. Carlton suggested that the statements proposed for the report discussion that relate to sun protection be directed to individuals within the population who are comparable to the subjects with a decreased MED (i.e. increased sun sensitivity)

following AHA exposure in the sunburn cell study.

Dr. Belsito agreed with Dr. Carlton's comments. He said that his Team had determined that the 10% concentration limit for AHAs in consumer products and the pH limitation ($\text{pH} \geq 3.5$) for such products would not create a problem for the vast majority of individuals. However, it was also acknowledged that there are individuals who are extremely sensitive who would need protection, and that the strict emphasis on sun protection is for those individuals undergoing superficial peels, under the direction of cosmetologists, with pHs of 3 and concentrations as high as 30%.

Ms. Fise said that if the report discussion somehow implies that only a small segment of the population needs to be concerned about sun protection while using AHA-containing products, then the concern about increased sun sensitivity will be greatly minimized. She also said that because the average consumer generally will have no idea as to whether or not he/she is included in the at risk group, from the standpoint of safety, the Panel needs to make sure that the directions for sun protection are meant for everyone.

Dr. Shank said that Ms. Fise's comments explain why he objected to use of the term outlier (atypical subjects) in describing the subjects in the sunburn cell study with increased sun sensitivity following AHA treatment. He said that the Panel has no idea as to what proportion of the population will be very sensitive, mildly sensitive, or not sensitive, and, therefore, the Panel's recommendations should be concerned with the protection of everyone.

Dr. Schroeter said that the presence of sunburn cells is not only an indication of

injury, but also represents a normal response of the epidermis to cytokines to eliminate those cells presumed to have DNA damage. Dr. Schroeter also noted that the sunburn cell is not an abnormality, but is only reflective of an injury. Thus, the subjects in the sunburn cell study with increased sun sensitivity should not be considered as outliers. He added that those subjects with highest numbers of sunburn cells may be the subjects who are protecting themselves the most. Dr. Schroeter also said that data are not available to support a conclusion beyond stating that the protection from the sun should be for all who use products containing AHAs.

Dr. Belsito recalled that when the design of the experiments was discussed with industry, the Panel selected a subpopulation that was most likely to respond by requesting that patients with skin type 1 (which essentially means that "you go out in the sun and you burn immediately") or skin type 2 (which means that "you go out in the sun for small amounts of time and you burn") be selected. Therefore, these studies were not done on a representative sample of the population.

Dr. Slaga said that not much is known about sunburn cells, except that these cells are progressing toward death. However, he noted that as sun exposure increases, there is also increased sunburn cell formation, and that this correlates with UV damage.

Dr. Bergfeld noted that at this point, the AHA report needs to be modified as follows: (1) Finalize the conclusion of safety with some restrictions and (2) Develop a discussion that will be mailed to Panel members for review prior to public announcement of the Tentative Report.

Dr. Bergfeld congratulated the CIR staff for its assistance and the Panel for the

excellent manner in which the review of this group of ingredients was conducted.

PEG-5, -10, -16, -25, -30, and -40 Soy Sterol

Dr. Belsito recalled that at the June 3-4, 1996 Panel meeting, the Panel determined that the available data were insufficient for evaluating the safety of these ingredients and issued an Insufficient Data Announcement. It was noted that data were not received in response to this announcement.

After further review of the Draft Report, Dr. Schroeter noted that his Team determined that only one genotoxicity assay (mammalian system) is needed because bacterial mutagenicity data are included. It was also determined that impurities data are still needed, but that the specification relating to the amount of 3-hydroxysterol that is present should be deleted from the request. Dr. Schroeter said that in modifying this request, hopefully, information will be provided on all of the impurities that may be present.

Dr. Shank requested that the lowest molecular weight PEG Soy Sterol being reviewed (PEG-5 Soy Sterol) be tested in the mammalian genotoxicity assay.

The Panel voted unanimously in favor of issuing a Tentative Report on PEG -5, -10, -16, -25, -30, and -40 Soy Sterol with an insufficient data conclusion. The data needed in order for the Panel to complete its safety assessment of these ingredients are listed in the discussion section of the report as follows:

- (1) Impurities data
- (2) Concentration of use
- (3) One genotoxicity assay on PEG-5 Soy Sterol in a mammalian system; if positive, then a 2-year dermal carcinogenicity study using NTP methods will

be needed

- (4) Dermal sensitization and irritation in humans (at concentration of use)
- (5) Dermal absorption of PEG-5 Soy Sterol; if significantly absorbed, then a 28-day dermal toxicity study and reproductive and developmental toxicity data may be needed. Alternatively, data showing that dietary intake results in the release/availability of phytosterols would suffice

PPG-9, -25, and -40 Diethylmonium Chloride

The Panel voted unanimously in favor of issuing a Tentative Report with an insufficient data conclusion. The data needed in order for the Panel to complete its safety assessment of this group of ingredients are listed in the discussion section of the report as follows:

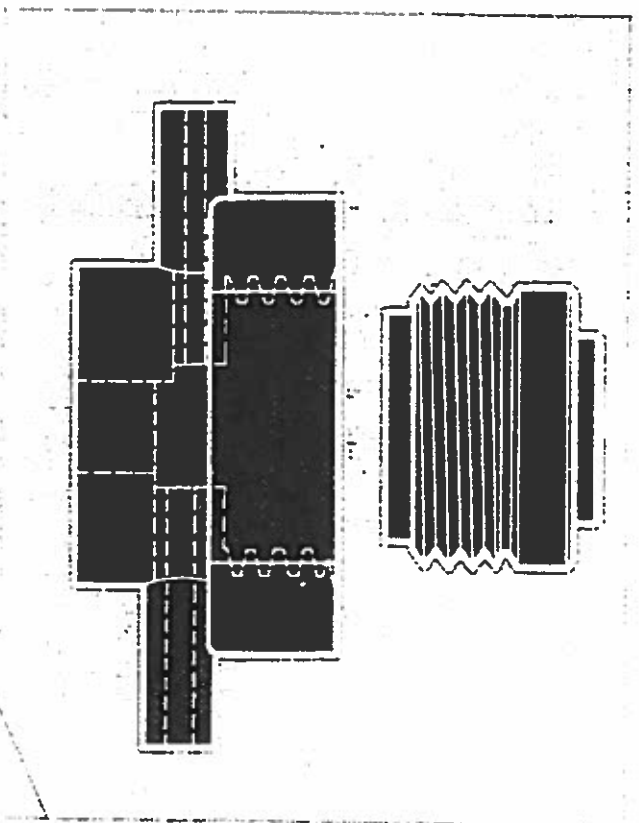
- (1) Concentration of use
- (2) Dermal absorption using PPG-9 Diethylmonium Chloride; if significantly absorbed, then a 28-day dermal toxicity study will be needed
- (3) Two genotoxicity assays on PPG-9 Diethylmonium Chloride; if positive, then a 2-year dermal carcinogenicity study using NTP methods will be needed
- (4) Dermal sensitization and irritation (at concentration of use)
- (5) Impurities data, especially nitrosamines

Stearalkonium Hectorite

Dr. Belsito recalled that at the September 19-20, 1996 Panel meeting, a letter addressing the impurities data on this ingredient was received from Dennis Laba of Rheox (manufacturer of Stearalkonium Hectorite). In the letter, it was argued that because of the impurities data, genotoxicity studies involving a mammalian system would not be needed, taking into consideration the tight binding of the stearalkonium moiety to the hectorite moiety and the limited impurities that would be able for release from this tightly bound molecule. Dr. Belsito noted that his Team was able to conclude

Percutaneous Absorption Studies

- Use of excised human skin in diffusion cells
- Maintenance of skin viability
- Simulate conditions of exposure during product usage



Oil in Water Emulsion (Formulation A)

5% Alpha Hydroxy Acid

<u>Ingredient</u>	<u>Grams</u>
Polyoxyethylene (100) glycerol stearate	2
Mineral oil	10
Cetearyl alcohol	3
Laureth-4	1
Propylene glycol	5
Alpha hydroxy acid	5
Phthalate-HCl buffer	73
Parabens	1

Glycolic Acid Absorption

Formulation A (5%)

Percent Applied Dose Absorbed

LOCATION	<u>pH 3.0</u>	<u>pH 7.0</u>
Receptor Fluid	2.6 ± 0.7	0.8 ± 0.3
Stratum Corneum	5.8 ± 2.8	1.2 ± 0.4
Viable Epidermis	6.6 ± 2.5	0.8 ± 0.3
Dermis	12.2 ± 1.4	0.6 ± 0.2
Total in Skin	24.6 ± 4.0	2.6 ± 0.6
Total Absorption	27.2 ± 3.3	3.5 ± 0.9

2-Hydroxyhexanoic Acid Absorption

Formulation A (5%)

Percent Applied Dose Absorbed

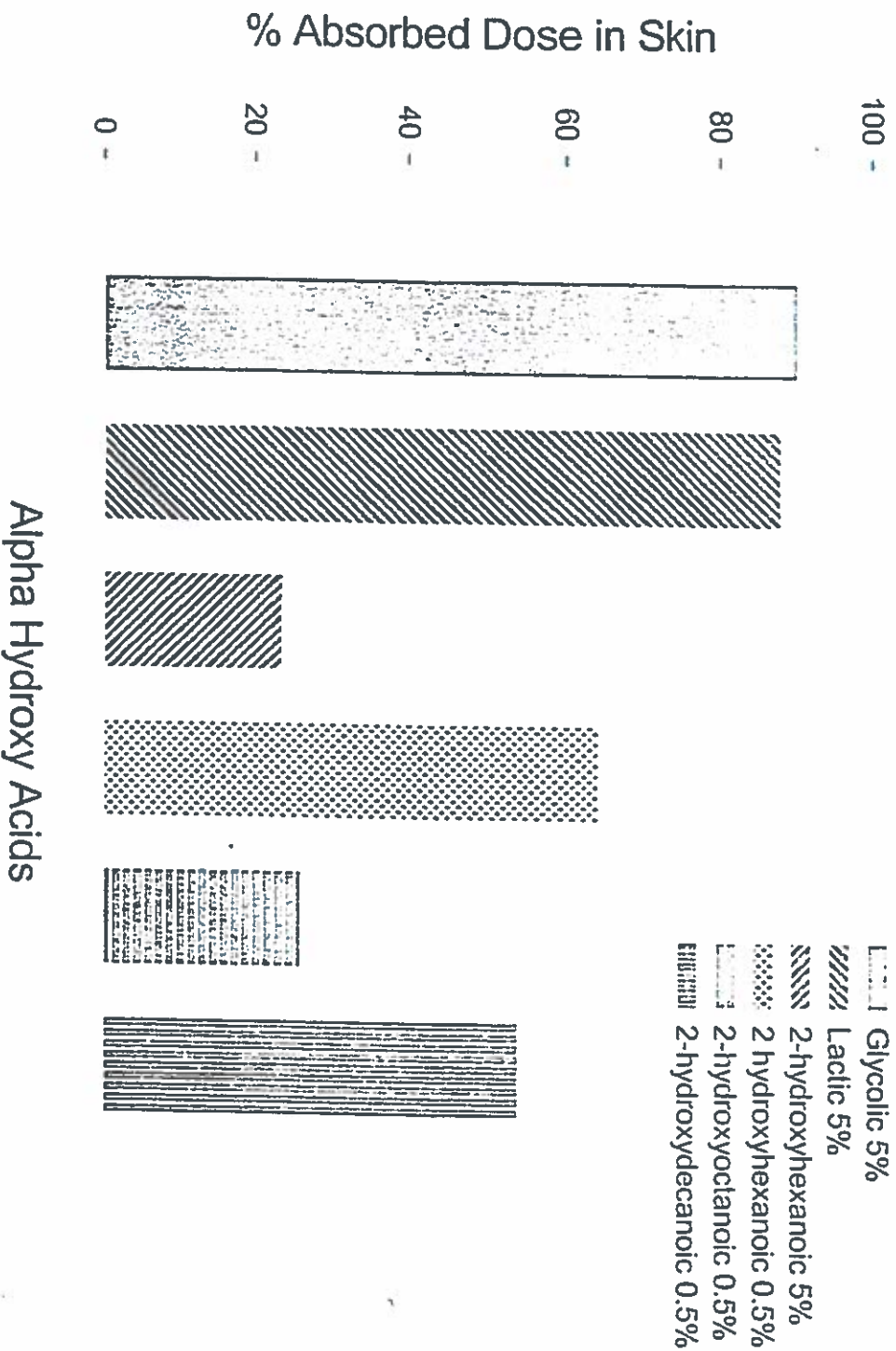
LOCATION	pH 3.0	pH 7.0
Receptor Fluid	32.9 ± 2.6	1.0 ± 0.2
Stratum Corneum	3.4 ± 0.4	2.8 ± 0.3
Viable Epidermis	2.8 ± 1.4	3.7 ± 1.3
Dermis	4.0 ± 1.8	2.0 ± 0.3
Total in Skin	10.2 ± 3.3	8.4 ± 1.0
Total Absorption	43.1 ± 5.9	9.4 ± 1.1

AHA Absorption, 0.5%, pH 3.0

Percent Applied Dose Absorbed

LOCATION	<u>2-Hydroxy- Hexanoic Acid</u>	<u>2-Hydroxy- Octanoic Acid</u>	<u>2-Hydroxy- Decanoic Acid</u>
Receptor Fluid	10.1 ± 2.7	15.4 ± 3.1	8.8 ± 2.5
Stratum Corneum	3.2 ± 0.9	1.4 ± 0.3	2.6 ± 0.6
Viable Epidermis	8.4 ± 1.1 ^a	2.8 ± 0.4 ^{a,b}	5.8 ± 0.9 ^b
Dermis	6.7 ± 0.7 ^{a,b}	1.4 ± 0.2 ^a	2.1 ± 0.3 ^b
Total in Skin ¹	18.3 ± 2.6 ^{a,b}	5.5 ± 0.9 ^a	10.5 ± 1.0 ^b
Total Absorption	28.4 ± 3.9	21.0 ± 2.5	19.3 ± 3.1

Effect of AHA Chain Length on Skin Levels



Measurement of Skin Turnover

- ☐ Dansyl chloride is applied to hairless guinea pig back skin
- ☐ Loss of fluorescence is observed each day with a UV light



Hairless Guinea Pig Pretreatment

Three week dosing prior to absorption studies

- ❑ HGP #1 dosed with 5% glycolic acid and VIC
- ❑ HGP #2 dosed with 10% glycolic acid and VIC
- ❑ Untreated skin taken from both HGPs
- ❑ Above 2 HGP experiment repeated 2 times

In Vitro Hydroquinone Absorption

Percent of Applied Dose Absorbed

PRETREATMENT FORMULATIONS				
	Untreated	Vaseline IC	5% Glycolic Acid	10% Glycolic Acid
Receptor Fluid	4.3 ± 0.6	5.9 ± 0.3	6.4 ± 0.9	4.4 ± 0.5
Skin	15.0 ± 0.7	13.2 ± 1.1	15.4 ± 1.0	16.1 ± 1.8
Total	19.3 ± 0.4	19.0 ± 1.0	21.8 ± 1.9	20.5 ± 2.1

June 1997

will be targeted, more so, to an international audience.

Dr. Andersen encouraged those who have not done so to access the CIR homepage, which has evolved into an extremely important method of communication. He said that CIR still provides all CIR announcements to its mailing list; however, a much broader audience is reached via the internet.

Finally, Dr. Andersen noted that efforts to include the complete set of published CIR Final Reports among the various CTFA electronic products (currently available) are underway. The CIR database, which will provide searchable access to this information, is under development, and the data entry phase is to be initiated this year.

APPROVAL OF FINAL REPORTS

Glycolic and Lactic Acid, their common salts, and simple esters

Dr. Belsito noted that comments were received from the Consumer Federation of America during the 90-day, public comment period for the Tentative Report. Some of the comments relate to the Panel's discussions on the use of urocanic acid-containing sunscreens and how to address the matter of patients using medications that have the potential for inducing photosensitization. The comment that Dr. Belsito's Team determined should not be included relates to the matter of patients who are taking photosensitizing medications. The Belsito Team continues to believe that this is a matter that is strictly between the patient and physician, and that it is not the responsibility of the cosmetic companies to alert patients to photosensitizing medications.

Dr. Belsito said that another comment, received from 3M Company, concerns the statistical analysis of the data from the sunburn cell study and whether the Bon Feroni adjustment of the data was correct. Dr. Belsito's Team concluded that both statistical analyses of the sunburn cell data that were provided should be included in the current report on AHAs. The Belsito Team also discussed making changes in the body of the text, as well as in the discussion, to indicate more clearly that Glycolic Acid significantly increased (compared to vehicle control) the number of sunburn cells. However, Dr. Belsito noted that uncertainty regarding the significance of this finding was expressed, and, also, that this effect could be prevented by using a sunscreen with an SPF of 2.

The Belsito Team determined that neither of the comments received substantively changed the Panel's original conclusion, which reads as follows: 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.

Dr. Schroeter proposed that the following statement relating to use of photosensitizing medications be deleted from the report discussion: While agreeing

with the basic need to alert individuals using such medications of the need to avoid sun exposure, the Expert Panel concluded that this concern was best left to the interaction between the prescribing physician, dispensing pharmacist, and the individual. Dr. Schroeter noted that this comment is not needed because it implies that the Panel could make this type of recommendation, and because it generates confusion. He also said that the purpose of the present review is to define safety, which is evident in terms of the analyses of the sunburn cell data that have been provided and the statement in the report conclusion to the effect that AHA products are safe when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection.

Dr. Belsito noted that his Team had suggested that the 3M Company's statistical analysis of the sunburn cell study should be included in the report discussion. He said that this should be done to bring attention to the fact that the Dunnett method could also be used for statistical analysis of the sunburn cell data.

Dr. Andersen noted that a bar chart (histogram) representing the conclusion of 3M Company's statistical analysis was submitted, but, as noted during Team discussions, this information does not provide enough detail in terms of the actual results. He said that if this information were presented graphically, it would be possible to visualize the range of the data points (error bars included) and the degree of scatter. With this in mind, Dr. Andersen stated that a graphical presentation of results of the statistical analysis will be included in the AHA report.

Referring to page 183 of the AHA report (sunburn cell study), Dr. Carlton called

the Panel's attention to the following text: 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, but only a marginal increase was observed when Glycolic Acid-treated skin was compared to skin treated with the sponge. He noted that the shaded portion of this statement was revised by the Belsito Team to read as follows: When comparing the Glycolic Acid group to the mechanical sponge using the analysis provided by the investigators, there was no significant difference. In analyzing the data in an alternate method, there was a significant difference (3M report cited).

Dr. Belsito noted that the revision actually indicates that depending on the statistical method used, there may or may not be a statistically significant difference between the use an exfoliating sponge and Glycolic Acid treatment. He added that similar language (see preceding paragraph) should be incorporated into the report discussion as well.

Dr. McEwen recalled from the Team discussions of the sunburn cell study (p. 183 of AHA report) that information on the magnitude of the results would be included in the report, relating it to MEDs (i.e. the # of sunburn cells at MEDs of 0.5, 1.0, and 1.5) and showing that the geometric mean relates to an MED of 1.5.

Dr. Andersen noted that data on the calibration of sunburn cell production as a function of UV exposure is currently presented on page 184 of the AHA report. Furthermore, he said that this information will be mentioned in the report discussion as a point of comparison, to determine the relative significance of the data on glycolic and

lactic acid.

Dr. Klaassen recommended the inclusion of values for the mean and standard error at the bottom of Tables 39 and 40 (data from sunburn cell study).

Ms. Fise asked that the minutes reflect the rationale for the Consumer Federation of America's comments on alerting the public of the need for sun protection when using photosensitizing medications. She said that such comments relate to the fact that 40%, or less, of consumers use sun protection. Furthermore, she noted that it was the Consumer Federation of America's concern that not only pharmacists and physicians may be misinformed, but consumers and manufacturers as well.

The Panel voted unanimously in favor of issuing a Final Report with the following 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.

The Panel also approved the revisions in the text and report discussion that were discussed.

Dr. Bergfeld asked Dr. Bailey to update the Panel on FDA's activities concerning



AHAs.

Dr. Bailey commended CIR for undertaking such a significant task as the review of AHAs, and noted that FDA has a supplement of all of the data that have been provided, as well as the CIR report on AHAs. He also announced that FDA has nominated AHAs for further study by the National Toxicology Program. This action means that FDA has already identified the safety issues and developed a discussion of these issues. Dr. Bailey noted that all of the industry data on AHAs and the CIR report on AHAs were forwarded through the FDA approval process, reviewed by FDA's toxicologists, and forwarded to the National Toxicology Program as the agency priority nomination. The end result was the acceptance of AHAs as FDA's priority nomination by the NTP executive committee. NTP's selection of AHA's has been announced and comments have been solicited for the record. Dr. Bailey informed the Panel that the 90-day comment period will close in a couple of weeks, and that CIR is free to recommend (for the record) any additional tests that would resolve the questions concerning the safety of AHAs. Furthermore, he stated that FDA will be working collaboratively with NTP to design studies that will allow the two groups to reach an endpoint regarding the safety of AHAs.

Dr. Bailey noted that, internally, FDA has convened a team of toxicologists and individuals who are knowledgeable of the various issues that were identified, discussed the data, and generated a document that describes the types of toxicology tests that would be necessary for addressing the safety of AHAs. This document will be used to interface with NTP in the process of actually designing studies that will serve to

address the safety of AHAs.

Dr. Bergfeld asked Dr. Bailey to reiterate the specific issues that will be examined.

Dr. Bailey said that NTP indicated in its publication that the long-term effects of dermal irritation and photocarcinogenicity will be studied; so, FDA is contemplating a photocarcinogenicity test of some type. Dr. Bailey noted that FDA understands the toxicological complications (in terms of models) associated with studying photocarcinogenicity, and will work very hard to make sure that these studies are as relevant and meaningful as possible. He also said that FDA's proposals for testing are not limited to dermal irritation and photocarcinogenicity, and that there may be other short-term tests that may be considered. Dr. Bailey recalled that tests on thymine dimer formation had been mentioned by the CIR Expert Panel, and might be considered by FDA.

Dr. Bailey said that in considering the dermal irritation potential of AHAs, one of the questions that arises relates to the promotion of carcinogenic effects induced by other substances. In other words, the skin irritation effect may cause an individual to become more susceptible to the carcinogenic effects of other substances.

Dr. Bergfeld asked Dr. Bailey if "cosmetic-like" concentrations and pH are being dealt with, or the entire spectrum of the AHAs.

Dr. Bailey said that this has not been decided totally, and that he thinks that FDA is more interested in, but may not be limited to, the mass market uses.

Ms. Fise wanted to know approximately when the NTP study will be completed, and, in the meantime, what FDA will be doing in terms of educating the consumer on

the use of AHAs.

Dr. Bailey said that the period between nomination of a chemical by NTP and the issuance of a final report may actually be five years. The following points were made by Dr. Bailey in response to Ms. Fise's concern about educating the consumer on the use of AHAs:

FDA probably has a body of data that can be reviewed in terms of the proper agency response at this point in time. The response could include consumer education and requiring warning statements on products. The best approach for dealing with these ingredients in products has not been decided. After all, there are hundreds of AHA products, many different types of formulations. To date, FDA has placed a statement regarding the use of AHAs on its homepage. The following issues are addressed in this statement: how people can identify products that contain AHAs, the issue of sun sensitivity, and the importance of using sunscreens or sun protection. The development of this statement is the first step in the process of consumer education.

Dr. Bergfeld asked Dr. Bailey for FDA's time frame on the consumer education program - warning system.

Dr. Bailey said that the agency is going to move as quickly as possible on this.

Dr. McEwen said that, based on his recollection, NTP proposed phototoxicity testing or chronic testing. He did not recall any proposal for photocarcinogenicity testing.

Dr. Bergfeld recommended that physicians, especially dermatologists, be alerted to the fact that there may be some sun sensitivity, because they are unknowledgeable

at this point in time. She said that most physicians, at least dermatologists, are aware of the irritation and slight stinging and burning that occurs in some patients, especially with the peels. She also said that a broader informational piece for physicians would be helpful.

Dr. McEwen suggested that someone, perhaps Dr. Bergfeld, on the Expert Panel may want to develop a statement for physicians that could be published in a journal.

It is important to reiterate that earlier in the discussion, the Panel voted unanimously in favor of issuing a Final Report with the following 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.

Acid Orange 3

Dr. Schroeter noted that a Tentative Report was issued at the December 16-17, 1996 Panel meeting, and that no comments were received during the 90-day public comment period. He also noted that the following conclusion on the safety of Acid

Orange 3 was approved by the Panel: On the basis of the animal and clinical data included in this report, the CIR Expert Panel concludes that Acid Orange 3 is safe for use in hair dye formulations at concentrations \leq 0.2%.

Dr. Bailey said that based on the structure of Acid Orange 3, he would predict that it contains impurities such as benzidine 4-aminobiphenylalanine and other free aromatic amines, which would need to be addressed in terms of their risk to the consumer. He noted that, many years ago, FDA banned a dye that is not too dissimilar to Acid Orange 3 because of its aromatic amine content. Furthermore, he noted that benzidine and 4-aminobiphenyl are very potent human carcinogens.

Dr. Shank said that the carcinogenicity of impurities is no longer a concern because of the negative dermal carcinogenicity data on Acid Orange 3 in the Tentative Report.

Dr. Belsito recalled that the Panel's concentration limit of 0.2% is the test concentration of Acid Orange 3 in the two-year skin painting carcinogenicity study.

The Panel voted unanimously in favor of issuing a Final Report with the following conclusion: On the basis of the animal and clinical data included in this report, the CIR Expert Panel concludes that Acid Orange 3 is safe for use in hair dye formulations at concentrations \leq 0.2%.

PPG-9, -25, and -40 Diethylmonium Chloride

Dr. Belsito noted that a Tentative Report with an insufficient data conclusion was issued at the December 16-17, 1996 Panel meeting, and that neither comments nor

Safety Assessment of Alpha Hydroxy Acids as Used in Cosmetics

Status: Re-Review for Panel Review
Release Date: November 15, 2013
Panel Meeting Date: December 8-9, 2013

The 2013 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This re-review document was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer.

TABLE OF CONTENTS

Introduction.....	1
Discussion from the 1998 Report.....	1
Use.....	3
Cosmetic	3
Industry Guidance	3
Adverse Reactions.....	4
Toxicokinetics.....	4
Penetration Enhancement.....	4
Toxicological studies	4
Repeated Dose Toxicity	4
Inhalation	4
Reproductive and Developmental Toxicity	4
Carcinogenicity	5
Anti-Proliferative Effects/Pro-Apoptotic Effects.....	5
In Vitro.....	5
Tables.....	6
Table 1. Current and historical frequency and concentration of use of AHAs according to duration and exposure	6
Table 2. AHAs not in current use according to VCRP and Council survey data	8
References.....	9

INTRODUCTION

A very robust assessment of the safety of the use of alpha hydroxy acids (AHAs) in cosmetics was published by the Cosmetic Ingredient Review (CIR) Expert Panel in 1998.¹ The Panel concluded 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. The report included the following 22 ingredients:

Glycolic Acid	Lactic acid
Ammonium Glycolate	Ammonium Lactate
Calcium Glycolate	Calcium Lactate
Potassium Glycolate	Potassium Lactate
Sodium Glycolate	Sodium Lactate
Methyl Glycolate	TEA-Lactate
Ethyl Glycolate	Methyl Lactate
Propyl Glycolate	Ethyl Lactate
Butyl Glycolate	Isopropyl Lactate
	Butyl Lactate
	Lauryl Lactate
	Myristyl Lactate
	Cetyl Lactate

Because it has been 15 years since the original report was published, the Panel is being asked to determine whether the safety assessment of these ingredients should be re-opened or, alternatively, the original conclusion should be reaffirmed. One ingredient, TEA-lactate, was re-reviewed in 2013 as part of the CIR safety assessment of triethanolamine and triethanolamine-containing ingredients as used in cosmetics.² In that safety assessment, the Panel concluded that TEA-lactate is safe as used when formulated to be non-irritating and when the levels of free diethanolamine do not exceed the present practices of use and concentration found to be safe for diethanolamine, and triethanolamine-containing ingredients should not be used in cosmetic products in which *N*-nitroso compounds can be formed. The highest reported maximum use concentration was 0.06% for TEA-lactate in leave-on formulations and 6% for triethanolamine in a leave-on product.

Relevant published reports that have become available since the CIR safety assessment of AHAs was issued in 1998 are listed at the end of this document.³⁻⁴¹ However, only sections that contain the noteworthy new data are included. The Discussion section of the original 1998 safety assessment is presented here; the Panel can refer to the original report for all of the data that was considered in that assessment of safety.

DISCUSSION FROM THE 1998 REPORT

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 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 UVB 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.⁴² 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.

USE

Cosmetic

The AHAs are often reported to function in cosmetics as exfoliants or pH adjusters (Table 1).⁴³ Lactic acid and some of the lactates also function as skin conditioning agents. The Food and Drug Administration (FDA) collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). VCRP data obtained from the FDA in 2013,⁶ and data received in response to a survey of the maximum reported use concentration by category conducted by the Personal Care Products Council (Council), indicate that 14 of 21 AHAs named in this review are in current use.

The current and historical frequency and concentration of use data for the AHAs are provided in Table 1. According to VCRP data, the frequency of use of the AHAs has increased considerably since the original assessment; glycolic acid was used in 42 formulations in 1997, but now is reported to be used in 337 cosmetic formulations, and lactic acid was reported in 342 formulations in 1997, but is now reported to be used in 1042 formulations.⁶ The maximum use concentrations of glycolic acid increased considerably as well, from 20% (1995 data) to up to 50% in face and neck products and in skin cleansing preparations; however, use concentrations for all other categories are $\leq 10\%$. The leave-on use concentration of lactic acid decreased slightly, from 11.8% to 10.1%, but the highest maximum use concentration increased to 30% in bath capsules.

According to the survey conducted by the Council in 2013, the highest maximum concentration of use reported for any of the AHA ingredients is 95% ethyl lactate in "other" manicuring formulations, and 50% for ethyl lactate in nail polish and enamel removers. Myristyl lactate is reported to be used in 215 formulations, with a highest maximum reported use concentration of 13.2% in lipsticks. All the other AHAs named in this report have 51 or less uses, and are used in leave-on products at $\leq 10.2\%$. Seven ingredients are not reported to be used; these ingredients are listed in Table 2.

Some AHAs are used in formulations that could possibly be inhaled. For example, glycolic acid is reported to be used in aerosol and pump hair sprays at concentrations of 0.0005 and 0.05%, respectively, and lactic acid is used in aerosol propellant hair spray formulations at a concentration of 0.0002% and in tonic, dressing, and other hair grooming aids pump spray formulations at concentration of 5.8%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters $>10\ \mu\text{m}$, with propellant sprays yielding a greater fraction of droplets/particles $<10\ \mu\text{m}$ compared with pump sprays.^{44,45} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.^{46,47}

Industry Guidance

In 2000, the Cosmetic, Toiletry, and Fragrance Association (CTFA; now known as the Personal Care Products Council, or Council) submitted a citizen's petition that advocated sun-protection labeling for cosmetic products containing AHAs as ingredients.⁵ In the petition, the CTFA requested that FDA issue a regulation under 21 U.S.C. 362(a) establishing labeling requirements addressing the need for sun protection with use of certain cosmetic products containing AHAs. The petition proposed the following regulation for 21 CFR Part 701-Cosmetic Labeling:

The label and labeling of a cosmetic product that contains an alpha hydroxy acid ingredient that is intended to function as an exfoliant shall bear the following prominent and conspicuous statement:

"Sun Alert: Because this product may make your skin more sensitive to the sun, be certain you have adequate sunscreen protection while using this product and for a week after you discontinue use."

In 2005, the FDA issued a "Guidance for Industry: Labeling for Cosmetics Containing Alpha Hydroxy Acids."⁵ The FDA considered evidence that suggested that topically applied cosmetic products containing AHAs as ingredients may increase the

sensitivity of skin to the sun while the products are used, and for up to a week after use is stopped, and that this increased skin sensitivity to the sun may increase the possibility of sunburn. The FDA stated that the purpose of their guidance was to educate consumers about the potential for increased skin sensitivity to the sun from the topical use of cosmetics containing AHAs as ingredients and to educate manufacturers to help ensure that their labeling for cosmetic products containing AHAs as ingredients is not false or misleading. The FDA recommended that the labeling of a cosmetic product that contains an AHA as an ingredient and that is topically applied to the skin or mucous membrane bear a statement that conveys the following information:

Sunburn Alert: This product contains an alpha hydroxy acid (AHA) that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen, wear protective clothing, and limit sun exposure while using this product and for a week afterwards.

The statement appear prominently and conspicuously once in the labeling of a cosmetic product. This guidance does not apply to drug-cosmetic products that contain an AHA as an ingredient and also are labeled to contain a sunscreen for sun protection.

In 2004, the European Union Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) issued a position paper concerning consumer safety of AHAs; this paper was an update of the 2000 SCCNFP position paper.¹³ After reviewing data on effects of AHAs on skin barrier function and UV skin sensitivity, the SCCNFP maintained its previous opinion, which stated that glycolic acid may be used safely at levels up to 4% and pH ≥ 3.8 and lactic acid can be used up to a maximum level of 2.5% and pH ≥ 5.0 ; it was also recommended that contact with eyes be avoided and that UV protection be used when using cosmetic products containing AHAs.¹² The original position paper reviewed phototoxicity and skin irritation studies of AHAs.

Adverse Reactions

The FDA received a total of 114 adverse dermatologic experience reports for AHA-containing skin care products between 1992 and February 2004.⁷ The reported adverse experiences included: burning (45); dermatitis or rash (35); swelling (29); pigmentary changes (15); blisters or welts (14); skin peeling (13); itching (12); irritation or tenderness (8); chemical burns (6); and increased sunburn (3). The maximum number of reports was received in 1994; the frequency of such reports for skin exfoliating products that contain AHAs was considerably lower in subsequent years. The more serious adverse reactions appeared to occur most often with products that cause the greatest degree of exfoliation, such as "skin peelers."

TOXICOKINETICS

Penetration Enhancement

The effect of glycolic and lactic acid, 1% and 5%, on penetration enhancement through human epidermal samples was evaluated using a hydrophilic compound (5-flouracil) and three phenylalcohols.²⁰ The decrease in the permeability coefficient was dependent on the concentration of the AHA and the lipophilicity of the compound. Lactic acid had a greater effect on penetration than glycolic acid (or sodium lauryl sulfate), and concentration of the acids also played a role. There were statistically significant differences in permeability coefficients through the skin samples to which glycolic or lactic acid, was applied, compared to the control samples, for all except the most lipophilic compound assayed (i.e., 5-phenylpentanol); for this compound, lactic acid, but not glycolic acid, increased the permeability coefficient in a statistically significant manner.

TOXICOLOGICAL STUDIES

Repeated Dose Toxicity

Inhalation

(Repeated dose inhalation toxicity data of lactic acid or any of the lactates were not included in the original safety assessment.) The inhalation toxicity potential of 0-2500 mg/m³ ethyl L-lactate and 0-600 mg/m³ butyl L-lactate was evaluated in 28-day vapor studies in rats; the animals were exposed 5 days/wk for 6 h/day.¹⁹ For both ethyl and butyl lactate, the no-observable adverse effect level (NOAEL) for systemic toxicity was 600 mg/m³, and the NOAEL for local toxicity was 200 mg/m³.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Glycolic Acid

Numerous studies have been published examining the role of glycolic acid, as a metabolite, in the developmental toxicity caused by ethylene glycol.^{8,16-18,21,22,31,36} Glycolic acid is the proximate developmental toxicant for ethylene glycol. Very high doses and dose rates that saturate glycolic acid oxidation are required for developmental effects; in one oral study, the peak maternal blood concentration of glycolic acid associated with the lowest observed effect level (LOEL) for develop-

mental toxicity in Sprague-Dawley rats was 363 µg/g, or 4.8 mM blood. However, the effects are species-specific. High doses of ethylene glycol administered via gavage were not teratogenic in rabbits; it appears that rate of maternal metabolism of ethylene glycol to glycolic acid is slower in rabbits than in rats. A physiologically based pharmacokinetic (PBPK) model was developed for use in developmental risk assessments to enable addressing inhalation, oral, dermal, intravenous, and subcutaneous routes of administration. The comparison of internal dose estimates in rats and humans over a broad range of exposures led to the conclusion that occupational and environmental exposures to ethylene glycol by humans are unlikely to yield blood levels of glycolic acid in humans that are associated with developmental toxicity in rats. The National Toxicology Program's Center for the Evaluation of Risks to Human Reproduction (NTP-CERHR) also found that, as long as ethylene glycol exposure does not result in saturation of enzymes that metabolize glycolic acid, there should be no developmental toxicity; in humans, saturation is estimated to occur at 125 mg/kg bw or greater.

CARCINOGENICITY

The photocarcinogenic potential of glycolic acid was evaluated in two studies. In a study conducted by the NTP, groups of hairless mice were exposed to creams containing 4% or 10% glycolic acid, creams without glycolic acid, or no cream in the morning. In the afternoon, the animals were exposed to one of three strengths of solar light for 4 h.⁹ Control groups were not exposed to solar light. The animals were treated and exposed five days/wk for 40 wks. Stronger light increased the incidence of skin cancers in mice not treated with cream and in mice treated with a cream without glycolic acid. Glycolic acid did not affect the photocarcinogenesis of simulated solar light, and it did not have a protective effect.

In the second study, groups of hairless female SKH-1 mice were exposed to UV radiation only, radiation + topically glycolic acid, or glycolic acid only; glycolic acid was applied to the treated mice two times/wk.²⁶ Mice were irradiated 5 days/wk for 22 wks, and the dose of UV was increased each week. Glycolic acid reduced UV-induced skin tumor development.

Anti-Proliferative Effects/Pro-Apoptotic Effects

In Vitro

Both glycolic acid and lactic acid had anti-proliferative effects and induced apoptosis in human keratinocyte cells (HaCaT). The effect of glycolic acid (5 mM) on keratinocytes was tested with and without 50 mJ/cm² UVB.³³ Glycolic acid inhibited cell proliferation and induced apoptosis with or without UVB but, without UVB, exposure to the acid did not affect the cell cycle. Lactic acid, 7.5-17.5 mM, investigated without UV irradiation also inhibited cell proliferation and induced apoptosis.²⁷ In both studies, the researchers stated that the mechanism of apoptosis involved multiple molecular pathways, including caspase-dependent and caspase-independent pathways.

TABLES**Table 1. Current and historical frequency and concentration of use of AHAs according to duration and exposure**

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	2013 ⁶	1997 ¹	2013 ¹¹	1995 ¹	2013 ⁶	1997 ¹	2013 ¹¹	1995 ¹
	Glycolic Acid				Ammonium Glycolate			
Totals*	337	42	0.0005-50	<1-20[#]	51	19	NR	NR^{**}
Duration of Use								
Leave-On	244	31	0.0005-50	<1-20 [#]	37	11	NR	NR ^{**}
Rinse-Off	92	11	0.0008-50	≤7.8-9.8 [#]	14	8	NR	NR ^{**}
Diluted for (Bath) Use	1	NR	NR	NR [#]	NR	NR	NR	NR ^{**}
Exposure Type								
Eye Area	7	NR	0.035-0.49	NR [#]	1	NR	NR	NR ^{**}
Incidental Ingestion	NR	NR	NR	7.04-14.29 [#] (70% aq; pH 3.89-4.01)	NR	NR	NR	NR ^{**}
Incidental Inhalation-Spray	definitive: 2 170 ^{a,c}	21 ^{a,c}	aerosol: 0.0005 pump: 0.05 0.12-0.6 ^a	NR [#]	25 ^{a,c}	7 ^{a,c}	NR	NR ^{**}
Incidental Inhalation-Powder	powder: 1 88 ^{b,c}	11 ^{b,c}	NR	NR [#]	12 ^{b,c}	3 ^{b,c}	NR	NR ^{**}
Dermal Contact	300	30	0.012-50	<1-20 [#]	48	16	NR	NR ^{**}
Deodorant (underarm)	NR	NR	NR	NR [#]	NR	NR	NR	NR ^{**}
Hair - Non-Coloring	35	2	0.0005-4.5	≤8 [#]	2	2	NR	NR ^{**}
Hair-Coloring	NR	NR	0.0008-4	NR [#]	NR	NR	NR	NR ^{**}
Nail	2	2	4.1	≤8 [#]	1	1	NR	NR ^{**}
Mucous Membrane	8	NR	0.06	≤8 [#]	NR	NR	NR	NR ^{**}
Baby Products	NR	NR	NR	NR [#]	NR	NR	NR	NR ^{**}
	Sodium Glycolate				Lactic Acid			
Totals*	25	1	0.0002-1.9	NR^{**}	1042	342	0.000023-30	0.1-11.8[#]
Duration of Use								
Leave-On	5	1	0.0002	NR ^{**}	642	177	0.000023-10.1	0.1-11.8 [#]
Rinse-Off	20	NR	0.005-0.25	NR ^{**}	389	162	0.000081-6.1	0.7-2 ^w
Diluted for (Bath) Use	NR	NR	1.9	NR ^{**}	11	3	0.085-30	≤6 ^u
Exposure Type								
Eye Area	1	NR	NR	NR ^{**}	17	1	0.000023-0.2	0.12-3.53 [#] (85% aq.)
Incidental Ingestion	NR	NR	NR	NR ^{**}	2	NR	0.0023-0.085	NR [#]
Incidental Inhalation-Spray	3 ^{a,c}	NR	NR	NR ^{**}	definitive: 28 ^c 452 ^{a,c}	9	0.00063-0.21 aerosol: 0.0002 pump: 0.17-5.8 1.1 ^a	NR [#]
Incidental Inhalation-Powder	2 ^{b,c}	NR	NR	NR ^{**}	definitive: 2 ^c 162 ^{b,c}	NR	definitive: 0.000023	NR [#]
Dermal Contact	15	1	0.01-1.9	NR ^{**}	680	229	0.000023-10	0.1-11.8 [#] (85% aq.)
Deodorant (underarm)	NR	NR	NR	NR ^{**}	2 ^a	NR	0.05-1.7	NR [#]
Hair - Non-Coloring	10	NR	0.0002-0.25	NR ^{**}	343	144	0.000081-5.8	0.1-5 [#]
Hair-Coloring	NR	NR	NR	NR ^{**}	11	46	0.014-5	≤1 [#]
Nail	NR	NR	NR	NR ^{**}	1	7	0.0006-10.1	≤10 [#]
Mucous Membrane	7	NR	0.01-1.9	NR ^{**}	69	3	0.01-30	≤6 [#]
Baby Products	NR	NR	NR	NR ^{**}	2	1	NR	NR [#]
	Ammonium Lactate				Calcium Lactate			
Totals*	17	NR	0.0003-0.06	NR	10	NR	0.072-1.5	NR
Duration of Use								
Leave-On	14	NR	0.0003-0.06	NR	3	NR	0.072-1	NR
Rinse-Off	3	NR	0.0064-0.032	NR	6	NR	0.3-1.5	NR
Diluted for (Bath) Use	NR	NR	NR	NR	1	NR	NR	NR
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	0.0003	NR	NR	NR	1	NR
Incidental Inhalation-Spray	4 ^{a,c}	NR	pump: 0.0064 0.023 ^a	NR	NR	NR	0.3-1.5 ^{a,c}	NR
Incidental Inhalation-Powder	4 ^{b,c}	NR	NR	NR	NR	NR	1.5 ^{b,c}	NR
Dermal Contact	16	NR	0.0004-0.06	NR	6	NR	0.072	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	0.0064-0.032	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	0.0003	NR	4	NR	0.3-1.5	NR
Baby Products	NR	NR	NR	NR	3	NR	NR	NR

Table 1. Current and historical frequency and concentration of use of AHAs according to duration and exposure

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	2013 ⁶	1997 ¹	2013 ¹¹	1995 ¹	2013 ⁶	1997 ¹	2013 ¹¹	1995 ¹
	Potassium Lactate				Sodium Lactate			
Totals*	27	3	0.0004-0.92	NR	337	93	0.0002-8	<0.1-50**
Duration of Use								
<i>Leave-On</i>	16	3	0.92	NR	254	66	0.0002-8	<0.1-10**
<i>Rinse-Off</i>	11	NR	0.0004	NR	82	26	0.0002-7.6	<0.1-50**
<i>Diluted for (Bath) Use</i>	NR	NR	NR	NR	1	1	NR	NR**
Exposure Type								
Eye Area	NR	NR	NR	NR	15	NR	0.02-0.6	NR**
Incidental Ingestion	NR	NR	NR	NR	1	NR	0.0018-0.1	NR**
Incidental Inhalation-Spray	14 ^{a,c}	NR	0.0004 ^a	NR	definitive: 1 196 ^{a,c}	NR	0.075-1.3 aerosol: 0.012- 0.013 pump: 0.035- 0.06	NR**
Incidental Inhalation-Powder	3 ^{b,c}	NR	NR	NR	definitive: 2 87 ^{b,c}	NR	definitive: 0.03	NR**
Dermal Contact	25	3	0.0004-0.92	NR	316	71	0.0002-8	<0.1-50**
Deodorant (underarm)	NR	NR	NR	NR	1 ^a	1	0.01-0.075	NR**
Hair - Non-Coloring	2	NR	NR	NR	20	20	0.0002	0.1-1**
Hair-Coloring	NR	NR	NR	NR	1	NR	0.07	NR**
Nail	NR	NR	NR	NR	2	NR	NR	NR**
Mucous Membrane	8	NR	NR	NR	16	1	0.0002-1.2	0.1-50**
Baby Products	NR	R	NR	NR	2	NR	NR	NR**
	TEA-Lactate				Butyl Lactate			
Totals*	16	13	0.06-0.07 (≤0.1**)	≤0.1**	NR	NR	1	NR
Duration of Use								
<i>Leave-On</i>	15	7	0.06-0.07 (≤0.1**)	≤0.1**	NR	NR	1	NR
<i>Rinse-Off</i>	1	6	NR	NR**	NR	NR	NR	NR
<i>Diluted for (Bath) Use</i>	NR	NR	NR	NR**	NR	NR	NR	NR
Exposure Type								
Eye Area	1	NR	NR	NR**	NR	NR	NR	NR
Incidental Ingestion	NR	1	NR	NR**	NR	NR	NR	NR
Incidental Inhalation-Spray	9 ^{a,c}	NR	NR	NR**	NR	NR	NR	NR
Incidental Inhalation-Powder	4 ^{b,c}	NR	NR	NR**	NR	NR	NR	NR
Dermal Contact	16	84	0.06-0.07 (≤0.1**)	≤0.1**	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR**	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR**	NR	NR	NR	NR
Hair-Coloring	NR	4	NR	NR**	NR	NR	NR	NR
Nail	NR	NR	NR	NR**	NR	NR	1	NR
Mucous Membrane	1	1	NR	NR**	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR**	NR	NR	NR	NR
	Cetyl Lactate				Ethyl Lactate			
Totals*	49	38	0.015-10.2	0.5-9[#]	5	3	0.15-95	50[#] (NR**)
Duration of Use								
<i>Leave-On</i>	47	36	0.5-10.2	0.5-9 [#]	2	3	95	50 [#] (NR**)
<i>Rinse-Off</i>	2	2	0.015-1.2	1 [#]	3	NR	0.15-50	NR**
<i>Diluted for (Bath) Use</i>	NR	NR	NR	NR [#]	NR	NR	NR	NR**
Exposure Type								
Eye Area	1	1	1.5-10	0.5-2 [#]	1	NR	NR	NR**
Incidental Ingestion	23	29	2-9	3-9 [#]	NR	NR	NR	NR**
Incidental Inhalation-Spray	17 ^{a,c}	4	1-2 ^{a,c}	NR [#]	1 ^a	NR	NR	NR**
Incidental Inhalation-Powder	2 ^{b,c}	4	1-2 ^{b,c}	NR [#]	NR	NR	NR	NR**
Dermal Contact	25	9	0.5-10.2	0.5-5 [#]	2	NR	0.15	NR**
Deodorant (underarm)	NR	NR	NR	NR [#]	NR	NR	NR	NR**
Hair - Non-Coloring	1	NR	0.015	NR [#]	NR	NR	NR	NR**
Hair-Coloring	NR	NR	NR	NR [#]	NR	NR	NR	NR**
Nail	NR	NR	NR	NR [#]	3	3	50-95	50 [#]
Mucous Membrane	23	NR	0.55-9	3-9 [#]	NR	NR	NR	NR**
Baby Products	NR	1	NR	NR [#]	NR	NR	NR	NR**

Table 1. Current and historical frequency and concentration of use of AHAs according to duration and exposure

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	2013 ⁶	1997 ¹	2013 ¹¹	1995 ¹	2013 ⁶	1997 ¹	2013 ¹¹	1995 ¹
	Lauryl Lactate				Methyl Lactate			
Totals*	26	13	0.14-10	0.1-5[#] (≤0.1-25 ^{**})	NR	NR	0.038-0.75	NR
Duration of Use								
<i>Leave-On</i>	24	9	0.14-10	0.15 [#] (0.1-25 ^{**})	NR	NR	0.038-0.75	NR
<i>Rinse-Off</i>	2	4	0.5-1	≤0.1-5 ^{**}	NR	NR	NR	NR
<i>Diluted for (Bath) Use</i>	NR	NR	NR	NR ^{#1} **	NR	NR	NR	NR
Exposure Type								
Eye Area	2	NR	1	0.1 [#]	NR	NR	NR	NR
Incidental Ingestion	NR	NR	1	1-25 ^{**}	NR	NR	NR	NR
Incidental Inhalation-Spray	18 ^{a,c}	NR	0.14-10 ^{a,c}	NR ^{**}	NR	NR	NR	NR
Incidental Inhalation-Powder	11 ^{b,c}	4	1-10 ^{b,c}	NR ^{**}	NR	NR	NR	NR
Dermal Contact	25	13	0.5-10	0.1-5 [#] 1-25 ^{**}	NR	NR	0.038-0.75	NR
Deodorant (underarm)	2 ^a	1	NR	NR ^{**}	NR	NR	aerosol: 0.038	NR
Hair - Non-Coloring	1	NR	0.14	≤0.1 ^{**}	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR ^{**}	NR	NR	NR	NR
Nail	NR	NR	1	NR ^{**}	NR	NR	NR	NR
Mucous Membrane	1	1	0.5	1-25 ^{**}	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR ^{**}	NR	NR	NR	NR
	Myristyl Lactate							
Totals*	215	195	0.01-13.2	>1.5-15[#] (0.1-50 ^{**})				
Duration of Use								
<i>Leave-On</i>	209	187	0.01-13.2	>1.5-15 [#] (0.1-50 ^{**})				
<i>Rinse-Off</i>	6	8	0.79-11.2	0.1-1 ^{**}				
<i>Diluted for (Bath) Use</i>	NR	NR	NR	0.1-1 ^{**}				
Exposure Type								
Eye Area	97	105	3.5-7.2	5-15 [#] (0.1-25 ^{**})				
Incidental Ingestion	70	53	6.3-13.2	11.54 [#] (0.1-50 ^{**})				
Incidental Inhalation-Spray	22 ^{a,c}	NR	1.2-1.5 ^{a,c}	0.1-50 ^{**}				
Incidental Inhalation-Powder	definitive: 2 11 ^{b,c}	1	1.2 ^{b,c}	NR ^{**}				
Dermal Contact	144	140	0.01-11.2	>1.5-15 [#] (0.1-50 ^{**})				
Deodorant (underarm)	1 ^a	NR	NR	NR ^{**}				
Hair - Non-Coloring	1	2	NR	0.1-1 ^{**}				
Hair-Coloring	NR	NR	NR	NR ^{**}				
Nail	NR	NR	NR	NR ^{**}				
Mucous Membrane	72	53	6.3-13.2	11.54 [#] (0.1-50 ^{**})				
Baby Products	NR	NR	NR	NR ^{**}				

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

**at the time of the 1998 safety assessment, concentration of use data were not reported by the FDA; 1984 data were presented.

[#] some concentration of use data were reported

^a It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

^b It is possible these products are powders, but it is not specified whether the reported uses are powders.

^c Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, there fore the information is captured in both categories
NR – no reported use

Table 2. AHAs not in current use according to VCRP and Council survey data

Butyl Glycolate
Calcium Glycolate
Ethyl Glycolate
Methyl Glycolate
Potassium Glycolate
Propyl Glycolate
Isopropyl Lactate

REFERENCES

1. Andersen FA (ed). 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, myristyl, and cetyl lactates. *International Journal of Toxicology*. 1998;17(1):1-241.
2. Fiume MM, Heldreth B, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler D, Marks JG Jr, Shank RC, Slaga TJ, Snyder PW, and Andersen FA. Safety assessment of triethanolamine and triethanolamine-containing ingredients as used in cosmetics. *Int J Toxicol*. 2013;32(Suppl 1):59S-83S.
3. European Chemicals Agency. Glycolic acid. <http://echa.europa.eu>. Date Accessed 10-10-2013.
4. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. <http://ec.europa.eu/consumers/cosmetics/cosing/>. Date Accessed 9-23-2013.
5. Food and Drug Administration (FDA). Guidance for Industry: Labeling for cosmetics containing Alpha Hydroxy Acids. <http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/ucm090816.htm>. Date Accessed 10-29-2013.
6. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database*. 2013. Dated Jan 15.
7. Food and Drug Administration (FDA). Alpha Hydroxy Acids in Cosmetics. Safety and regulatory information. <http://www.fda.gov/cosmetics/productandingredientsafety/selectedcosmeticingredients/ucm107940.htm>. Date Accessed 10-29-2013.
8. National Toxicology Program (NTP). NTP-CEHR Monograph on the potential human reproductive and developmental effects of ethylene glycol. 2004. Date Accessed 10-8-2013.
9. National Toxicology Program (NTP). NTP Technical Report on the photocarcinogenesis study of glycolic acid and salicylic acid (CAS Nos. 79-14-1 and 69-72-7) in SKH-1 mice. (Simulated solar light and topical application study). 2007. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr524.pdf. Date Accessed 10-7-2013. Report No. NTP TR 524.
10. Organisation for Economic Co-operation and Development (OECD). SIDS Initial Assessment Profile - Lactic Acid. <http://webnet.oecd.org/HPV/UI/handler.axd?id=fd79fce6-c7e2-48ed-aead-8728c961980c>. Date Accessed 10-8-2013.
11. Personal Care Products Council. 9-12-2013. Concentration of Use by FDA Product Category: Glycolic and Lactic Acids and their salts and esters. Unpublished data submitted by Personal Care Products Council. 8 pages.
12. Scientific Committee on Consumer Products and Non-Food Products Intended for Consumers (SCCNFP). Position paper concerning the safety of alpha-hydroxy acids. http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out121_en.pdf. Date Accessed 10-8-2013.
13. Scientific Committee on Consumer Products and Non-Food Products Intended for Consumers (SCCNFP). Updated position paper concerning consumer safety of alpha-hydroxy acids. http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out284_en.pdf. Date Accessed 10-8-2013.
14. U.S. Environmental Protection Agency (EPA). Supporting Documents for Initial Risk-Based Prioritization of High Production Volume Chemicals. Sponsored chemical: Lactic acid (CASRN 50-21-5); supporting chemical: L (+)-Lactic acid (CASRN 79-33-4). http://www.epa.gov/chemrtk/hpvis/rbp/Lactic%20Acid_Web_SuppDocs_August%202008.pdf. Date Accessed 10-8-2013.
15. Bernstein EF, Lee J, Brown DB, Yu R, and vanScott E. Glycolic acid treatment increases type I collagen mRNA and hyaluronic acid content of human skin. *Dermatol Surg*. 2001;27(5):429-433.
16. Carney EW, Freshour NL, Dittenber DA, and Dryzga MD. Ethylene glycol developmental toxicity: Unraveling the roles of glycolic acid and metabolic acidosis. *Toxicological Sciences*. 1999;50:117-126.
17. Carney EW, Tornesi B, Markham, DA, Rasoulpour RJ, and Moore N. Species-specificity of ethylene glycol-induced developmental toxicity: toxicokinetic and whole embryo culture studies in the rabbit. *Birth Defects Res B Dev Reprod Toxicol*. 2008;83(6):573-581.

18. Carney EW, Tornesi B, Liberacki AB, Markham DA, Weitz KK, Luders TM, Studniski KG, Blessing JC, Gies RA, and Corley RA. The impact of dose rate on ethylene glycol developmental toxicity and pharmacokinetics in pregnant CD rats. *Toxicological Sciences*. 2011;119(1):178-188.
19. Clary JJ, Feron VJ, and van Velthuisen JA. Safety assessment of lactate esters. *Regul Toxicol Pharmacol*. 1998;27(2):88-97.
20. Copovi A, Diez-Sales O, Herraiez-Domnquez JV, and Herraiez-Dominquez M. Enhancing effect of alpha-hydroxyacids on "in vitro" permeation across the human skin of compounds with different lipophilicity. *Int J Pharm*. 2006;314(1):31-36.
21. Corley RA, Meek ME, and Carney EW. Mode of action: oxalate crystal-induced renal tubule degeneration and glycolic acid-induced dysmorphogenesis--renal and developmental effects of ethylene glycol. *Crit Rev Toxicol*. 2005;35(8-9):691-702.
22. Corley RA, Bartels MJ, Carney EW, Weitz KK, Soelberg JJ, Gies RA, and Thrall KD. Development of a physiologically based pharmacokinetic model for ethylene glycol and its metabolite, glycolic acid, in rats and humans. *Toxicological Sciences*. 2005;85:476-490.
23. Corley RA, Saghir SA, Bartels MJ, Hansen SC, Creim J, McMartin KE, and Snellings WM. Extension of a PBPK model for ethylene glycol and glycolic acid to include the competitive formation and clearance of metabolites associated with kidney toxicity in rats and humans. *Toxicol Appl Pharmacol*. 2011;250(3):229-244.
24. Cruzan G, Corley RA, Hard GC, Mertens JJWM, McMartin KE, Snellings WM, Gingell R, and Deyo JA. Subchronic toxicity of ethylene glycol in Wistar and F-344 rats related to metabolism and clearance of metabolites. *Toxicological Sciences*. 2004;81:502-511.
25. Fartasch M, Teal J, and Menon GK. Mode of action of glycolic acid on human stratum corneum: ultrastructural and functional evaluation of the epidermal barrier. *Arch Dermatol Res*. 1997;289(7):404-409.
26. Hong JT, Ahn KS, Jung KM, Yun YP, Park YK, and Lee SH. Inhibitory effect of glycolic acid on ultraviolet-induced skin tumorigenesis in SKH-1 hairless mice and its mechanism of action. *Mol Carcinog*. 2001;31(3):152-160.
27. Hsiao YP, Huang HL, Lai WW, and Yand JH. Antiproliferative effects of lactic acid via the induction of apoptosis and cell cycle arrest in a human keratinocyte cell line (HaCaT). *J Dermatol Sci*. 2009;54(3):175-184.
28. Jiang M and Quereshi SA. Assessment of in vitro percutaneous absorption of glycolic acid through human skin sections using a flow-through diffusion cell system. *J Dermatol Sci*. 1998;18(3):181-188.
29. Kaidbey K, Sutherland B, Bennett P, Warner WG, Barton C, Dennis D, and Kornhauser A. Topical glycolic acid enhances photodamage by ultraviolet light. *Photodermatol Photoimmunol Photomed*. 2003;19(1):21-27.
30. Kim TH, Choi EH, Kang YC, Lee SH, and Ahn SK. The effects of topical alpha-hydroxyacids on the normal skin barrier of hairless mice. *Br J Dermatol*. 2001;144(2):267-273.
31. Klug S, Merker HJ, and Jackh R. Effects of ethylene glycol and metabolites on in vitro development of rat embryos during organogenesis. *Toxicol In Vitro*. 2001;15(6):635-642.
32. Kornhauser A, Wei R-R, Yamaguchi Y, Coelho SG, Kaidbey K, Barton C, Takahashi K, Ceer JZ, Miller SA, and Hearing VJ. The effectsof topically applied glycolic acid and salicylic acid on ultraviolet radiation-induced erythema, DNA damage and sunburn cell formation in human skin. *J Dermatol Sci*. 2009;55(1):10-17.
33. Lai WW, Hsiao YP, Chung JG, Wei YH, Chenh YW, and Yand JH. Synergistic phototoxic effects of glycolic acid in a human keratinocyte cell line (HaCaT). *J Dermatol Sci*. 2011;64(3):191-198.
34. Okano Y, Abe Y, Masaki H, Santhanam U, Ichihashi M, and Funasaka Y. Biological effects of glycolic acid on dermal matrix metabolism mediated by dermal fibroblasts and epidermal keratinocytes. *Exp Dermatol*. 2003;12(Suppl 2):57-63.
35. Okuda M, Donahue DA, Kaufman LE, Avalos J, Simion FA, Story DC, Sakaguchi H, Fautz R, and Fuchs A. Negligible penetration of incidental amounts of alpha-hydroxy acid from rinse-off personal care products in human skin using an in vitro static diffusion cell model. *Toxicol In Vitro*. 2011;25(8):2041-2047.
36. Pottenger LH, Carney EW, and Bartels MJ. Dose-dependent nonlinear pharmacokinetics of ethyl glycol metabolites in pregnant (GD 10) and nonpregnant Sprague-Dawley rats followig oral administraton of ethylene glycol. *Toxicological Sciences*. 2001;62(1):10-19.

37. Rendl M, Mayer C, Weninger W, and Tschachler E. Topically applied lactic acid increases spontaneous secretion of vascular endothelial growth factor by human reconstructed epidermis. *Br J Dermatol*. 2001;145(1):3-9.
38. Sams RL, Couch LH, Miller BJ, Okerberg CV, Warbritton AR, Wildnauer RH, Beer JZ, and Howard PC. Basal cell proliferation in female SKH-1 mice treated with alpha- and beta-hydroxy acids. *Toxicol Appl Pharmacol*. 2001;175(1):76-82.
39. Sams RL, Couch LK, Miller BJ, Okerberg CV, Warbritton AR, Warner WG, Beer JZ, and Howard PC. Effects of alpha- and beta-hydroxy acids on the edema response induced in female SKH-1 mice by simulated solar light. *Toxicol Appl Pharmacol*. 2002;184(3):136-143.
40. Schliemann-Willers S, Fuchs S, Kleesz P, Grieshaber R, and Elsner P. Fruit acids do not enhance sodium lauryl sulphate-induced cumulative irritant contact dermatitis *in vivo*. *Acta Derm Venereol*. 2005;85:206-210.
41. Usuki A, Ohashi A, Sato, Ochiai Y, Ichihashi M, and Funasaka Y. The inhibitory effect of glycolic acid and lactic acid on melanin synthesis in melanoma cells. *Exp Dermatol*. 2003;12(Suppl 2):43-50.
42. Andersen FA (ed). Final report on the safety assessment of urocanic acid. *J Am Coll Toxicol*. 2005;14:386-423.
43. Gottschalck TE and Breslawec H. International Cosmetic Ingredient Dictionary and Handbook. Washington, DC: Personal Care Products Council, 2012.
44. Johnsen MA. The influence of particle size. *Spray Technology and Marketing*. 2004;14(11):24-27.
45. Rothe H. Special Aspects of Cosmetic Spray Evaluation. 9-26-2011. Unpublished data presented at the 26 September CIR Expert Panel meeting. Washington, D.C.
46. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104.
47. Bremmer HJ, Prud'homme de Lodder LCH, and Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. Report No. RIVM 320104001/2006. pp. 1-77.

GLYCOLIC ACID	02D - Other Bath Preparations	1	
GLYCOLIC ACID	03D - Eye Lotion	5	7
GLYCOLIC ACID	03G - Other Eye Makeup Preparations	2	
GLYCOLIC ACID	05A - Hair Conditioner	19	35
GLYCOLIC ACID	05B - Hair Spray (aerosol fixatives)	2	
GLYCOLIC ACID	05F - Shampoos (non-coloring)	11	
GLYCOLIC ACID	05G - Tonics, Dressings, and Other Hair Grooming Aids	2	
GLYCOLIC ACID	05I - Other Hair Preparations	1	
GLYCOLIC ACID	07B - Face Powders	1	
GLYCOLIC ACID	07C - Foundations	2	300
GLYCOLIC ACID	07I - Other Makeup Preparations	3	
GLYCOLIC ACID	08B - Cuticle Softeners	1	
GLYCOLIC ACID	08C - Nail Creams and Lotions	1	
GLYCOLIC ACID	10A - Bath Soaps and Detergents	6	
GLYCOLIC ACID	10E - Other Personal Cleanliness Products	1	
GLYCOLIC ACID	11A - Aftershave Lotion	1	
GLYCOLIC ACID	11D - Preshave Lotions (all types)	1	
GLYCOLIC ACID	12A - Cleansing	41	
GLYCOLIC ACID	12C - Face and Neck (exc shave)	65	170
GLYCOLIC ACID	12D - Body and Hand (exc shave)	23	
GLYCOLIC ACID	12F - Moisturizing	54	88
GLYCOLIC ACID	12G - Night	21	
GLYCOLIC ACID	12H - Paste Masks (mud packs)	13	
GLYCOLIC ACID	12I - Skin Fresheners	4	
GLYCOLIC ACID	12J - Other Skin Care Preps	53	244
GLYCOLIC ACID	13A - Suntan Gels, Creams, and Liquids	1	92
GLYCOLIC ACID	13B - Indoor Tanning Preparations	2	
		337	
AMMONIUM GLYCOLATE	03D - Eye Lotion	1	
AMMONIUM GLYCOLATE	05F - Shampoos (non-coloring)	2	
AMMONIUM GLYCOLATE	08C - Nail Creams and Lotions	1	
AMMONIUM GLYCOLATE	12A - Cleansing	10	
AMMONIUM GLYCOLATE	12C - Face and Neck (exc shave)	6	
AMMONIUM GLYCOLATE	12D - Body and Hand (exc shave)	6	
AMMONIUM GLYCOLATE	12F - Moisturizing	12	
AMMONIUM GLYCOLATE	12G - Night	1	
AMMONIUM GLYCOLATE	12H - Paste Masks (mud packs)	2	
AMMONIUM GLYCOLATE	12J - Other Skin Care Preps	9	
AMMONIUM GLYCOLATE	13A - Suntan Gels, Creams, and Liquids	1	
		51	
Caclium Glycolate		0	
Potassium Glycolate		0	
SODIUM GLYCOLATE	03D - Eye Lotion	1	
SODIUM GLYCOLATE	04E - Other Fragrance Preparation	1	
SODIUM GLYCOLATE	05F - Shampoos (non-coloring)	9	
SODIUM GLYCOLATE	05I - Other Hair Preparations	1	
SODIUM GLYCOLATE	10A - Bath Soaps and Detergents	1	
SODIUM GLYCOLATE	10E - Other Personal Cleanliness Products	6	
SODIUM GLYCOLATE	12A - Cleansing	4	
SODIUM GLYCOLATE	12D - Body and Hand (exc shave)	2	
		25	
Methyl Glycolate		0	
Ethyl Glycolate		0	
Propyl Glycolate		0	
Butyl Glycolate		0	

NOT IN REPORT

ISOSTEARYL GLYCOLATE	05A - Hair Conditioner	4	
LACTIC ACID	01B - Baby Lotions, Oils, Powders, and Creams	2	164
LACTIC ACID	02B - Bubble Baths	8	
LACTIC ACID	02D - Other Bath Preparations	3	
LACTIC ACID	03D - Eye Lotion	4	17
LACTIC ACID	03E - Eye Makeup Remover	1	
LACTIC ACID	03F - Mascara	1	
LACTIC ACID	03G - Other Eye Makeup Preparations	11	28
LACTIC ACID	04A - Cologne and Toilet waters	3	
LACTIC ACID	04E - Other Fragrance Preparation	3	
LACTIC ACID	05A - Hair Conditioner	162	
LACTIC ACID	05B - Hair Spray (aerosol fixatives)	9	
LACTIC ACID	05C - Hair Straighteners	2	
LACTIC ACID	05E - Rinses (non-coloring)	3	
LACTIC ACID	05F - Shampoos (non-coloring)	54	
LACTIC ACID	05G - Tonics, Dressings, and Other Hair Grooming Aids	77	452
LACTIC ACID	05H - Wave Sets	3	
LACTIC ACID	05I - Other Hair Preparations	32	
LACTIC ACID	06A - Hair Dyes and Colors (all types requiring caution state	11	
LACTIC ACID	07C - Foundations	6	680
LACTIC ACID	07E - Lipstick	2	
LACTIC ACID	07F - Makeup Bases	1	
LACTIC ACID	07I - Other Makeup Preparations	4	
LACTIC ACID	08B - Cuticle Softeners	1	
LACTIC ACID	10A - Bath Soaps and Detergents	32	
LACTIC ACID	10B - Deodorants (underarm)	2	
LACTIC ACID	10C - Douches	4	
LACTIC ACID	10E - Other Personal Cleanliness Products	20	
LACTIC ACID	11A - Aftershave Lotion	49	
LACTIC ACID	12A - Cleansing	67	
LACTIC ACID	12C - Face and Neck (exc shave)	111	
LACTIC ACID	12D - Body and Hand (exc shave)	46	
LACTIC ACID	12E - Foot Powders and Sprays	2	
LACTIC ACID	12F - Moisturizing	140	
LACTIC ACID	12G - Night	19	
LACTIC ACID	12H - Paste Masks (mud packs)	27	
LACTIC ACID	12I - Skin Fresheners	16	
LACTIC ACID	12J - Other Skin Care Preps	59	
LACTIC ACID	13A - Suntan Gels, Creams, and Liquids	3	
LACTIC ACID	13B - Indoor Tanning Preparations	28	
LACTIC ACID, L-	05F - Shampoos (non-coloring)	1	
LACTIC ACID, L-	12A - Cleansing	2	
LACTIC ACID, L-	12C - Face and Neck (exc shave)	4	
LACTIC ACID, L-	12D - Body and Hand (exc shave)	1	
LACTIC ACID, L-	12F - Moisturizing	3	
LACTIC ACID, L-	12J - Other Skin Care Preps	1	642
LACTIC ACID, L-	13B - Indoor Tanning Preparations	1	389
LACTIC ACID, L-	13C - Other Suntan Preparations	1	
		1042	
AMMONIUM LACTATE	05A - Hair Conditioner	1	
AMMONIUM LACTATE	12A - Cleansing	1	
AMMONIUM LACTATE	12C - Face and Neck (exc shave)	3	
AMMONIUM LACTATE	12D - Body and Hand (exc shave)	1	
AMMONIUM LACTATE	12F - Moisturizing	7	
AMMONIUM LACTATE	12G - Night	1	
AMMONIUM LACTATE	12H - Paste Masks (mud packs)	1	

AMMONIUM LACTATE	12J - Other Skin Care Preps	2
CALCIUM LACTATE	01C - Other Baby Products	3
CALCIUM LACTATE	02A - Bath Oils, Tablets, and Salts	1
CALCIUM LACTATE	09A - Dentifrices	2
CALCIUM LACTATE	09C - Other Oral Hygiene Products	2
CALCIUM LACTATE	12A - Cleansing	1
CALCIUM LACTATE	12H - Paste Masks (mud packs)	1
POTASSIUM LACTATE	05A - Hair Conditioner	1
POTASSIUM LACTATE	05F - Shampoos (non-coloring)	1
POTASSIUM LACTATE	10A - Bath Soaps and Detergents	8
POTASSIUM LACTATE	11A - Aftershave Lotion	2
POTASSIUM LACTATE	12A - Cleansing	1
POTASSIUM LACTATE	12D - Body and Hand (exc shave)	3
POTASSIUM LACTATE	12F - Moisturizing	6
POTASSIUM LACTATE	12J - Other Skin Care Preps	5
SODIUM LACTATE	01B - Baby Lotions, Oils, Powders, and Creams	1
SODIUM LACTATE	01C - Other Baby Products	1
SODIUM LACTATE	02B - Bubble Baths	1
SODIUM LACTATE	03D - Eye Lotion	7
SODIUM LACTATE	03F - Mascara	1
SODIUM LACTATE	03G - Other Eye Makeup Preparations	7
SODIUM LACTATE	05A - Hair Conditioner	9
SODIUM LACTATE	05B - Hair Spray (aerosol fixatives)	1
SODIUM LACTATE	05F - Shampoos (non-coloring)	6
SODIUM LACTATE	05G - Tonics, Dressings, and Other Hair Grooming Aids	3
SODIUM LACTATE	05I - Other Hair Preparations	1
SODIUM LACTATE	06H - Other Hair Coloring Preparation	1
SODIUM LACTATE	07B - Face Powders	2
SODIUM LACTATE	07C - Foundations	1
SODIUM LACTATE	07E - Lipstick	1
SODIUM LACTATE	07I - Other Makeup Preparations	2
SODIUM LACTATE	08B - Cuticle Softeners	2
SODIUM LACTATE	10A - Bath Soaps and Detergents	12
SODIUM LACTATE	10B - Deodorants (underarm)	1
SODIUM LACTATE	10E - Other Personal Cleanliness Products	2
SODIUM LACTATE	11A - Aftershave Lotion	8
SODIUM LACTATE	12A - Cleansing	41
SODIUM LACTATE	12C - Face and Neck (exc shave)	59
SODIUM LACTATE	12D - Body and Hand (exc shave)	27
SODIUM LACTATE	12F - Moisturizing	85
SODIUM LACTATE	12G - Night	11
SODIUM LACTATE	12H - Paste Masks (mud packs)	11
SODIUM LACTATE	12I - Skin Fresheners	13
SODIUM LACTATE	12J - Other Skin Care Preps	19
SODIUM LACTATE	13B - Indoor Tanning Preparations	1
TEA-LACTATE	03G - Other Eye Makeup Preparations	1
TEA-LACTATE	11A - Aftershave Lotion	1
TEA-LACTATE	12A - Cleansing	1
TEA-LACTATE	12C - Face and Neck (exc shave)	3
TEA-LACTATE	12D - Body and Hand (exc shave)	1
TEA-LACTATE	12F - Moisturizing	5
TEA-LACTATE	12I - Skin Fresheners	1
TEA-LACTATE	12J - Other Skin Care Preps	3

CETYL LACTATE	01B - Baby Lotions, Oils, Powders, and Creams	1
CETYL LACTATE	03C - Eye Shadow	1
CETYL LACTATE	05A - Hair Conditioner	1
CETYL LACTATE	07A - Blushers (all types)	1
CETYL LACTATE	07E - Lipstick	23
CETYL LACTATE	11A - Aftershave Lotion	4
CETYL LACTATE	12A - Cleansing	1
CETYL LACTATE	12C - Face and Neck (exc shave)	1
CETYL LACTATE	12D - Body and Hand (exc shave)	1
CETYL LACTATE	12F - Moisturizing	15
ETHYL LACTATE	03G - Other Eye Makeup Preparations	1
ETHYL LACTATE	08F - Nail Polish and Enamel Removers	3
ETHYL LACTATE	12I - Skin Fresheners	1
LAURYL LACTATE	03D - Eye Lotion	2
LAURYL LACTATE	05G - Tonics, Dressings, and Other Hair Grooming Aids	1
LAURYL LACTATE	10A - Bath Soaps and Detergents	1
LAURYL LACTATE	10B - Deodorants (underarm)	2
LAURYL LACTATE	12A - Cleansing	1
LAURYL LACTATE	12C - Face and Neck (exc shave)	3
LAURYL LACTATE	12D - Body and Hand (exc shave)	8
LAURYL LACTATE	12F - Moisturizing	6
LAURYL LACTATE	12G - Night	1
LAURYL LACTATE	12J - Other Skin Care Preps	1
MYRISTYL LACTATE	03A - Eyebrow Pencil	12
MYRISTYL LACTATE	03B - Eyeliner	41
MYRISTYL LACTATE	03C - Eye Shadow	41
MYRISTYL LACTATE	03G - Other Eye Makeup Preparations	3
MYRISTYL LACTATE	05G - Tonics, Dressings, and Other Hair Grooming Aids	1
MYRISTYL LACTATE	07A - Blushers (all types)	5
MYRISTYL LACTATE	07B - Face Powders	2
MYRISTYL LACTATE	07E - Lipstick	70
MYRISTYL LACTATE	07I - Other Makeup Preparations	10
MYRISTYL LACTATE	10B - Deodorants (underarm)	1
MYRISTYL LACTATE	10E - Other Personal Cleanliness Products	2
MYRISTYL LACTATE	12A - Cleansing	3
MYRISTYL LACTATE	12C - Face and Neck (exc shave)	6
MYRISTYL LACTATE	12D - Body and Hand (exc shave)	5
MYRISTYL LACTATE	12F - Moisturizing	8
MYRISTYL LACTATE	12G - Night	2
MYRISTYL LACTATE	12H - Paste Masks (mud packs)	1
MYRISTYL LACTATE	12J - Other Skin Care Preps	2
Butyl Lactate		0
Isopropyl Lactate		0
Methyl Lactate		0

NOT IN REPORT

C12-13 ALKYL LACTATE	03C - Eye Shadow	15
C12-13 ALKYL LACTATE	03D - Eye Lotion	1
C12-13 ALKYL LACTATE	05G - Tonics, Dressings, and Other Hair Grooming Aids	1
C12-13 ALKYL LACTATE	07I - Other Makeup Preparations	1
C12-13 ALKYL LACTATE	10A - Bath Soaps and Detergents	2
C12-13 ALKYL LACTATE	11A - Aftershave Lotion	1

C12-13 ALKYL LACTATE	12A - Cleansing	3
C12-13 ALKYL LACTATE	12C - Face and Neck (exc shave)	7
C12-13 ALKYL LACTATE	12D - Body and Hand (exc shave)	4
C12-13 ALKYL LACTATE	12F - Moisturizing	6
C12-13 ALKYL LACTATE	12G - Night	3
C12-13 ALKYL LACTATE	12H - Paste Masks (mud packs)	1
C12-13 ALKYL LACTATE	12J - Other Skin Care Preps	2
C12-15 ALKYL LACTATE	02B - Bubble Baths	4
C12-15 ALKYL LACTATE	03C - Eye Shadow	1
C12-15 ALKYL LACTATE	03D - Eye Lotion	1
C12-15 ALKYL LACTATE	04A - Cologne and Toilet waters	4
C12-15 ALKYL LACTATE	04E - Other Fragrance Preparation	1
C12-15 ALKYL LACTATE	05F - Shampoos (non-coloring)	1
C12-15 ALKYL LACTATE	07A - Blushers (all types)	1
C12-15 ALKYL LACTATE	07I - Other Makeup Preparations	2
C12-15 ALKYL LACTATE	10A - Bath Soaps and Detergents	4
C12-15 ALKYL LACTATE	10E - Other Personal Cleanliness Products	6
C12-15 ALKYL LACTATE	11A - Aftershave Lotion	10
C12-15 ALKYL LACTATE	12A - Cleansing	2
C12-15 ALKYL LACTATE	12C - Face and Neck (exc shave)	3
C12-15 ALKYL LACTATE	12D - Body and Hand (exc shave)	15
C12-15 ALKYL LACTATE	12F - Moisturizing	39
C12-15 ALKYL LACTATE	12G - Night	1
C12-15 ALKYL LACTATE	12J - Other Skin Care Preps	9
C12-15 ALKYL LACTATE	13B - Indoor Tanning Preparations	5
ISOSTEARYL LACTATE	05A - Hair Conditioner	4
ISOSTEARYL LACTATE	05I - Other Hair Preparations	1
ISOSTEARYL LACTATE	07E - Lipstick	1
ISOSTEARYL LACTATE	07I - Other Makeup Preparations	2
ISOSTEARYL LACTATE	12C - Face and Neck (exc shave)	1
ISOSTEARYL LACTATE	12F - Moisturizing	2
ISOSTEARYL LACTATE	12J - Other Skin Care Preps	2
MENTHYL LACTATE	02D - Other Bath Preparations	1
MENTHYL LACTATE	03C - Eye Shadow	1
MENTHYL LACTATE	03D - Eye Lotion	2
MENTHYL LACTATE	03G - Other Eye Makeup Preparations	1
MENTHYL LACTATE	04A - Cologne and Toilet waters	6
MENTHYL LACTATE	04E - Other Fragrance Preparation	6
MENTHYL LACTATE	05A - Hair Conditioner	5
MENTHYL LACTATE	05F - Shampoos (non-coloring)	5
MENTHYL LACTATE	05G - Tonics, Dressings, and Other Hair Grooming Aids	4
MENTHYL LACTATE	05I - Other Hair Preparations	1
MENTHYL LACTATE	07E - Lipstick	19
MENTHYL LACTATE	07I - Other Makeup Preparations	4
MENTHYL LACTATE	09C - Other Oral Hygiene Products	1
MENTHYL LACTATE	10A - Bath Soaps and Detergents	1
MENTHYL LACTATE	10B - Deodorants (underarm)	28
MENTHYL LACTATE	10E - Other Personal Cleanliness Products	7
MENTHYL LACTATE	11A - Aftershave Lotion	11
MENTHYL LACTATE	11E - Shaving Cream	1
MENTHYL LACTATE	11G - Other Shaving Preparation Products	6
MENTHYL LACTATE	12A - Cleansing	29
MENTHYL LACTATE	12C - Face and Neck (exc shave)	21
MENTHYL LACTATE	12D - Body and Hand (exc shave)	14
MENTHYL LACTATE	12E - Foot Powders and Sprays	1
MENTHYL LACTATE	12F - Moisturizing	25
MENTHYL LACTATE	12H - Paste Masks (mud packs)	9

MENTHYL LACTATE	12I - Skin Fresheners	9
MENTHYL LACTATE	12J - Other Skin Care Preps	18
MENTHYL LACTATE	13B - Indoor Tanning Preparations	1
MENTHYL LACTATE	13C - Other Suntan Preparations	2
OCTYLDODECYL LACTATE	03C - Eye Shadow	10
OCTYLDODECYL LACTATE	07A - Blushers (all types)	14
OCTYLDODECYL LACTATE	07B - Face Powders	23
OCTYLDODECYL LACTATE	07C - Foundations	4
OCTYLDODECYL LACTATE	07I - Other Makeup Preparations	1
OCTYLDODECYL LACTATE	12F - Moisturizing	1
OLEYL LACTATE	08G - Other Manicuring Preparations	2

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 site 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.

Monice Zondlo Fiume, Scientific Analyst/ Report Management Coordinator, prepared this report.

Address correspondence to Dr. F. A. Andersen at the Cosmetic Ingredient Review, 1101 17th St., NW, Suite 310, Washington, DC 20036, USA.

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 $\leq 10\%$, 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.

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

INTRODUCTION

3

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.

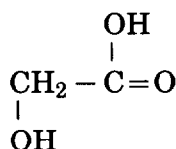
Myristyl and Cetyl Lactate have previously been reviewed by CIR (Elder, 1982), but updated information is included in this review. It is assumed that all data submitted citing testing with Glycolic Acid are for cosmetic-grade (70%) Glycolic Acid unless otherwise stated. The Expert Panel considered that 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).

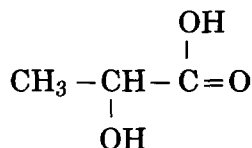
Methyl Glycolate. Methyl Glycolate is also known as Hydroxyacetic Acid, Methyl Ester (Lide, 1993).

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).

Lactic Acid

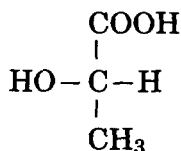
Lactic Acid (CAS No. 50-21-5) is the organic acid that generally conforms to the following formula (Wenninger and McEwen, 1995b):



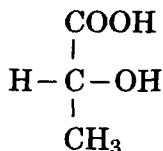
Lactic Acid can exist in a DL-, D-, or L- form. The L- and the D- forms are enantiomorphous isomers (mirror images). The L- form, which is dextro-rotatory, is sometimes referred to as *d*-Lactic Acid in the literature and the D- form, which is levorotatory, is sometimes referred to as *l*-Lactic Acid 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); Propanoic 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 Sarcosine (Rosan, 1994; Budavari, 1989).

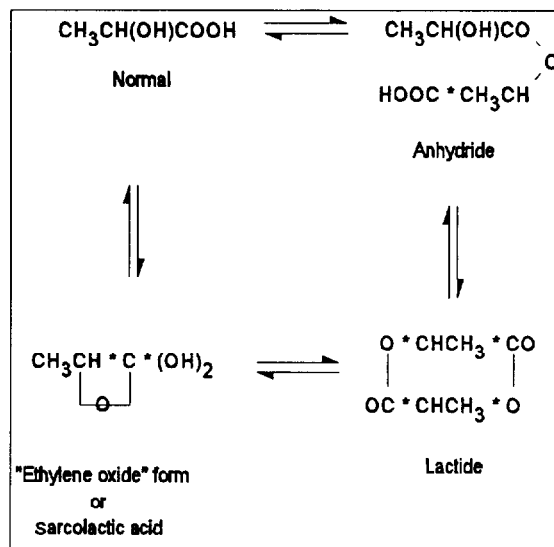


Figure 1. Equilibrium forms of Lactic Acid in water.

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 α -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:

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

where $[\text{HA}]$ represents the concentration of the free acid, $[\text{A}^-]$ is the concentration of the salt, and $\text{p}K_a$ 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 $\text{p}K_a$, 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 $\text{p}K_a$ values different from published dissociation constants. These variations could drastically change the distribution of weak acids in the pH region close to the $\text{p}K_a$. An equation has been developed that purports to take into consideration both partitioning and dissociation in calculating the concentration of free acid:

$$[\text{HA}]_w = \frac{C}{Kq + 1 + K_a/[\text{H}_3\text{O}^+]}$$

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 $[\text{H}_3\text{O}^+]$ 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
<i>Glycolic Acid</i>		
Physical properties	Rhombic needles from water and leaflets from ether Crystalline solid Colorless Odorless	Lide, 1993 Patty et al., 1963 Lewis, 1993a 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 80°C 78–79°C	Rosan, 1994 Lide, 1993 Lewis, 1993a
Boiling point	Decomposes	Lide, 1993
pH of aq. solution	0.5%: 2.5 5.0%: 1.91 1.0%: 2.33 10%: 1.73 2.0%: 2.16 5%: 1.7 40%: 1.3 10%: 1.6 50%: 1.2 20%: 1.5 60%: 1.0 30%: 1.4 70%: 0.6	Budavari, 1989 Yu and Van Scott, 1994
pK _a (pH of 50% dissociation)	3.83 (25°C)	Rosan, 1994
<i>Technical grade (70%) Glycolic Acid</i>		
Physical properties	Clear, light amber-colored liquid with a mild (burnt sugar) odor Light, straw-colored liquid having an odor similar to burnt sugar	Elson, 1993 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 Combustible	Elson, 1993 Lewis, 1993a
<i>Calcium Glycolate</i>		
Molecular formula	(CH ₃ OHCOO) ₂ Ca Ca(C ₂ H ₃ O ₃) · H ₂ O	Lewis, 1993a Grant, 1972
Molecular weight	190.18 208.1	RTECS, 1995 Grant, 1972
Physical properties	White solid White crystals	Lewis, 1993a 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
<i>Sodium Glycolate</i>		
Molecular formula	NaOOCCH ₂ OH	Lewis, 1993a
Molecular weight	98.04 (calculated)	
Physical properties	White powder	Lewis, 1993a
<i>Methyl Glycolate</i>		
Molecular formula	HOCH ₂ CO ₂ CH 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
<i>Ethyl Glycolate</i>		
Molecular formula	HOCH ₂ CO ₂ C ₂ H 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
<i>Propyl Glycolate</i>		
Molecular formula	HOCH ₂ CO ₂ C ₃ H 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
<i>Butyl Glycolate</i>		
Molecular formula	C ₆ H 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
<i>Lactic Acid</i>		
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 ₃ H ₆ O 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 furfural, 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
<i>Lactic Acid</i>		
Specific rotation	between -0.05° and $+0.05^\circ$ (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 Incompatible with oxidizing agents, iodides, nitric acid, and albumin in pharmaceuticals	Budavari, 1989 Informatics, Inc., 1975
<i>L-Lactic Acid</i>		
Physical properties	Hygroscopic prisms obtained from ether solvent Crystals formed from acetic acid or chloroform	Lide, 1993 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) 3.79 (25°C)	Yu and Van Scott, 1994 Budavari, 1989
<i>D-Lactic Acid</i>		
Physical properties	Plates obtained from chloroform and acetic acid solvents Crystals from ether + isopropyl ether Solid	Lide, 1993 Budavari, 1989 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 Soluble in water, alcohol, acetone, ether, and glycerol; practically insoluble in chloroform	Lide, 1993 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
<i>Ammonium Lactate</i>		
Molecular formula	$C_3H_9NO_3$	Budavari, 1989
Physical properties	Crystals from propanol Colorless syrup	Budavari, 1989 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
Density	Miscible with water 1.2006 (20°C/4°C); 1.1984 (25°C/4°C); 1.1904 (40°C/4°C)	Grant, 1972 Budavari, 1989
Refractive index	1.4543 (20°C); 1.4536 (25°C); 1.4503 (40°C)	Budavari, 1989
<i>Calcium Lactate</i>		
Empirical formula	$C_6H_{10}CaO_6$	Budavari, 1989
Structural formula	$Ca(C_3H_5O_3)_2 \cdot 5H_2O$ $Ca(CH_3CH(OH)COO)_2 \cdot xH_2O$	Sax, 1979 Informatics, Inc., 1975
Physical properties	Available as dry powder, mono-, or pentahydrate Pentahydrate, almost odorless, slightly efflorescent granules or powder White, almost odorless powder 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	Shelef, 1994 Budavari, 1989 Sax, 1979 Informatics, Inc., 1975
Molecular weight	218.22 308	Budavari, 1989 Sax, 1979
Melting point	–5H ₂ O @ 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
pH	Not less than 98.0% and not more than 101.0% of $C_6H_{10}CaO_6$ after drying	Informatics, Inc., 1975
Loss on drying	6–7 Pentahydrate: 24–30% Trihydrate: 15–20% Monohydrate: 5–8% Dried form: $\leq 3\%$	Budavari, 1989 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
<i>Methyl Lactate</i>		
Molecular formula	$C_4H_8O_3$	Budavari, 1989
Physical properties	Colorless, transparent liquid Colorless liquid	Budavari, 1989 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 144°C	Budavari, 1989 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 Decomposes in water	Budavari, 1989 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
<i>Ethyl Lactate</i>		
Molecular formula	$C_5H_{10}O_3$	Budavari, 1989
Physical characteristics	Colorless liquid; mild odor Colorless liquid; characteristic odor	Lewis, 1993a 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-	$154.5^\circ\text{C}; 58^\circ\text{C}$ (19 mm Hg)	Lide, 1993
D-	58°C (20 mm Hg)	
L-	$69\text{--}70^\circ\text{C}$ (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 ($20^\circ\text{C}/20^\circ\text{C}$)	Lewis, 1993a
	1.042 ($14^\circ\text{C}/4^\circ\text{C}$)	Budavari, 1989
DL-	1.0302 ($20^\circ\text{C}/4^\circ\text{C}$)	Lide, 1993
D-	1.0324 ($20.4^\circ\text{C}/4^\circ\text{C}$)	
L-	1.0314 ($20^\circ\text{C}/4^\circ\text{C}$)	
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
<i>Isopropyl Lactate</i>		
Molecular formula	$\text{CH}_3\text{CH}(\text{OH})\text{CO}_2\text{CH}(\text{CH}_3)_2$	Lide, 1993
Molecular weight	132.16	Lide, 1993
Boiling point	$166\text{--}8^\circ\text{C}; 75\text{--}80^\circ\text{C}$ (12 mm Hg)	Lide, 1993
Solubility	Soluble in water, alcohol, ether, benzene	Lide, 1993
Specific gravity	0.9980 ($20^\circ\text{C}/4^\circ\text{C}$)	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
<i>Butyl Lactate</i>		
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	$-43^\circ C$	Lewis, 1993a,b; Sax, 1979
DL-	$-49^\circ C$	Lide, 1993
Boiling point	$188^\circ C$	Lewis, 1993a,b; Sax, 1979
DL-	$83^\circ C$ (13 mm Hg)	Lide, 1993
D-	$77^\circ C$ (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 ($20^\circ C/20^\circ C$)	Lewis, 1993a
	0.986	Sax, 1979
DL-	0.9807 ($22^\circ C/4^\circ C$)	Lide, 1993
D-	0.9744 ($27^\circ C/4^\circ C$)	
Refractive index	1.4126 ($20^\circ C$)	Lewis, 1993a
DL-	1.4217 ($^\circ C$)	Lide, 1993
Flash point	$168^\circ F$	Lewis, 1993a
	$160^\circ F$ (open cup)	Lewis, 1993b; Sax, 1979
Reactivity	Combustible	Lewis, 1993a
<i>Myristyl Lactate</i>		
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
<i>Cetyl Lactate</i>		
Molecular formula	$C_{19}H_{38}O_2$	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)	Budavari, 1989
	170°C (1 mm Hg)	
	219°C (10 mm Hg)	
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)	Budavari, 1989
	1.4370 (50°C)	
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-(lactoloxo) 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 (Ovrebø 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 (Informat-ics, 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 ≤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

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 ≥ 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
<i>Glycolic Acid (grade not specified)</i>		
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
<i>99% Pure Glycolic Acid</i>		
Face lotion	8.08% (pH 3.70–3.90)	Avon Products Inc., 1995a
<i>70% Aq. Glycolic Acid, nontechnical</i>		
	<8%	ESLUR, 1994b
<i>70% Aq. Glycolic Acid (assumed nontechnical)</i>		
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	
Eyeliners	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.)

[illegible]

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.)

34

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
<i>Lactic Acid (% aq. not specified)</i>		
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
<i>85% Aq. Lactic Acid</i>		
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
<i>L-Lactic Acid</i>		
Skin care product	<8%	ESLUR, 1994a
<i>Potassium Lactate</i>		
Body lotion	<0.1%	CTFA, 1995b
<i>60% Aq. Sodium Lactate</i>		
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
<i>Ethyl Lactate</i>		
Nail enamel corrector	50.00%	Avon Products Inc., 1995d
<i>Lauryl Lactate</i>		
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
<i>Myristyl Lactate</i>		
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
<i>Cetyl Lactate</i>		
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 $\leq 50\%$; 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 $\leq 0.1\%$ (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 $\leq 25\%$; 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 $\leq 50\%$; 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 (%)							Total
	25-50	10-25	5-10	1-5	0.1-1	0-0.1	Unknown	
<i>Lactic Acid</i>								
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 (%)							Total
	25-50	10-25	5-10	1-5	0.1-1	0-0.1	Unknown	
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
<i>Sodium Lactate</i>								
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
<i>TEA Lactate</i>								
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
<i>Lauryl Lactate</i>								
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 (%)							Total
	25-50	10-25	5-10	1-5	0.1-1	0-0.1	Unknown	
1984 Totals (Lauryl Lactate)		2		10		3		15
<i>Myristyl Lactate</i>								
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
<i>Cetyl Lactate</i>								
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*)

Product category	Concentration of use (%)						Unknown	Total
	25-50	10-25	5-10	1-5	0.1-1	0-0.1		
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 $\mu\text{g/kg}$, 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).

GENERAL BIOLOGY

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

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

pH	Bioav. @25°C	Bioavailable concentration (%) at Glycolic Acid concentration:						
		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 μ L of the test formulation were applied without an occlusive patch to a 4-cm² 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 ($\% \pm$ 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
<i>Aqueous solution</i>						
0	40.0 \pm 3.7	28.4 \pm 1.7	16.1 \pm 3.7	1.04 \pm 0.14	N/A	85.7 \pm 2.2
4	55.9 \pm 9.1	19.9 \pm 2.1	11.8 \pm 2.1	0.96 \pm 0.18	N/A	88.5 \pm 3.8
8	40.1 \pm 7.9	17.0 \pm 1.1	16.3 \pm 0.9	0.32 \pm 0.01	N/A	73.7 \pm 5.6
<i>Non-1 liposomes</i>						
0	18.4 \pm 4.2	49.7 \pm 4.5	17.2 \pm 4.0	2.59 \pm 0.90	0.22 \pm 0.07	88.1 \pm 3.2
1	23.1 \pm 4.9	32.1 \pm 3.5	20.6 \pm 3.4	2.83 \pm 0.84	0.40 \pm 0.07	79.0 \pm 3.6
2	23.4 \pm 5.0	26.0 \pm 4.2	19.8 \pm 5.8	2.95 \pm 0.82	1.15 \pm 0.11	72.5 \pm 7.0
4	19.7 \pm 4.5	29.8 \pm 6.0	17.5 \pm 8.1	2.02 \pm 0.80	1.81 \pm 0.49	69.0 \pm 8.0
8	16.3 \pm 2.0	28.0 \pm 5.3	10.9 \pm 3.9	0.81 \pm 0.27	2.10 \pm 0.59	58.1 \pm 5.5
<i>Non-2 liposomes</i>						
0	13.2 \pm 2.0	52.6 \pm 5.1	13.6 \pm 3.8	1.92 \pm 0.93	0.15 \pm 0.03	81.5 \pm 2.3
1	12.6 \pm 3.3	48.8 \pm 8.7	14.7 \pm 4.0	1.45 \pm 0.15	0.13 \pm 0.02	77.6 \pm 2.3
2	21.2 \pm 2.6	41.6 \pm 3.5	9.9 \pm 2.6	1.02 \pm 0.39	0.20 \pm 0.10	73.9 \pm 3.0
4	17.6 \pm 3.7	33.1 \pm 5.7	14.7 \pm 2.5	1.15 \pm 0.34	0.49 \pm 0.11	67.1 \pm 4.1
8	11.0 \pm 0.8	34.3 \pm 1.3	14.6 \pm 1.2	0.95 \pm 0.36	0.83 \pm 0.12	61.7 \pm 2.6
<i>30% PG/water solution</i>						
0	62.8 \pm 4.0	24.6 \pm 3.2	5.3 \pm 1.6	0.36 \pm 0.05	0.09 \pm 0.05	93.1 \pm 1.2
1	68.0 \pm 5.5	16.4 \pm 2.2	7.2 \pm 3.5	0.29 \pm 0.11	0.27 \pm 0.08	92.2 \pm 0.3
2	68.9 \pm 2.7	13.9 \pm 3.1	6.6 \pm 2.3	0.33 \pm 0.07	0.41 \pm 0.16	90.2 \pm 0.5
4	61.9 \pm 6.4	16.0 \pm 3.0	7.4 \pm 0.4	0.51 \pm 0.09	0.42 \pm 0.10	86.3 \pm 2.8
8	68.8 \pm 3.4	12.7 \pm 2.6	5.3 \pm 1.4	0.26 \pm 0.06	0.32 \pm 0.13	87.4 \pm 1.7
<i>O/W emulsion</i>						
0	60.8 \pm 1.3	25.5 \pm 0.9	2.9 \pm 0.7	0.85 \pm 0.28	0.04 \pm 0.03	90.0 \pm 2.0
1	56.1 \pm 6.1	24.9 \pm 2.6	4.9 \pm 2.9	0.77 \pm 0.27	0.06 \pm 0.02	86.8 \pm 2.1
2	57.2 \pm 2.3	21.6 \pm 0.9	6.9 \pm 1.4	0.87 \pm 0.30	0.10 \pm 0.03	86.6 \pm 0.3
4	54.0 \pm 2.0	20.3 \pm 4.0	7.8 \pm 1.0	0.98 \pm 0.23	0.14 \pm 0.05	83.2 \pm 1.8
8	53.9 \pm 1.5	16.2 \pm 1.9	8.1 \pm 0.7	0.89 \pm 0.26	0.36 \pm 0.05	79.3 \pm 1.8
<i>W/O emulsion</i>						
0	46.9 \pm 5.2	22.4 \pm 1.5	6.0 \pm 0.2	0.77 \pm 0.40	0.11 \pm 0.02	76.2 \pm 6.7
1	54.1 \pm 3.4	18.8 \pm 2.0	7.6 \pm 1.4	0.63 \pm 0.31	0.20 \pm 0.06	81.3 \pm 5.2
2	50.0 \pm 3.2	18.1 \pm 2.5	8.2 \pm 1.2	0.88 \pm 0.29	0.32 \pm 0.070	77.5 \pm 0.7
4	57.4 \pm 4.7	12.1 \pm 2.6	5.0 \pm 0.9	0.66 \pm 0.28	.35 \pm 0.15	75.6 \pm 5.1
8	55.1 \pm 7.2	16.2 \pm 8.2	6.1 \pm 0.4	0.57 \pm 0.04	0.47 \pm 0.33	78.5 \pm 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 cm²) 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 ¹⁴C radioactivity per cell. The emulsions were applied to the skin at 3 mg/cm² of exposed skin in the diffusion cells (exposed skin = 0.64 cm²). 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/cm², 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 [³H]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

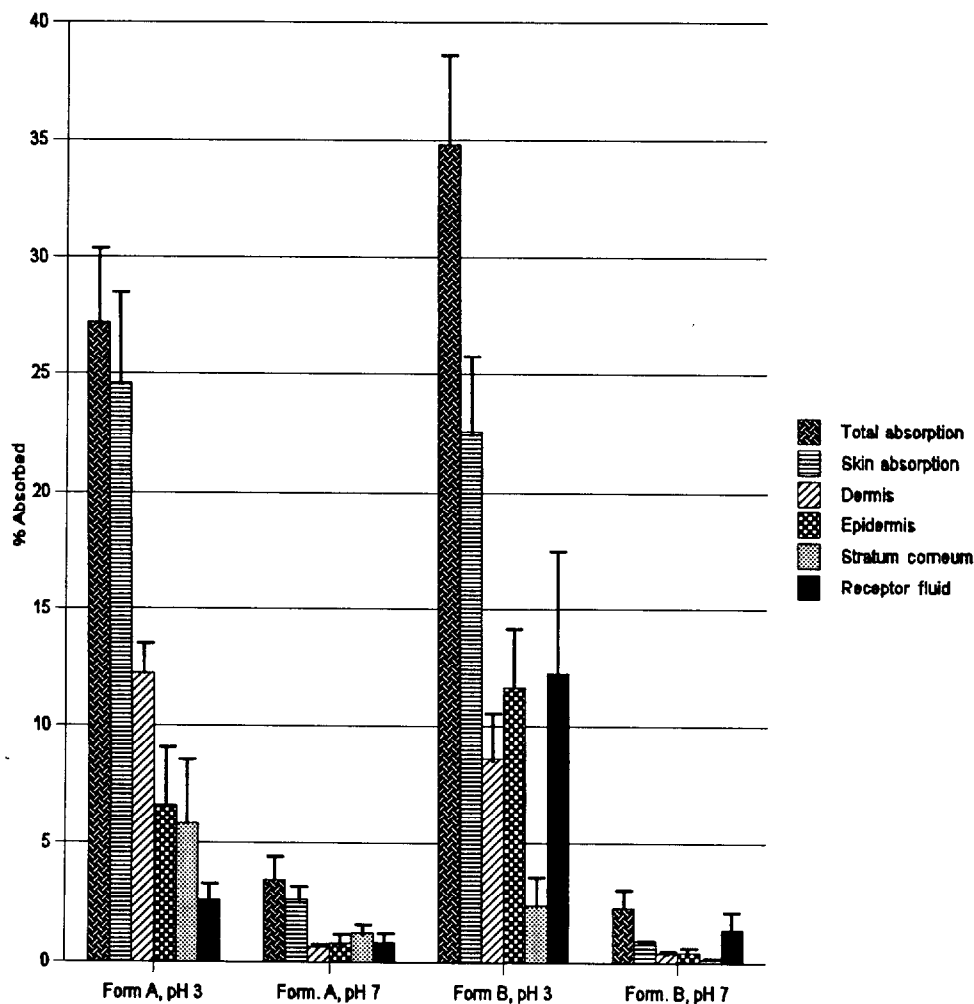


Figure 2. Percentage of applied Glycolic Acid appearing in the receptor fluid, stratum corneum, epidermis, and dermis as a function of the pH of the formulation for two formulations. Skin absorption (stratum corneum + epidermis + dermis) and total absorption (skin absorption + receptor fluid) are also 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 [^3H]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 [^3H]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
<i>Formulation A</i>		
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
<i>Formulation B</i>		
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 [2-¹⁴C]Glycolic Acid solution, 44 mCi/mmol or 250 μ Ci/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 μ L, 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 $2.6 \pm 0.37 \mu\text{g}/\text{cm}^2$, representing $0.15 \pm 0.02\%$ 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 $0.13 \mu\text{g}/\text{cm}^2\text{h}^{-1}$. After 24 h, $0.48 \pm 0.05\%$ of the dose was recovered in the skin and $0.15 \pm 0.02\%$ was found in the receptor phase. Total recovery was $102 \pm 2.9\%$.

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/cm² 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. [¹⁴C(U)]Hydroquinone (specific activity 22.9 mCi/mmol) and [5-¹⁴C]musk xylol (specific activity 19.76 mCi/mmol) in ethanol were applied to the skin in o/w emulsion vehicles (3 mg/cm²) at a chemical dose of approximately 2.5 and 5.0 μg/cm², 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 μ mol/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 μ mol/day (92–429 mg/day).

Two female rhesus monkeys were dosed orally with 4 mL/kg of 500 mg/kg homogenous [14 C]Glycolic Acid, 0.73 μ C/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 cm² 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- μ L 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, $2.2 \pm 1.6\%$ 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 $50.7 \pm 2.2\%$ for fasted rats and from 2.8 ± 1.0 to $49.9 \pm 7.6\%$ 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 [$1\text{-}^{14}\text{C}$]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 $81\text{--}2\text{ mg/kg h}^{-1}$ in

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

pH	Bioav. @25°C	Bioavailable concentration (%) at Lactic Acid concentration:						
		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-[¹⁴C(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- μ m thickness, was mounted on Bronaugh flow-through cells, and barrier integrity was assessed using transepidermal water loss. A finite dose, 2 μ L, and an infinite dose, 75 μ L, 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 \pm 1.2	0.37 \pm 0.09
Stratum corneum	6.3 \pm 1.4	3.24 \pm 0.77
Viable epidermis	6.6 \pm 0.9	3.22 \pm 0.84
Dermis	13.9 \pm 2.3	2.90 \pm 1.3
Total in skin	26.8 \pm 4.5	9.36 \pm 2.08
Total absorption	30.4 \pm 3.3	9.73 \pm 2.03

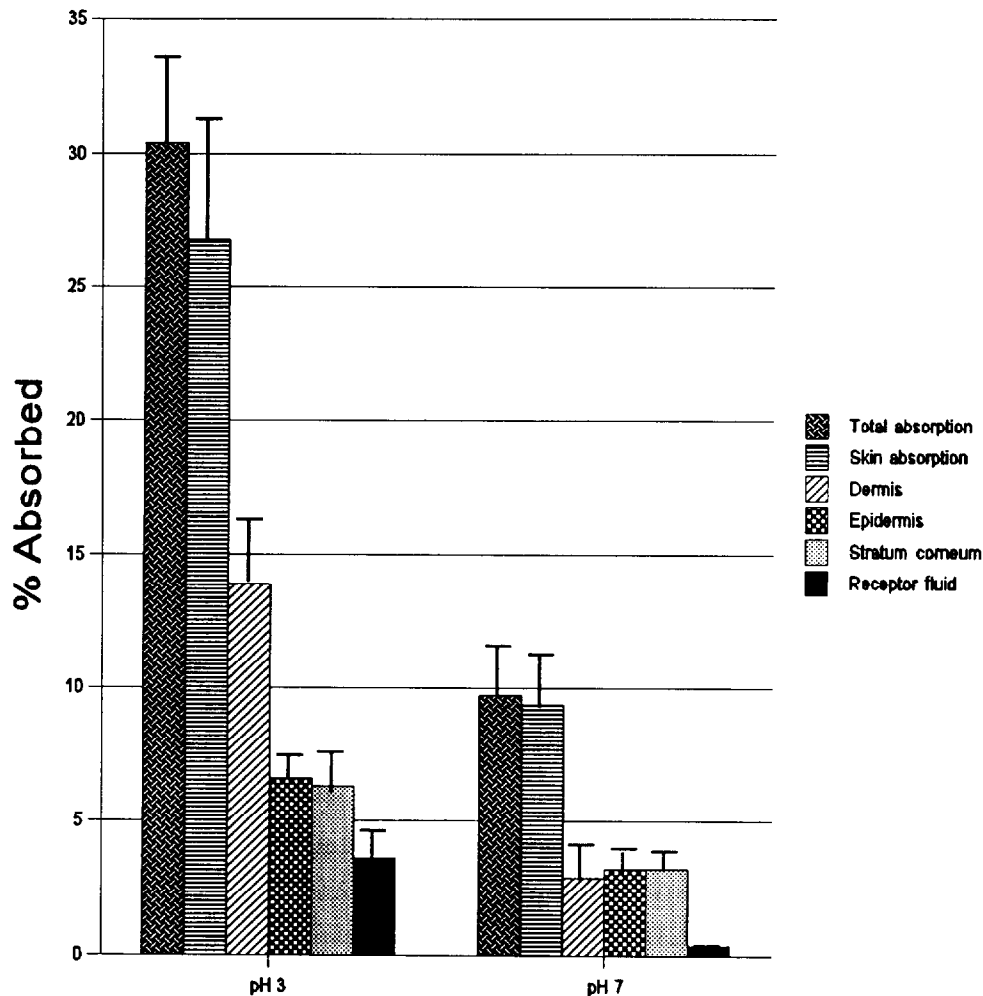


Figure 3. Percentage of applied Lactic Acid appearing in the receptor fluid, stratum corneum, epidermis, and dermis as a function of the pH of the formulation. Skin absorption (stratum corneum + epidermis + dermis) and total absorption (skin absorption + receptor fluid) are also shown. Samples were taken 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 ± 0.03 as compared to 7.50 ± 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 $\mu\text{mol/kg min}^{-1}$ 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 \times 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 [¹⁴C]hydrocortisone or [¹⁴C]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 C₈, 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 C₄.

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.

ANIMAL TOXICOLOGY

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 LD₅₀ 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 LD₅₀ of Butyl Lactate was >5000 mg/kg (MB Research Laboratories, Inc., 1977).

ACUTE ORAL TOXICITY

Glycolic Acid

The oral LD₅₀ 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 LD₅₀ 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.

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 LD₅₀ 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 LD₅₀ 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 NADH₂.

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 ≥ 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 LD₅₀ 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 LD₅₀ 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 LD₅₀ of Lactic Acid for mice was 4875 mg/kg (FAO/WHO, 1967).

L-Lactic Acid. The oral LD₅₀ of L-Lactic Acid for rats was 3730 mg/kg (Smyth et al., 1941).

Ammonium Lactate. The oral LD₅₀ 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 LD₅₀ 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 LD₅₀ 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 LD₅₀ of Ethyl Lactate for rats was 8200 mg/kg.

Using 10 rats the oral LD₅₀ 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 LD₅₀ was 2500 mg/kg (Opdyke and Letizia, 1982). The oral LD₅₀ and LD₁₀₀ 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 LD₅₀ 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
<i>60% Aq. Sodium Lactate</i>						
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
<i>Lauryl Lactate</i>						
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
<i>Cetyl Lactate</i>						
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	0	>15,000 mg/kg	Prac. nontoxic
			50% in corn oil			
Lipstick	3	N/A	10,000 mg/kg	0	>10,000 mg/kg	Acceptable
			33.3% in corn oil			
Lipstick	3	N/A	10,000 mg/kg	0	>10,000 mg/kg	Acceptable
			33.3% in corn oil			
Lipstick	3	N/A	10,000 mg/kg	0	>10,000 mg/kg	Acceptable
			33.3% in corn oil			
Lipstick	3	N/A	10,000 mg/kg	0	>10,000 mg/kg	Acceptable
			33.3% in corn oil			
Lipstick	3	N/A	10,000 mg/kg	0	>10,000 mg/kg	Acceptable
			33.3% in corn oil			
Lipstick	3	N/A	10,000 mg/kg	0	>10,000 mg/kg	Acceptable
			33.3% in corn oil			
Lip Pencil	3	N/A	10,000 mg/kg	0	>10,000 mg/kg	Acceptable
			33.3% in corn oil			

(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	0	>15,000 mg/kg	Prac. nontoxic
			50% in corn oil			
Foundation	5	6.0	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
Lipstick	7.5	N/A	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
			33.3% in corn oil			
Lipstick	9	N/A	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
			50% in corn oil			
Lipstick	9	N/A	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
			50% in corn oil			
Lipstick	9	N/A	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
			50% in corn oil			
Lipstick	9	N/A	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
			50% in corn oil			
Lipstick	9	N/A	15,000 mg/kg	0	>15,000 mg/kg	Prac. nontoxic
			50% in corn oil			

^aNumber of deaths out of 5 fasted female rats given oral doses.

10,000 mg/kg. No deaths were observed. The rat oral LD₅₀ 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 LD₅₀ 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 LD₅₀ was >20 mL/kg.

ACUTE INHALATION TOXICITY

Glycolic Acid

The 4-h inhalation LC₅₀ 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 LD₅₀ of Glycolic Acid for the rat was 1000 mg/kg (Sax, 1979).

Calcium Glycolate. The IV LD₅₀ 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 LD₅₀ 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 LD₅₀ 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 LD₅₀ 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) LD₅₀ and LD₁₀₀ 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 LD₅₀ and LD₁₀₀ 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 ≤ 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 $463\times$ 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 pre-hydrated 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
<i>Lauryl Lactate</i>					
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
<i>Myristyl Lactate</i>					
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
<i>Cetyl Lactate</i>					
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

^aPII = 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 MMIs of 0.73 and 0.33, respectively. With 70% Sodium Lactate, both the undiluted and diluted (14%) solutions were relatively well tolerated, with MMIs 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 (Sander-son, 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 RC₅₀ 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
<i>Glycolic Acid</i>							
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% <i>unrinsed</i> : severe irritation 24% <i>rinsed</i> : 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
<i>Potassium Glycolate</i>							
—	100 mg	—	Rabbit	Not available	—	Mild irritant	RTECS, 1995
<i>Ethyl Glycolate</i>							
—	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
<i>Lactic Acid</i>							
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.	<i>Positives:</i> 4/day 1-2; 0/day 3-4, and 7 <i>Opacities:</i> 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	<i>Journal Officiel de la République Française</i> 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.	<i>Undiluted:</i> total destruction of the entire eye structure and surrounding membrane was evident. <i>Diluted:</i> no irritation		Stauffer chemical Co., 1971
<i>Ammonium Lactate</i>							
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
<i>Potassium Lactate</i>							
—	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 <i>Mean ocular irritation index:</i> 0 after 4 days Slight corneal opacity was seen after 1 h	Slightly irritating	Guillot et al., 1982b
<i>Sodium Lactate</i>							
—	50% 70%	—	Rabbits	<i>Journal Officiel de la République Française</i> 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
<i>60% Aq. Sodium Lactate</i>							
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.	<i>Positives:</i> 0/day 1 <i>Opacities:</i> 0/day 1	No irritation	Avon Products, Inc., 1995c
Face cream	0.1%	N/A			<i>Positives:</i> 0/day 2 <i>Opacities:</i> 0/day 2	Minimal irritation	Avon Products, Inc., 1995c
Night cream	0.2%	N/A			<i>Positives:</i> 0/day 2 <i>Opacities:</i> 0/day 2	Minimal irritation	Avon Products, Inc., 1995c
Hair conditioner	0.2%	3.4			<i>Positives:</i> 3/day 1; 1/day 2–4; 0/day 7 <i>Opacities:</i> 0/days 1–4, 7	Mild irritation	Avon Products, Inc., 1995c
Hair conditioner	0.2%	3.45 5			<i>Positives:</i> 1/day 1–2; 0/day 3 <i>Opacities:</i> 0/day 1–3	Minimal irritation	Avon Products, Inc., 1995c

Hair conditioner	0.2%	4.9			<i>Positives:</i> 0/day 1 <i>Opacities:</i> 0/day 1	No irritation	Avon Products, Inc., 1995c
Hair conditioner	0.2%	5.0			<i>Positives:</i> 0/day 1 <i>Opacities:</i> 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.	<i>Positives:</i> 1/day 1; 0/day 2 <i>Opacities:</i> 0/day 1-2 <i>Positives:</i> 1/day 1; 0/day 2 <i>Opacities:</i> 1/day 1 0/day 2	Minimal irritation	Avon Products, Inc., 1995c
Shampoo	0.2%	5.5			<i>Positives:</i> 1/day 1; 0/day 2 <i>Opacities:</i> 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.	<i>Positives:</i> 2/day 1; 0/day 2-4; 1/day 7 <i>Opacities:</i> 0/day 1-4, 7	Mild irritation	Avon Products, Inc., 1995c
Face lotion	0.2%	6.55			<i>Positives:</i> 0/day 1 <i>Opacities:</i> 0/day 1	No irritation	Avon Products, Inc., 1995c
Face lotion	0.2%	7.0			<i>Positives:</i> 1/day 1, 3, 7; 0/day 2, 4 <i>Opacities:</i> 0/day 1-4, 7 <i>Positives:</i> 3/day 1; 0/day 2 <i>Opacities:</i> 0/day 1, 2	Mild irritation	Avon Products, Inc., 1995c
Face cream	0.2%	7.9			<i>Positives:</i> 3/day 1; 0/day 2 <i>Opacities:</i> 0/day 1, 2 <i>Positives:</i> 1/day 1 0/day 2, 3 <i>Opacities:</i> 0/day 1-3	Minimal irritation	Avon Products, Inc., 1995c
Night cream	0.2%	8.6			<i>Positives:</i> 1/day 1 0/day 2, 3 <i>Opacities:</i> 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.	<i>Positives:</i> 6/day 1, 3/day 2; 1/day 3; 0/day 4 <i>Opacities:</i> 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.	<i>Positives:</i> 0/day 1-4, 7 <i>Opacities:</i> 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		<i>Positives:</i> 0/day 3 <i>Opacities:</i> 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).	<i>AOI:</i> 12.00/110 <i>MOI:</i> 2.50 after 2 days No corneal opacity	Slight irritant	Guillot et al., 1982b
—	—	—	Guinea pig	<i>Methyl Lactate</i> 10 μ L was applied to the corneal surface of one eye and the other eye served as a control		No irritation	Sanderson, 1959
Nail enamel corrector pen	50%	N/A	3 albino rabbits	<i>Ethyl Lactate</i> Standard operating procedures as described earlier (Avon Products, Inc., 1988). One instillation of undiluted material was made, and the eyes were not rinsed.	<i>Positives:</i> 6/day 1–2; 1/day 3–4; 2/day 7 <i>Opacities:</i> 6/day 1; 5/day 2	Moderate irritation	Avon Products Inc., 1995d
Nail enamel corrector pen	50%	N/A			<i>Positives:</i> 6/day 1–2; 4/day 3; 2/day 4; 0/day 7 <i>Opacities:</i> 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
Face cream	5%	4.65	5 rabbits	<i>Lauryl Lactate</i> 0.5 mL was instilled into the eye for 1 min; the other eye served as a control.	<i>Positives:</i> 5/day 1; 2/day 2; 0/day 4–7 <i>Opacities:</i> 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.	<i>Positives:</i> 4/day 1; 1/day 2-3; 0/day 7 <i>Opacities:</i> 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.	<i>Positives:</i> 5/day 1; 3/day 2; 1/day 3; 0/day 7 <i>Opacities:</i> 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.	<i>Positives:</i> 2/day 1; 0/Day 2-4, 7 <i>Opacities:</i> 0/day 1-4, 7	Minimal irritation	Avon Products Inc., 1995e
<i>Myristyl Lactate</i>							
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.	<i>Positives:</i> 1/day 1-2; 0/day 3-7 <i>Opacities:</i> 0/day 1-4, 7	Mild irritation	Avon Products Inc., 1995f
Lip pencil	11.54%	N/A			<i>Positives:</i> 0/day 1-4, 7 <i>Opacities:</i> 0/day 1-4, 7	No irritation	Avon Products Inc., 1995f
<i>Cetyl Lactate</i>							
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.	<i>Positives:</i> 0/day 1-2; 1/day 3; 0 day 4, 7 <i>Opacities:</i> 0/day 1-4, 7	Mild irritation	Avon Products Inc., 1995g
Face lotion	0.75%	N/A			<i>Positives:</i> 0/day 1; 1/day 2-4, 7 <i>Opacities:</i> 0/day 1-4; 1/day 7	Mild irritation	Avon Products Inc., 1995g
Aftershave moisturizer	0.75%	7.0-8.0			<i>Positives:</i> 0/day 1-4, 7 <i>Opacities:</i> 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.	<i>Positives:</i> 4/day 1; 2/day 2; 0/day 3 <i>Opacities:</i> 0/day 1-3	Minimal irritation	Avon Products Inc., 1995g
Face lotion	0.75%	7.85			<i>Positives:</i> 2/day 1-2; 1/day 3; 0/day 4, 7 <i>Opacities:</i> 0/day 1-4, 7	Mild irritation	Avon Products Inc., 1995g
Face lotion	0.75%	7.9			<i>Positives:</i> 0/day 1-4, 7 <i>Opacities:</i> 0/day 1-4, 7	No irritation	Avon Products Inc., 1995g
Moisturizing cream	1%	N/A			<i>Positives:</i> 2/day 1-2; 1/day 3-4; 0/day 7 <i>Opacities:</i> 0/day 1-4, 7	Mild irritation	Avon Products Inc., 1995g
Body lotion	1%	N/A			<i>Positives:</i> 6/day 1-4; 4/day 4 <i>Opacities:</i> 6/day 1-4; 5/day 7	Severe irritation	Avon Products Inc., 1995g
Night cream	1%	6.2			<i>Positives:</i> 0/day 1 <i>Opacities:</i> 0/day 1	No irritation	Avon Products Inc., 1995g
Moisture cream	1%	6.5			<i>Positives:</i> 2/day 1, 2, 7; 1/day 3; 0/day 4 <i>Opacities:</i> 0/day 1-4, 7	Mild irritation	Avon Products Inc., 1995g
Moisture lotion	1%	7.0			<i>Positives:</i> 1/day 1, 3, 7; 0/day 2, 4 <i>Opacities:</i> 0/day 1-4, 7	Mild irritation	Avon Products Inc., 1995g
Cleansing cream	1%	7.15			<i>Positives:</i> 3/day 1; 1/day 2; 0/day 3-4, 7 <i>Opacities:</i> 0/day 1-4, 7	Mild irritation	Avon Products Inc., 1995g
Cleansing cream	1%	7.2-8.0			<i>Positives:</i> 1/day 1; 0/day 2; <i>Opacities:</i> 0/day 1-2	Minimal irritation	Avon Products Inc., 1995g

Moisturizing cream	1%	7.2-8.0			<i>Positives:</i> 0/day 1 <i>Opacities:</i> 0/day 1	No irritation	Avon Products Inc., 1995g
Moisturizing cream	1%	7.8			<i>Positives:</i> 0/day 1 <i>Opacities:</i> 0/day 1	No irritation	Avon Products Inc., 1995g
Body lotion	1.1%	7.0			<i>Positives:</i> 2/day 1, 3 ; 3/day 2; 1/day 4, 7 <i>Opacities:</i> 0/day 1-4, 7 <i>Positives:</i> 0/day 1-4, 7 <i>Opacities:</i> 0/day 1-4, 7	Mild irritation	Avon Products Inc., 1995g
Moisturizing cream	1.5%	6.1			<i>Positives:</i> 0/day 1-4, 7 <i>Opacities:</i> 0/day 1-4, 7		Avon Products Inc., 1995g
Lip pencil	3%	N/A			<i>Positives:</i> 0/day 1-4, 7 <i>Opacities:</i> 0/day 1-4, 7	No irritation	Avon Products Inc., 1995g
Lipstick	3%	N/A			<i>Positives:</i> 0/day 1 <i>Opacities:</i> 0/day 1	No irritation	Avon Products Inc., 1995g
Lipstick	3%	N/A			<i>Positives:</i> 0/day 1 <i>Opacities:</i> 0/day 1	No irritation	Avon Products Inc., 1995g
Lipstick	3%	N/A			<i>Positives:</i> 0/day 1 <i>Opacities:</i> 0/day 1	No irritation	Avon Products Inc., 1995g
Lipstick	3%	N/A			<i>Positives:</i> 0/day 1 <i>Opacities:</i> 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.	<i>Positives:</i> 1/day 1; 0/day 2 <i>Opacities:</i> 0/day 1-2	No irritation	Avon Products Inc., 1995g
Lipstick	3%	N/A			<i>Positives:</i> 1/day 1; 0/day 2 <i>Opacities:</i> 0/day 1-2	No irritation	Avon Products Inc., 1995g
Lipstick	3%	N/A			<i>Positives:</i> -/day 1; 0/day 2 <i>Opacities:</i> -/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			<i>Positives:</i> 2/day 1; 5/day 2; 0/day 3-4, 7 <i>Opacities:</i> 0/day 1-4, 7	Minimal irritation	Avon Products Inc., 1995g
Foundation	3%	7.05			<i>Positives:</i> 0/day 1-4, 7 <i>Opacities:</i> 0/day 1-4, 7	No irritation	Avon Products Inc., 1995g
Lipstick	4.5%	N/A			<i>Positives:</i> 0/day 1-4, 7 <i>Opacities:</i> 0/day 1-4, 7	No irritation	Avon Products Inc., 1995g
Lipstick	5%	N/A			<i>Positives:</i> 1/day 1; 0/day 2-4, 7 <i>Opacities:</i> 0/day 1-4, 7	Minimal irritation	Avon Products Inc., 1995g
Foundation	5%	6.0			<i>Positives:</i> 1/day 1; 0/day 2-4, 7 <i>Opacities:</i> 0/day 1-4, 7	Minimal irritation	Avon Products Inc., 1995g
Foundation	5%	6.0			<i>Positives:</i> 2/day 1; 1/day 2; 0/day 3-4 <i>Opacities:</i> 0/day 1-4	Minimal irritation	Avon Products Inc., 1995g

Lipstick	7.5%	N/A	<i>Positives: 3/day 1; 0/day 2</i>	Minimal irritation	Avon Products Inc., 1995g
Lipstick	9%	N/A	<i>Opacities: 0/day 1-2 Positives: 0/day 1 Opacities: 0/day 1</i>	No irritation	Avon Products Inc., 1995g
Lipstick	9%	N/A	<i>Positives: 0/day 1 Opacities: 0/day 1</i>	No irritation	Avon Products Inc., 1995g
Lipstick	9%	N/A	<i>Positives: 0/day 1 Opacities: 0/day 1</i>	No irritation	Avon Products Inc., 1995g
Lipstick	9%	N/A	<i>Positives: -/day 1; 0/day 2 Opacities: -/day 1; 0/day 2</i>	Minimal irritation	Avon Products Inc., 1995g
Lipstick	9%	N/A	<i>Positives: -/day 1; 0/day 2 Opacities: -/day 1; 0/day 2;</i>	Minimal irritation	Avon Products Inc., 1995g
Lipstick	9%	N/A	<i>Positives: 5/day 1; 1/day 2; 0/day 3-4, 7 Opacities: 0/day 1-4, 7</i>	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
<i>85% Aq. Lactic Acid</i>							
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
<i>85% Aq. Lactic Acid tested at 25%</i>							
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
<i>60% Aq. Sodium Lactate</i>							
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	8.7	Minimal irritant	Avon Products Inc., 1995c
				Minimal-RMA	5.0		
<i>Lauryl Lactate</i>							
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
<i>Myristyl Lactate</i>							
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
<i>Cetyl Lactate</i>							
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.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

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 sternbrae, hemi-vertebrae, misaligned and incompletely ossified sternbrae, 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 CrI: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

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 hair-coats 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 embryoletality. 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 B₆C₃F₁ 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 of 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-K₁) 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 $\mu\text{g}/\text{mL}$ active ingredient, the concentration range used for the assay was 625–5000 $\mu\text{g}/\text{mL}$ 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

cultures, and untreated cultures served as negative control groups. At the highest dose concentration, 5000 $\mu\text{g/mL}$, 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 $\mu\text{g/mL}$ 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 $\mu\text{L/plate}$ 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
<i>Lactic Acid</i>				
Ames test	<i>S. typhimurium</i> TA100	2 mg/mL	Negative	Yamaguchi and Nakagawa, 1983 ESLUR, 1994a
Ames test	<i>S. typhimurium</i> TA92, TA1535, TA100, TA98, TA1537, TA94	≤10.0 mg/plate of 90.5% pure Lactic Acid	Chromosomal damage in the absence of metabolic activation 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	<i>S. typhimurium</i> 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	<i>S. typhimurium</i> TA1535, TA1537, TA1538	0.045–0.18% USP grade Lactic Acid	Negative with and without metabolic activation	Litton Bionetics, Inc., 1976
Suspension tests	<i>S. typhimurium</i> ; <i>Saccharomyces cerevisiae</i>		Negative in nonactivation and activation tests	Litton Bionetics, Inc., 1976
"Streptomycin" method	<i>E. coli</i> B/Sd-4/1, 3, 4, 5, B/Sd-4/3, 4	0.01–0.021% Lactic Acid 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 μ M Lactic Acid	Negative in the presence and absence of lysozyme, liver extract, and lysozyme and liver extract	Kubinski et al., 1981
Reversion test	<i>S. typhimurium</i> hisC3076	Treated in growth and nongrowth media with 9-aminoacridine	"Intermediate" mutant yields in the presence of Lactic Acid	Kopsidas and MacPhee, 1994
<i>Ammonium Lactate</i>				
Ames test	<i>S. typhimurium</i> TA1515, TA1517, TA1538, TA98; <i>Saccharomyces</i> D4	1-1000 μ g/plate of a 12% lotion	Negative with and without metabolic activation	FDA, 1988
<i>Sodium Lactate</i>				
Ames test	<i>S. typhimurium</i> TA92, TA1535, TA1537, TA100, TA94, TA98	\leq 100.0 mg/plate 50.8% pure Sodium Lactate	Negative with metabolic activation	Ishidate et al., 1984
Chromosomal aberration test	Chinese hamster fibroblast cells	\leq 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 \leq 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 ≤ 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 ≤ 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 μ M 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 μ g/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 ≤ 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 ≤ 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 subtilis*. 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

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.

CLINICAL ASSESSMENT OF SAFETY

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/cm²). 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

Table 25. TEWL (G/m²/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/cm² 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/cm² 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/cm² 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/cm² 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 ($3\text{--}8\text{ g/m}^2\text{ h}^{-1}$). 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 $\text{g/m}^2\text{ h}^{-1}$ 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 non-statistically significant trend of improved barrier function capabilities, with higher pH having a greater increase in barrier function (13, 17, and

Table 27. TEWL ($\text{g/m}^2/\text{h}$) 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 ($\text{g/m}^2 \text{ h}^{-1}$)

	Pre-SLS	Post-SLS	Difference
Study 1			
<i>4.0% Glycolic Acid, pH 4.0</i>			
Mean	4.38	12.00	7.62
SD	1.48	4.64	3.78
<i>Vehicle</i>			
Mean	5.90	15.92	10.02
SD	2.31	3.67	1.64
<i>P</i> value	0.090	0.073	0.20
Study 2			
<i>4.0% Glycolic Acid, pH 3.7</i>			
Mean	3.45	9.90	6.45
SD	0.95	3.24	2.62
<i>Vehicle</i>			
Mean	4.15	12.12	7.97
SD	1.53	3.91	2.99
<i>P</i> 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 skin-care 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/cm² 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/cm² 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			
<i>4.0% D, L-Lactic Acid, pH 4.0</i>			
Mean	4.38	12.00	7.62
SD	1.48	4.64	3.78
<i>Vehicle</i>			
Mean	5.90	15.92	10.02
SD	2.31	3.67	1.64
P Value	0.090	0.073	0.20
Study 2			
<i>4.0% D, L-Lactic Acid, pH 3.7</i>			
Mean	3.45	9.90	6.45
SD	0.95	3.24	2.62
<i>Vehicle</i>			
Mean	4.15	12.12	7.97
SD	1.53	3.91	2.99
P Value	0.081	0.006	0.008
<i>4.0% L-Lactic Acid, pH 3.7</i>			
Mean	4.15	12.12	7.97
SD	1.53	3.91	2.99
<i>Vehicle</i>			
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 $18 \text{ g/cm}^2 \text{ h}^{-1}$ 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 [¹⁴C] 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 hygroscopicity 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 punch 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 2² 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 antebrachio-radialis 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 $\text{g/m}^2 \text{ h}^{-1}$, 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 $\text{g/m}^2 \text{ h}^{-1}$, 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 untreated 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 (CO₂ [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

^aPII = Primary irritation index.^bDrops 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

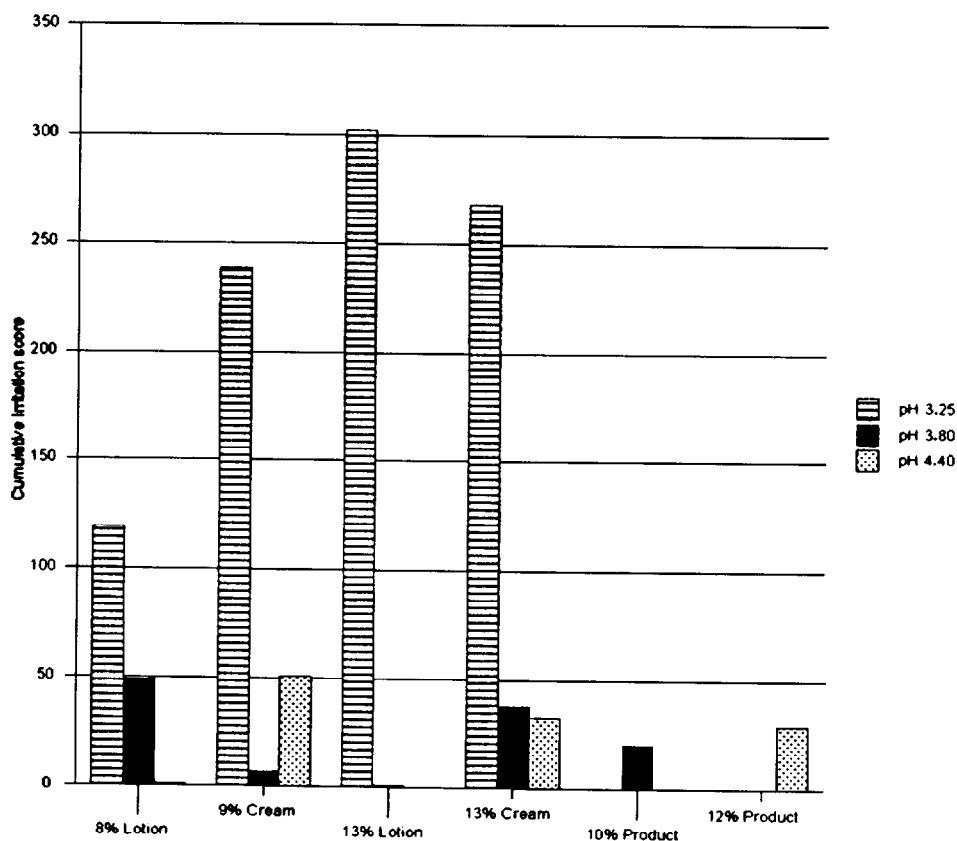


Figure 4. Cumulative irritation scores in 21 subjects using creams containing 9 and 13% Glycolic Acid and lotions containing 8 and 13% Glycolic Acid, each at three pH levels, 3.25, 3.80, and 4.40, compared to a marketed 12% Lactic Acid product at pH 4.40 and a marketed 10% Glycolic Acid product at pH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

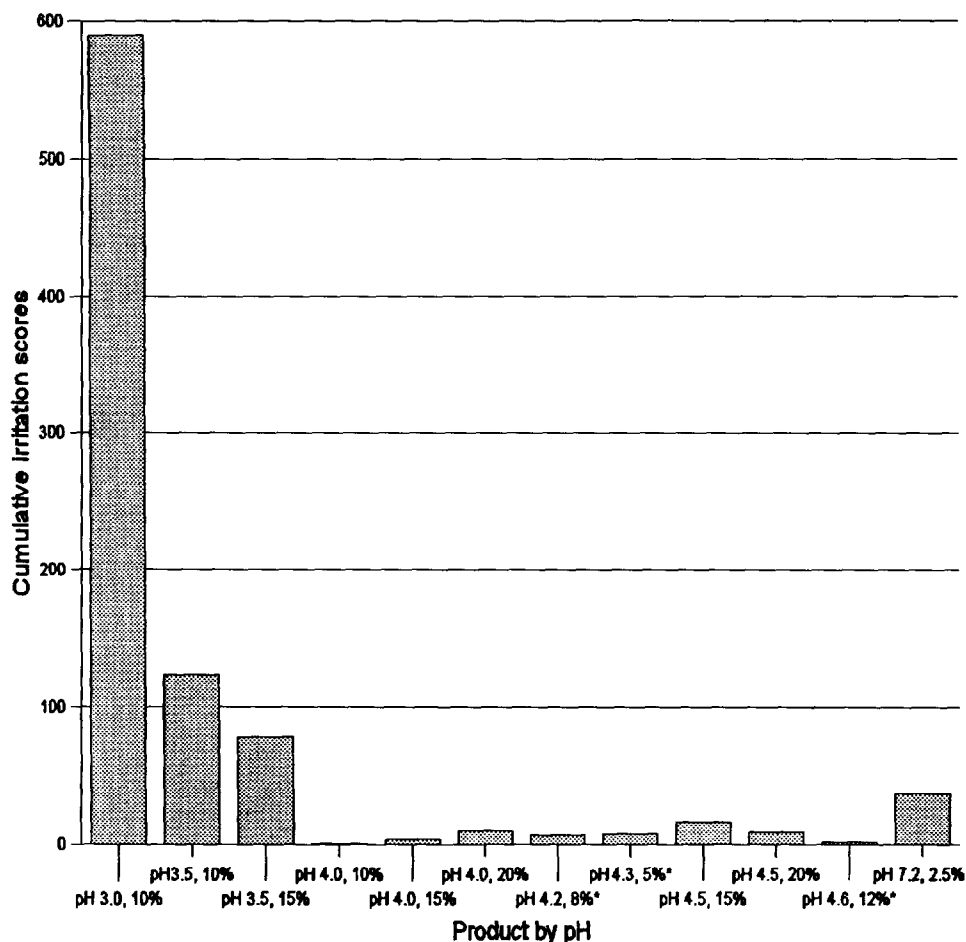


Figure 5. Cumulative irritation scores (maximum score = 966) as a function of pH of Glycolic Acid treatment. A total of 23 subjects were tested with a formulation containing 10% Glycolic Acid at pH 2.0, 2.5, 3.0, 3.25, 3.8, and 4.4. Formulations containing 15 and 20% Glycolic Acid at pH 3.8, and four 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

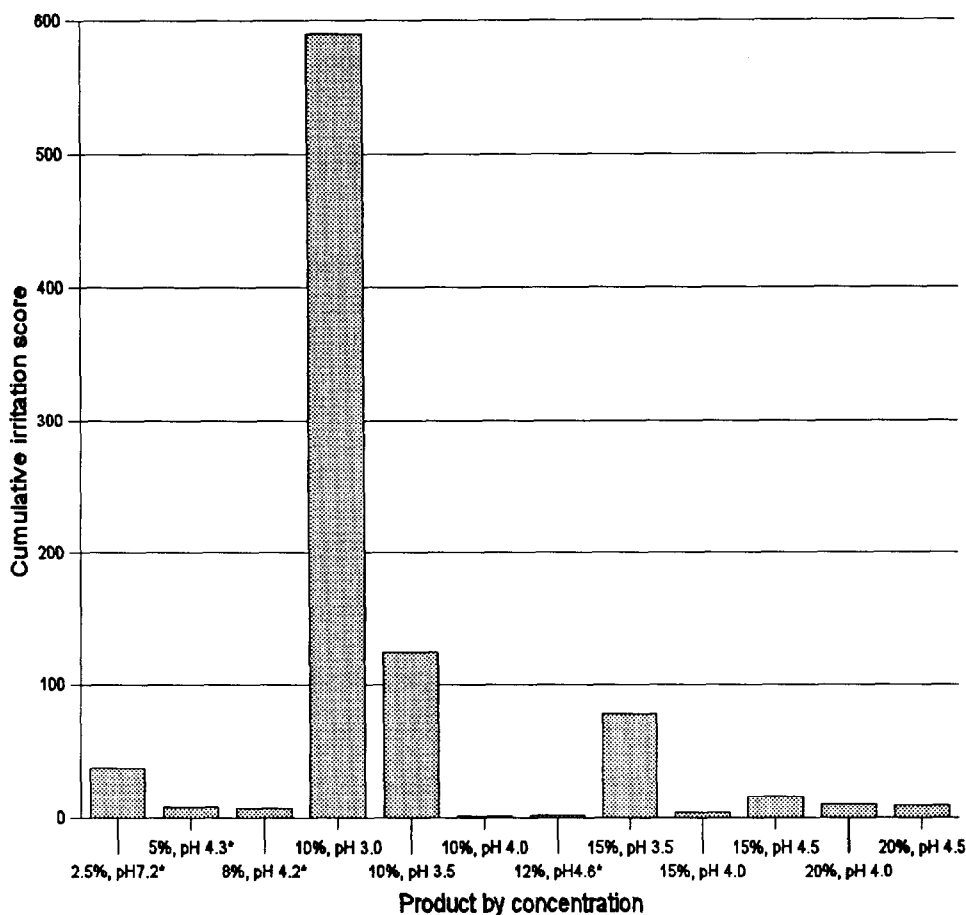


Figure 6. Cumulative irritation scores as described in Figure 5 as a function of concentration of the preparation. Asterisk denotes commercial preparations (DiNardo, 1995).

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 stinging 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	Dis-comfort ^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

^aDiscomfort denotes the number of test subjects that perceived discomfort.

^bTSS denotes the total sting score, which is the sum of all scores at 0, 2.5, and 5.0 min.

^cDMS denotes delayed mean sting score.

^dDiscomfort 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/cm² 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/reactions	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	3.9	20- 2%	Follicular irritation chest test in which gels/vehicle were applied 2×/day for 7 days.	2%: 10% (2/20) follicular activity	CTFA, 1991f
	4	3.9	10- 4% 10- vehicle		4%: 40% (4/10) follicular activity	
Gel	2	3.9	10- 2%	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	CTFA, 1991f
	4	3.9	20- 4%		4%: 30% (6/20) significant follicular irritation Vehicle: no follicular activity	
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	4	3.7	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	CTFA, 1992b
Lotion	4	3.8			1 subject had mild flaking with both substances	
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	CTFA, 1990b
Lotion	4 8	3.8 3.7	34	4-wk split-face test was done in which subjects applied the lotions 2x/day.	3 (6%) with the moisturizer 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 2x/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 1x/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/reactions	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 2x/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 2x/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	Mildly 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

^aPII = Primary irritation index.^bDrops 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

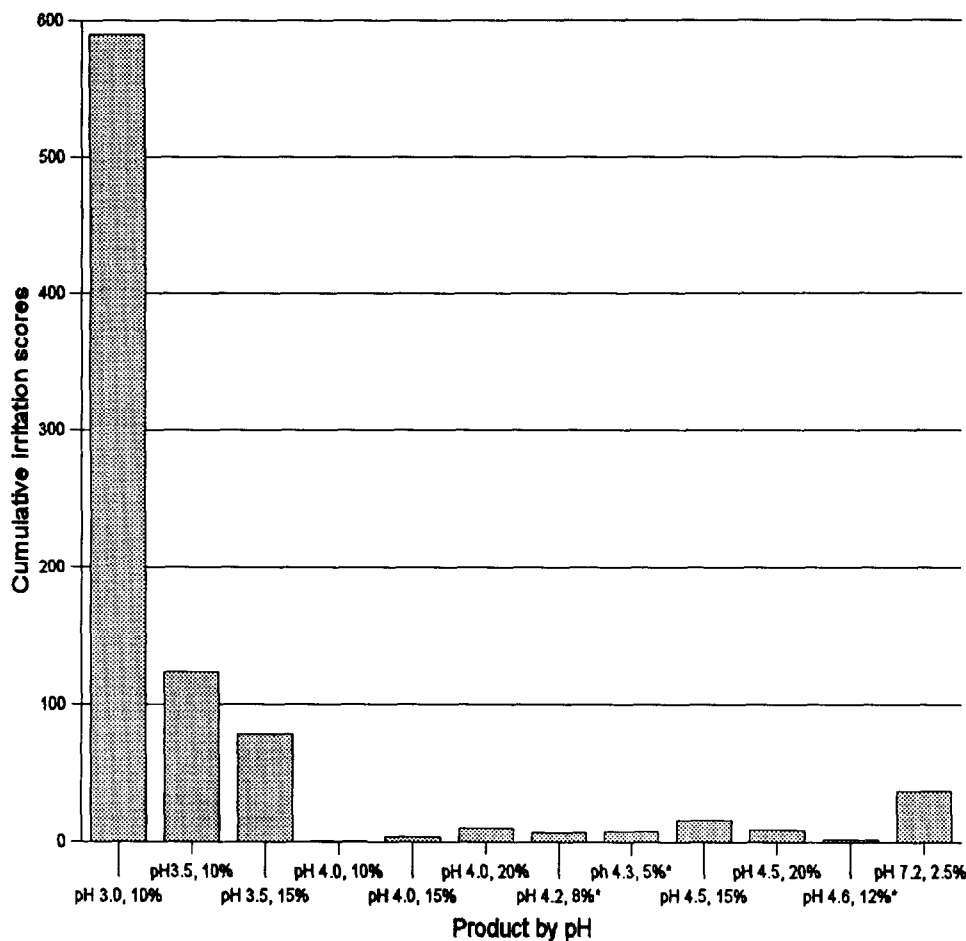


Figure 7. Cumulative irritation scores (maximum score = 966) as a function of pH of Lactic Acid treatment. A total of 23 subjects were tested using three formulations containing 10, 15, and 20% Lactic Acid at pH 3.5–4.5. Four commercially available formulations (see asterisk), containing 2.5–12% Lactic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

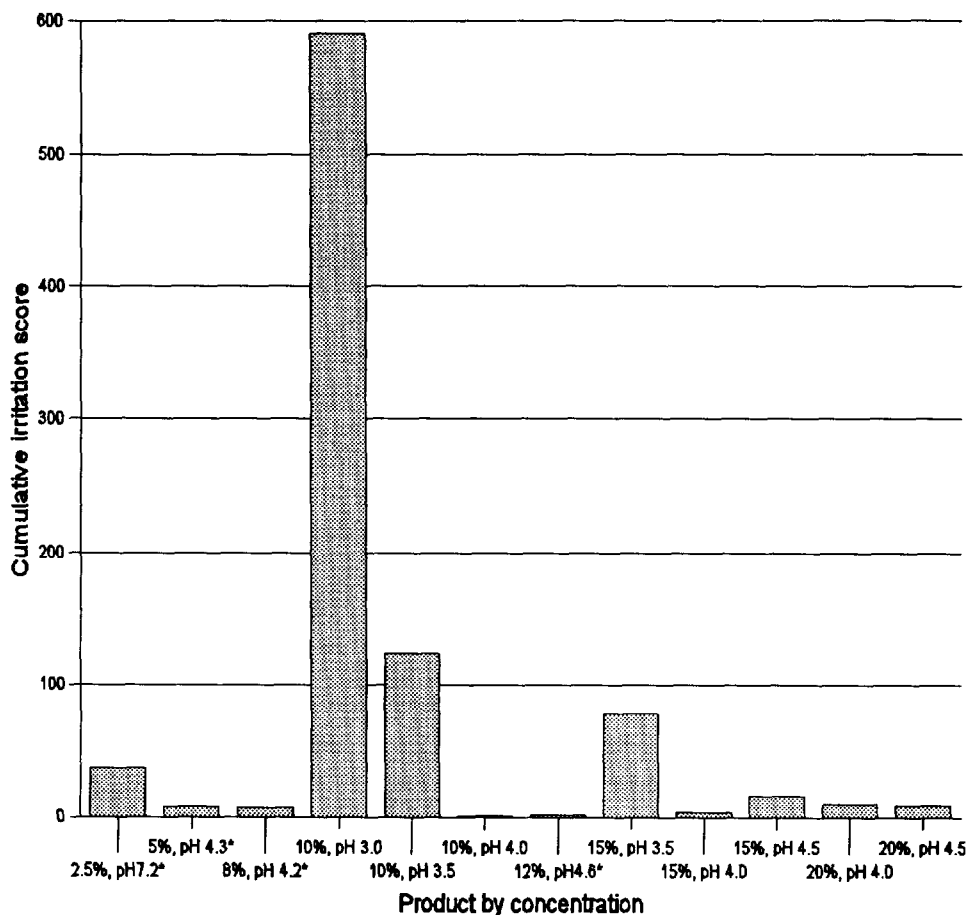


Figure 8. Cumulative irritation scores as described in Figure 7 as a function of concentration of the formulation. See asterisk for commercial preparations (Essex Testing Clinic, 1996).

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

^aDiscomfort denotes the number of test subjects that perceived discomfort.

^bTSS denotes the total sting score which is the sum of all scores at 0, 2.5, and 5.0 min.

^cDMS denotes delayed mean sting score.

^dDiscomfort 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/cm² 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 (CO₂ [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 (Recherche e Technologie Cosmetologique [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	AMA Labs., Inc., 1993a
RIPT	—	3%	3.8 ± 0.1	53/57 (15M, 38F)	Nonprimary sensitizer	AMA Labs., Inc., 1993b
RIPT	Lotion	1% MFA 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

^aETC = Essex Testing Clinic, Inc.

^bCPT = 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 non-treatment 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 μ L 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 pre-treatment 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 pre-treatment 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 $\mu\text{L}/\text{cm}^2$ 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 $0.22 \text{ J/cm}^2 \text{ min}^{-1}$ at $15 \pm 2 \text{ cm}$, for a total dose of 3.3 J and to UVB light from a Solarium 300, which delivers a dose of approximately $1.2 \text{ mJ/cm}^2 \text{ min}^{-1}$ at $22 \pm 2 \text{ cm}$, 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 $0.22 \text{ J}/\text{cm}^2 \text{ min}^{-1}$ at $15 \pm 2 \text{ cm}$, 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 $\leq 20.04\%$ 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 ($\sim 4 \text{ mm} \times 4 \text{ mm}$) was taken from each irradiated site 20 ± 4 h after irradiation. The number of SBCs were determined in sections obtained at $50\text{-}\mu$ intervals. A minimum of 80 high-powered fields (HPFs) from each skin specimen using a magnification of $400\times$ 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 $33.1\text{--}81.6 \text{ mJ/cm}^2$. 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/cm², and the range was 26.5–102 mJ/cm².

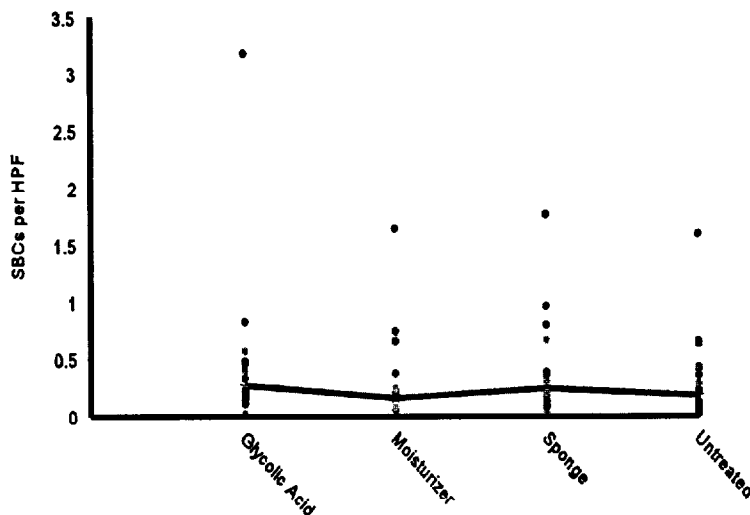


Figure 9. Number of sunburn cells produced in each of 15 subjects exposed to 1 MED of primarily UVB radiation as a function of the pretreatment regimen: 10% Glycolic Acid, moisturizer without Glycolic Acid, a mechanical sponge, and no treatment; once daily for 4 days. The geometric means are connected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

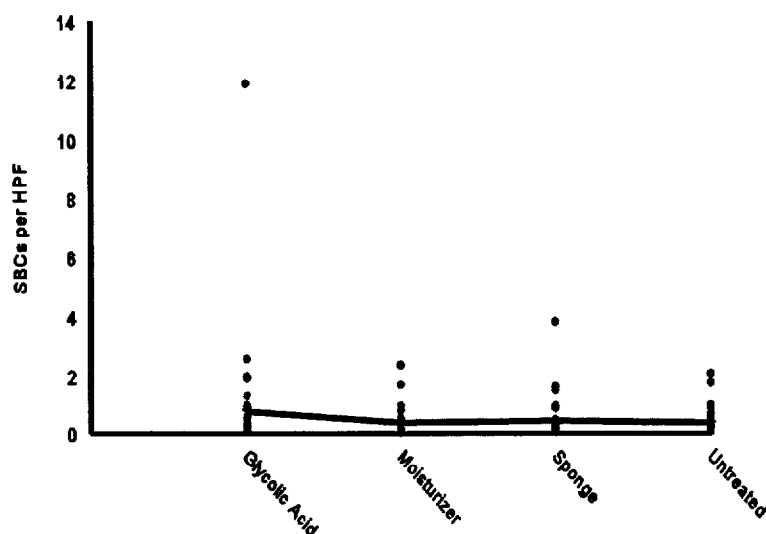
The number of SBCs for each subject and treatment in the groups 1 and 2 is given in Tables 40 and 41, respectively, and the data are depicted in Figures 10 and 11, respectively.

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).

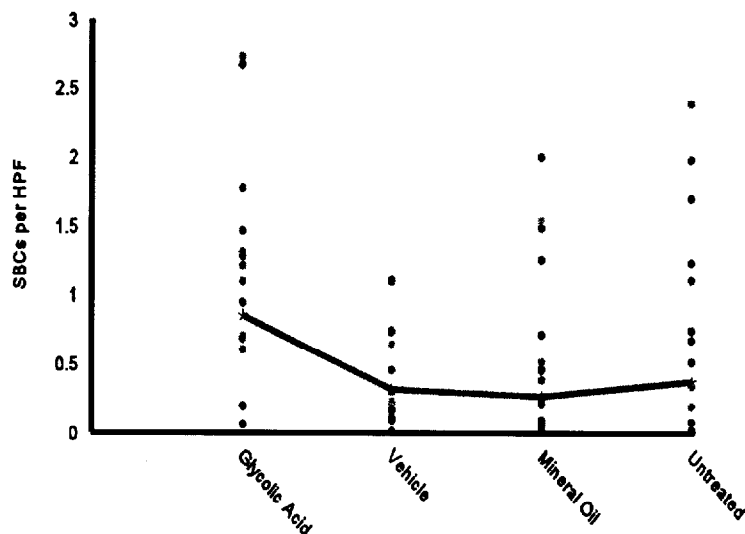


Figure 11. Number of sunburn cells produced in each of 16 subjects (group 2) exposed to 1 MED of primarily UVB radiation as a function of the pretreatment regimen: 10% Glycolic Acid, vehicle alone, mineral oil, and no treatment; once daily for 12 weeks. The geometric means are connected with a line (KGL,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

^aThis 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

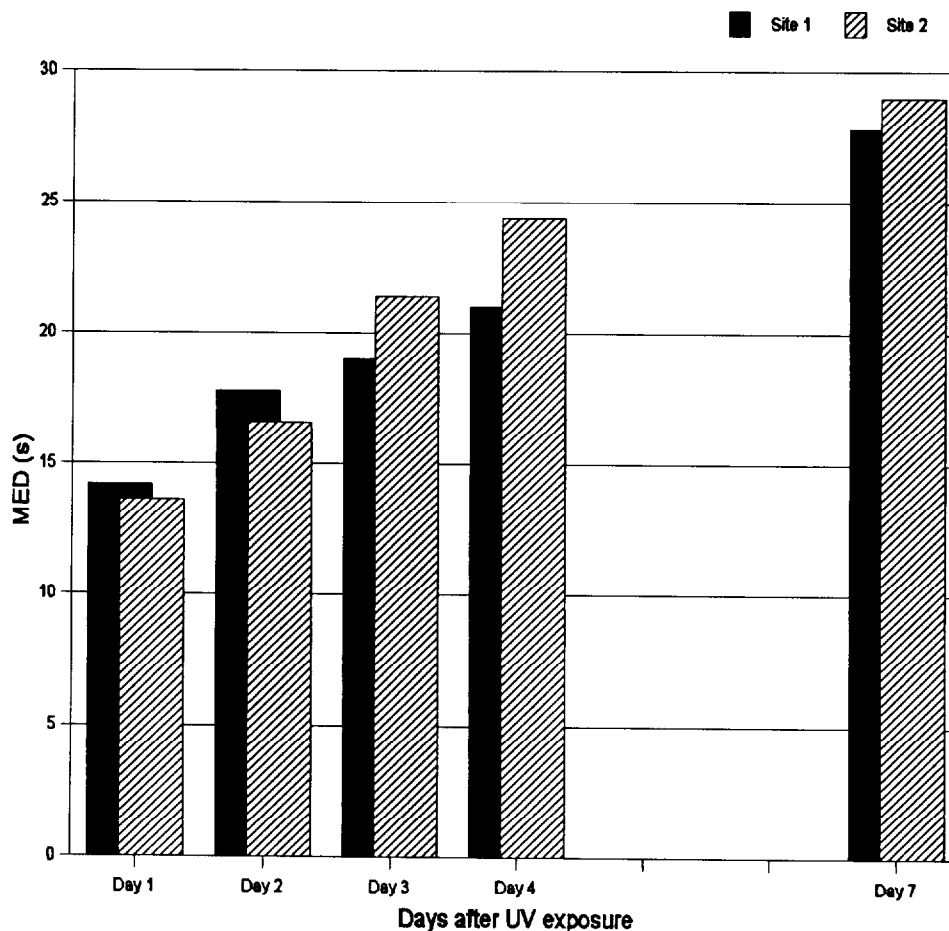


Figure 12. Effect of posttreatment (7 daily applications) with 8% Glycolic Acid, pH 3.25 (site 2), or no treatment (site 1) on erythema expressed as seconds of UV exposure to reach 1 MED (Perricone and DiNardo, 1996).

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

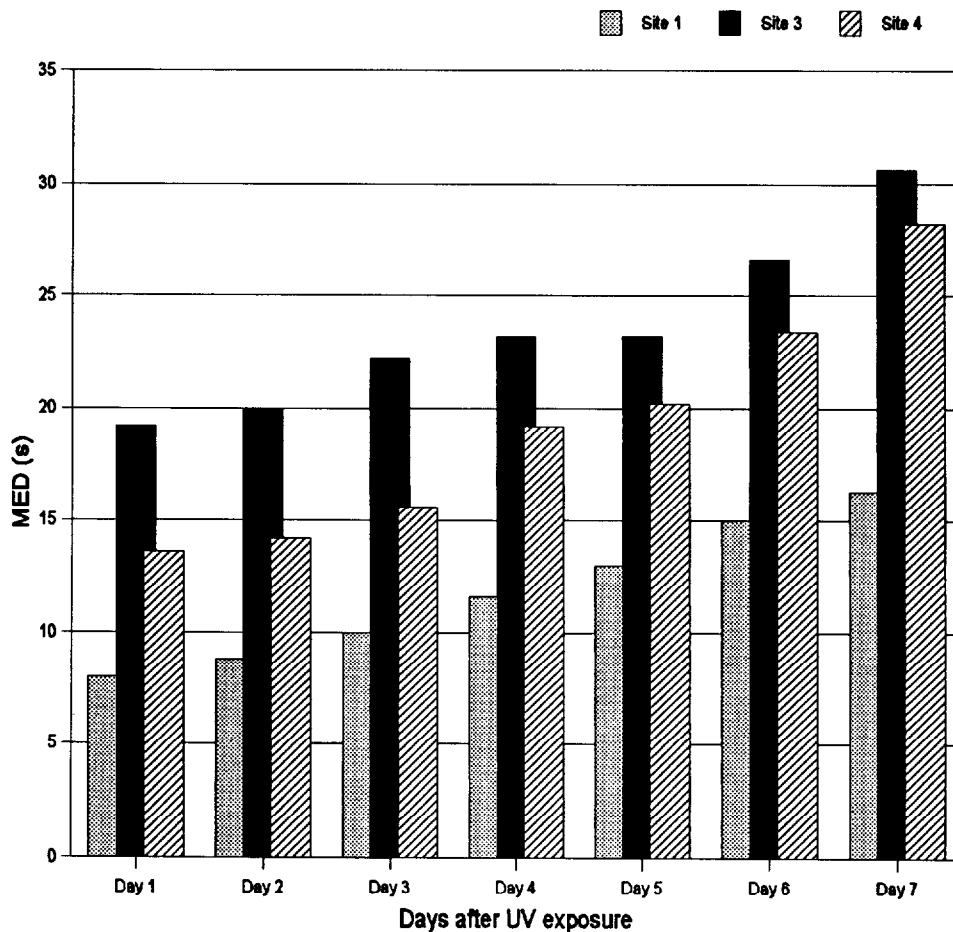
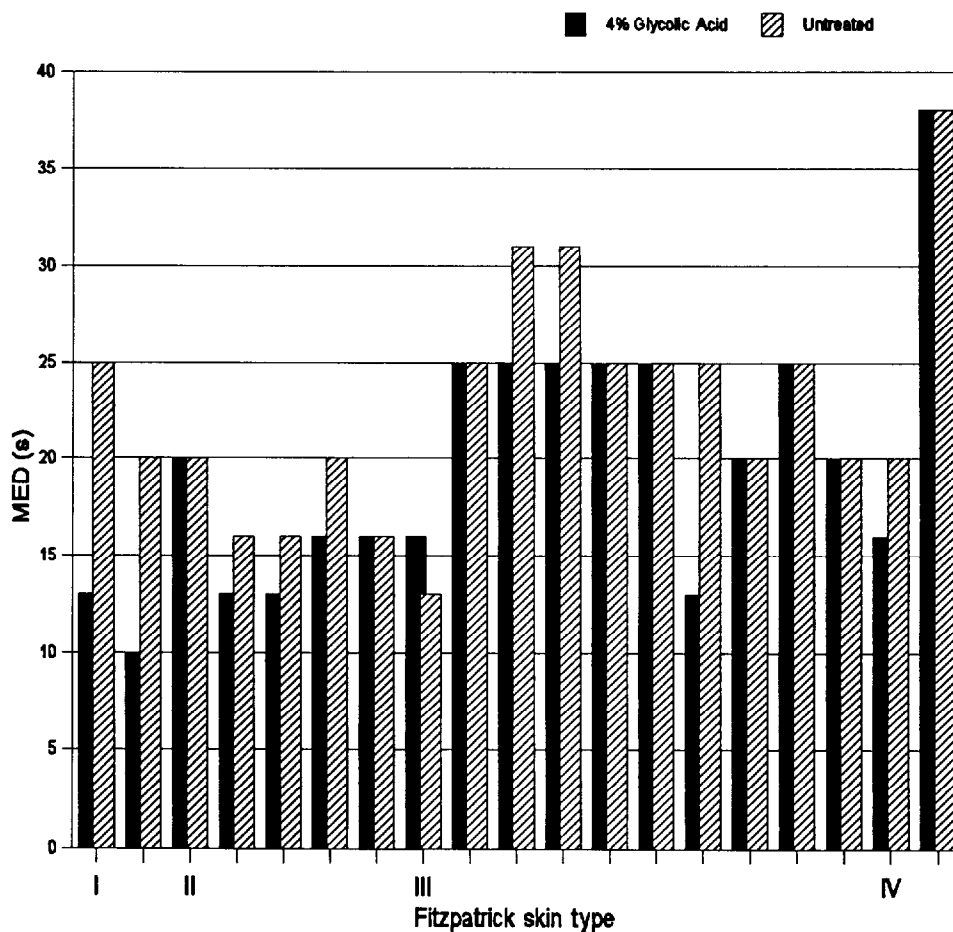


Figure 13. Effect of pretreatment (daily) with 8% Glycolic Acid, pH 3.25, for 3 weeks (site 3); the same pretreatment plus a 6-min chemical peel with a 50% Glycolic Acid solution, pH 2.75, 15 min prior to UV exposure (site 4); or no treatment (site 1) on erythema seen following UV exposure. Erythema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

^aUsed 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 $0.16 \text{ mg/kg day}^{-1}$. 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 $250 \text{ mg/kg day}^{-1}$ (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 $0.16 \text{ mg/kg day}^{-1}$ (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 $\mu\text{g/mL}$ Glycolic Acid and 25 $\mu\text{g/mL}$ ascorbic acid for 4 or 24 h, and the cells were then labeled with [^3H]-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 Glycolic 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

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%)

^aIf 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 (LD₅₀ 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

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.

REFERENCES

- Al-Ani, F. Y., and Al-Lami, S. K. 1988. Absence of mutagenic activity of acidity regulators in the Ames *Salmonella*/microsome test. *Mutat. Res.* 206:467-470.
- Alderson, S. G., Barratt, M. D., and Black, J. G. 1984. Effect of 2-hydroxy-acids on guinea-pig footpad stratum corneum: mechanical properties and binding studies. *Int. J. Cosmet. Sci.* 6:91-100.
- AMA Laboratories, Inc. 1993a. Fifty human subject repeat insult patch test skin irritation/sensitization evaluation of a substance containing 2% Glycolic Acid. Study date May 19. Unpublished data submitted by CTFA (95-AHA-0002). 8 pp.*
- AMA Laboratories, Inc. 1993b. Fifty human subject repeat insult patch test skin irritation/sensitization evaluation of a substance containing 3% Glycolic Acid. Study date August 27. Unpublished data submitted by CTFA (95-AHA-0005). 8 pp.*
- AMA Laboratories, Inc. 1994a. Fifty human subject repeat insult patch test skin irritation/sensitization evaluation of a substance containing 6% Glycolic Acid. Study date July 22. Unpublished data submitted by CTFA (95-AHA-0004). 8 pp.*
- AMA Laboratories, Inc. 1994b. Fifty human subject repeat insult patch test skin irritation/sensitization evaluation of a substance containing 6% Glycolic Acid. Study date September 22. Unpublished data submitted by CTFA (95-AHA-0003). 8 pp.*
- Andersen, F. A. 1995. Final report on the safety assessment of urocanic acid. *J. Am. Coll. Toxicol.* 14:386-423.
- An-eX Analytical Services, Ltd. 1994. Human skin penetration of radio-labelled Glycolic Acid: in vitro assessment. Unpublished data submitted by CTFA (95-AHA-43). 17 pp.*
- Association Française de Normalisation. 1982. Evaluation de l'irritation et/ou de la corrosion oculaires, chez le Lapin AFNOR (Project): TD3-B doc. 37.
- Avon Products, Inc. 1986a. Standard operating procedures for the conduct of a nonclinical laboratory study, acute toxicity methods: tests for acute (systemic) toxicity; acute oral toxicity test. Unpublished data submitted by CTFA (95-AHA-52). 13 pp.*
- Avon Products, Inc. 1986b. Standard operating procedures for the conduct of a nonclinical laboratory study, primary irritancy methods:

- guinea pig immersion test. Unpublished data submitted by CTFA (95-AHA-61). 6 pp.*
- Avon Products, Inc. 1986c. Standard operating procedures for the conduct of a nonclinical laboratory study, contact phototoxicity and photoallergy methods: tests for UV light mediated irritancy and allergy. Unpublished data submitted by CTFA (95-AHA-60). 3 pp.*
- Avon Products, Inc. 1987. Standard operating procedures for the conduct of a nonclinical laboratory study, Avon primary skin irritation—single occlusive patch. Unpublished data submitted by CTFA (95-AHA-55). 4 pp.*
- Avon Products, Inc. 1988. Standard operating procedures for the conduct of a nonclinical laboratory study, primary irritancy methods—Avon Draize eye irritation—single contact. Unpublished data submitted by CTFA (95-AHA-53). 13 pp.
- Avon Products, Inc. 1994. Standard operating procedures for the conduct of a nonclinical laboratory study, alternative assays, Eytex assay. Unpublished data submitted by CTFA (95-AHA-57). 32 pp.*
- Avon Products, Inc. 1995a. Summary of the ocular irritation potential of several cosmetic formulations containing 70% aqueous and 99% pure Glycolic Acid determined in vitro using the Eytex assay. Unpublished data submitted by CTFA (95-AHA-45). 17 pp.*
- Avon Products, Inc. 1995b. Summary of safety data on several cosmetic formulations containing 85% aqueous Lactic Acid, including acute oral, Draize eye, single skin, subchronic dermal, phototoxicity tests, and determination of ocular irritation potential in vitro using the Eytex and CAMVA assays. Unpublished data submitted by CTFA (95-AHA-32). 54 pp.*
- Avon Products, Inc. 1995c. Summary of safety data on several cosmetic formulations containing 60% aqueous Sodium Lactate, including acute oral, Draize eye, single skin, subchronic dermal, and guinea pig emersion tests and determination of ocular irritation potential in vitro using the Eytex assay. Unpublished data submitted by CTFA (95-AHA-39). 52 pp.*
- Avon Products, Inc. 1995d. Summary of safety data on Ethyl Lactate that includes acute oral, Draize eye, and single skin tests. Unpublished data submitted by CTFA (95-AHA-34). 3 pp.*
- Avon Products, Inc. 1995e. Summary of safety data on Lauryl Lactate that includes acute oral, Draize eye, single skin, in vitro ocular irritation, and contact allergy tests. Unpublished data submitted by CTFA (95-AHA-35). 29 pp.*
- Avon Products, Inc. 1995f. Summary of data on Myristyl Lactate 100% that includes acute oral, subchronic oral, single skin, Draize eye, and in vitro ocular irritation tests. Unpublished data submitted to CTFA (95-AHA-37). 22 pp.*
-

- Avon Products, Inc. 1995g. Summary of data on Cetyl Lactate 100% that includes acute oral, short-term oral subchronic dermal, single skin, contact allergy, Draize eye, and in vitro ocular irritation tests. Unpublished data submitted to CTFA (95-AHA-33). 99 pp.*
- Avon Products, Inc. 1995h. Summary of the ocular irritation potential of Glycolic Acid/copolymer powder 50% and Glycolic Acid powder 99% determined in vitro using the Eytex assay. Unpublished data submitted by CTFA (95-AHA-44). 2 pp.*
- Battelle. 1996. Characterizing the dose-response relationship between UVR and sunburn cell production in human skin, and applying the results in an investigation of the effects of several topical treatments on the sensitivity of the human skin to UVR. (KGL Protocols #3929 and #3813). Unpublished data submitted by CTFA. 12 pp.*
- Battelle. 1997. Response to comments by 3M Healthcare on review of the CIR tentative report pertaining to statistical analysis on KGL, Inc. (protocol #3813) "12-week sunburn cell study." Dated April 29. Unpublished data submitted by CTFA. 4 pp.*
- Becker, F. F., Langford, F. P. J., Rubin, M. G., and Speelman, P. 1996. A histological comparison of 50% and 70% Glycolic Acid peels using solutions with various pHs. *Dermatol. Surg.* 22:463-465.
- Berardesca, E., Distanto, F., Oresajo, C., and Green, B. 1997. Alpha-hydroxyacids (AHAs) modulate stratum corneum barrier function. Poster presented at the American Academy of Dermatology Annual Meeting, San Francisco, CA, 21-26 March.
- Bertani, G. 1951. A method of detection of mutations, using streptomycin dependence in *Escherichia coli*. *Genetics* 36.
- Best, L., Trebilcock, R., and Tomlinson, S. 1992. Lactate transport in insulin-secreting β -cells: contrast between rat islets and HIT-T15 insulinoma cells. *Mol. Cell. Endocrinol.* 86:49-56.
- Blake, J. D., Clarke, M. L., and Richards, G. N. 1987. Determination of organic acids in sugar cane process juice by high-performance liquid chromatography: improved resolution using dual aminex HPX-87H cation-exchange columns equilibrated to different temperatures. *J. Chromatogr.* 398:265-277.
- Bolognani, L., Buttafoco, P., Ferrari, R., Venturelli, T., and Volpi, N. 1992. Effects of monocarboxylic and dicarboxylic acids on myosin ATPase activity tested by luminometric procedure. *Biochem. Int.* 26:231-239.
- Bove, K. E. 1966. Ethylene glycol toxicity. *Am. J. Clin. Pathol.* 45:46-50.
- Bronaugh, R. L., and Stewart, R. F. 1985. Methods for in vitro percutaneous absorption studies, IV: the flow-through diffusion cell. *J. Pharm. Sci.* 74:64-67.
- Bronaugh, R. L., and Stewart, R. F. 1986. Methods for in vitro percutaneous absorption studies, VI: preparation of the barrier layer. *J. Pharm. Sci.* 75:487-491.

- Browning, E. 1965. *Toxicity and Metabolism of Industrial Solvents*, 568–570. London: Elsevier.
- Budavari, S. 1989. *The Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals*, 11th ed., 311, 707, 842. Rahway, NJ: Merck Index & Company, Inc.
- Carney, B. W., Liberacki, A. B., Bartels, M. J., and Breslin W. J. 1996. Identification of proximate toxicant for ethylene glycol development toxicity using rat whole embryo culture. *Teratology* 53:38–46.
- Carpenter, C. P., and Smyth, H. F., Jr. 1946. Chemical burns of the rabbit cornea. *Am. J. Ophthalmol.* 29:1363–1372.
- Chow, F. H. C., Dysart, M. I., Hamar, D. W., and Udall, R. H. 1975. Control of oxalate urolithiasis by DL-alanine. *Invest. Urol.* 13:113–116.
- Chow, F. H. C., Hamar, D. W., Boulay, J. P., and Lewis, L. D. 1978. Prevention of oxalate urolithiasis by some compounds. *Invest. Urol.* 15:493–495.
- Clar, E. J., Her, C. P., and Sturelle, C. G. 1975. Skin impedance and moisturization. *J. Soc. Cosmet. Chem.* 26:337–353.
- Coleman, W. P. III, and Futrell, J. 1994. The Glycolic Acid trichloroacetic acid peel. *J. Dermatol. Surg. Oncol.* 20:76–80.
- Colomina, M. T., Gómez, M., Domingo, J. L., Llobet, J. M., and Corbella, J. 1992. Concurrent ingestion of lactate and aluminum can result in developmental toxicity in mice. *Res. Commun. Chem. Pathol. Pharmacol.* 77:95–106.
- Conant, J. B., Cramer, R. D., Hastings, A. B., Klemperer, F. W., Solomon, A. K., and Vennesland, B. 1941. Metabolism of Lactic Acid containing radioactive carboxyl carbon. *J. Biol. Chem.* 137:557–566.
- Consumer Product Testing Co. (CPT). 1993a. Final Report: sting evaluation of a lotion containing ~1.5% Glycolic Acid. Experiment Ref. No. C-441-93. Report dated October 4. Unpublished data submitted by CTFA (95-AHA-0104). 8 pp.*
- Consumer Product Testing Co. (CPT). 1993b. Final Report: repeated insult patch test of a lotion containing ~1.5% Glycolic Acid. Experiment Ref. No. C-439-93. Report dated November 18. Unpublished data submitted by CTFA (95-AHA-0105). 12 pp.*
- Consumer Product Testing Co. (CPT). 1993c. Final Report: repeated insult patch test on anhydrous microemulsions containing 2.0–5.0% Lactic Acid. Experiment Ref. No. C-465-93. Report dated December 17. Unpublished data submitted by CTFA (95-AHA-0015). 31 pp.*
- Consumer Product Testing Co. (CPT). 1993d. Final Report: Sunscreen efficacy of PEX Lotion 585901 containing ~1.5% Glycolic Acid. Experiment Ref. No. TS-142-93. Report dated October 29. Unpublished data submitted by CTFA (95-AHA-0107). 6 pp.*
- Consumer Product Testing Co. (CPT) Co. 1994a. Final Report: Photoallergy study on PEXA3-484901B containing ~1.5% Glycolic Acid.

- Experiment Ref. No. S94-0014-1. Report dated March 18. Unpublished data submitted by CTFA (95-AHA-0103). 9 pp.*
- Consumer Product Testing Co. 1994b. Final Report: Phototoxicity test on PEXA3-585901B containing ~1.5% Glycolic Acid. Experiment Ref. No. S94-0013-94. Report dated March 10. Unpublished data submitted by CTFA (95-AHA-0102). 7 pp.*
- Consumer Product Testing Co. 1994c. Final Report: Sunscreen efficacy of PEX Cream 536543 containing ~0.5% of Glycolic/Lactic Acid mix. Experiment Ref. No. TS-234-93. Report dated February 2. Unpublished data submitted by CTFA (95-AHA-0097). 6 pp.*
- Cori, G. T. 1930. Studies on intestinal absorption; I: the absorption of Lactic Acid. *J. Biol. Chem.* 87:13–18.
- Cori, C. F., and Cori, G. T. 1929. Glycogen formation in the liver from *d*- and *l*-Lactic Acid. *J. Biol. Chem.* 81:389–403.
- Cosmair, Inc. 1996. Letter from JP Tedeschi, Cosmair, to JE Bailey, FDA, dated Mar 21 regarding FDA's list of Consumer Adverse Experience Reports stating that Lancome Noctosome Renewal Night Treatment listed in FDA's report does not contain AHAs. Unpublished data submitted by CTFA. 1 p.*
- Cosmetic, Toiletry, and Fragrance Association [CTFA]. 1989. Two-month use test of a cream containing 10% Glycolic Acid. Study dated January 8. Unpublished data submitted by CTFA (95-AHA-0027). 4 pp.*
- CTFA. 1990a. Results of a supervised two-week use test of a cream containing 4% Glycolic Acid. Study dated November 14. Unpublished data submitted by CTFA (95-AHA-0023). 4 pp.*
- CTFA. 1990b. Clinical use test results of a cream containing 4% Glycolic Acid. Study dated December 21. Unpublished data submitted by CTFA (95-AHA-0022). 28 pp.*
- CTFA. 1990c. Two-month use test of a cream containing 10% Glycolic Acid. Study dated April 10. Unpublished data submitted by CTFA (95-AHA-0028). 5 pp.*
- CTFA. 1991a. Tech/Reg Notes 469: OTC Drug Review Ingredient Status Report (December 2).
- CTFA. 1991b. Two-week use test results of a lotion containing 10% Glycolic Acid. Unpublished data submitted by CTFA (95-AHA-0030). 8 pp.*
- CTFA. 1991c. Arm and leg use test irritation results of a lotion containing 10% Glycolic Acid. Unpublished data submitted by CTFA (95-AHA-0029). 5 pp.*
- CTFA. 1991d. Final report on the efficacy of 4% and 8% AHA formulations. KGL #2459. Report dated July 3. Unpublished data submitted by CTFA (95-AHA-66). 17 pp.*
- CTFA. 1991e. Follicular irritation chest test of a gel containing 2% Glycolic Acid. Unpublished data submitted by CTFA (95-AHA-0019). 8 pp.*

- CTFA. 1991f. Follicular irritation chest test of gels containing 2% and 4% Glycolic Acid. Unpublished data submitted by CTFA (95-AHA-0020). 12 pp.*
- CTFA. 1992a. Three-month study of a hand and body lotion (86743-02) containing 10% Glycolic Acid. KGL #2757. Study dated June 16. Unpublished data submitted by CTFA (95-AHA-68). 23 pp.*
- CTFA. 1992b. Clinical use test of a lotion containing 4% Glycolic Acid. Unpublished data submitted by CTFA (95-AHA-0025). 12 pp.*
- CTFA. 1992c. Clinical use test of a cream containing 4% Glycolic Acid. Unpublished data submitted by CTFA (95-AHA-0024). 12 pp.*
- CTFA. 1992d. Six month chest and neck study of a gel (86740-16) containing 2% Glycolic Acid. KGL #2668. Memorandum dated April 13. Unpublished data submitted by CTFA (95-AHA-65). 13 pp.*
- CTFA. 1993. Clinical use test of a lotion containing 6.0% Glycolic Acid. Study dated October 25. Unpublished data submitted by CTFA (95-AHA-0031). 31 pp.*
- CTFA. 1994a. Histologic evaluation of skin effects resulting from one month usage of GA [Glycolic Acid, 8%] treatment for face. KGL #3360. Dated December 20. Unpublished data submitted by CTFA (95-AHA-0062). 80 pp.*
- CTFA. 1994b. A histological examination of skin effects resulting from chronic usage of Glycolic Acid. Memorandum dated October 24. Unpublished data submitted by CTFA (95-AHA-63). 134 pp.*
- CTFA. 1994c. Summary of results of published and unpublished toxicity, dermal irritation, sensitization, ocular irritation, embryotoxicity, and clinical studies on Glycolic Acid. Unpublished data submitted by CTFA (AHA-0053). 4 pp.*
- CTFA. 1994d. Clinical use test results of products containing 4% and 8% Glycolic Acid. Unpublished data submitted by CTFA (95-AHA-0026). 28 pp.*
- CTFA. 1994e. Three month clinical study of a gel containing 6.0% Lactic Acid. KGL #3163. Memorandum dated February 25. Unpublished data submitted by CTFA (95-AHA-69). 21 pp.*
- CTFA. 1994f. Six month clinical study of a lotion containing 6.0% Lactic Acid. KGL #3164. Memorandum dated July 12; final report dated April 18. Unpublished data submitted by CTFA (95-AHA-70). 15 pp.*
- CTFA. 1994g. Human contact photoallergy procedure: maximization test. Includes summary of clinical results of formulations containing Glycolic and Lactic Acid. Unpublished data submitted by CTFA (95-AHA-50). 10 pp.*
- CTFA. 1994h. Human contact phototoxicity test procedure. Includes summary of clinical results of a formulation containing Glycolic Acid. Unpublished data submitted by CTFA (95-AHA-48). 6 pp.*
- CTFA. 1995a. Memorandum from G. N. McEwen, CTFA, to F. A. Andersen, CIR, regarding comments on [the] Scientific Literature Review

- (SLR) on Glycolic and Lactic Acids, Their Common Salts and Their Simple Esters. Dated August 8. 7 pp.*
- CTFA. 1995b. Use levels for various ingredients; memorandum dated July 17. Three pages referring to Glycolic and Lactic Acid and their simple salts and common esters.*
- CTFA. 1995c. Product use concentration information for Glycolic Acid and Lactic Acid; memorandum dated August 8. Unpublished data submitted by CTFA. 2 pp.*
- CTFA. 1995d. Ultrastructural evaluation of skin treated with 4% Glycolic Acid. [Summary dated May 23.] A study report entitled "Effect of Glycolic Acid on human stratum corneum: evaluation using ultrastructural and bioengineering methods for analysis." [Study dated March 14.] Performed by Dr. Manigé Fartasch, University of Erlangen, Germany. Unpublished data submitted by CTFA (95-AHA-0096). 14 pp.*
- CTFA. 1995e. Effect of alpha-hydroxy acids on stratum corneum barrier function. A report of in vivo effects of Glycolic and Lactic Acids on improved resistance to an SLS challenge. Dated Dec. Unpublished data submitted by industry. 4 pp.*
- CTFA. 1995f. Ultrastructure features of skin treated with Glycolic Acid for six months. Memorandum dated February 2. Unpublished data submitted by CTFA (95-AHA-64). 110 pp.*
- CTFA. 1995g. Proliferative activity of epidermis after twenty-four weeks of chronic treatment with 4% Glycolic Acid or moisturizer. Report summary dated July 11. Unpublished data submitted by CTFA (95-AHA-109). 40 pp.*
- CTFA. 1995h. Mini-cumulative irritation patch assay. Includes summary of clinical results of formulations containing Glycolic and Lactic Acid. Study dated January 5. Unpublished data submitted by CTFA (95-AHA-47). 6 pp.*
- CTFA. 1995i. Facial discomfort assay. Includes summary of results of formulations containing Glycolic and Lactic Acid. Study dated February 8. Unpublished data submitted by CTFA (95-AHA-46). 5 pp.*
- CTFA. 1995j. Human contact allergy procedure: maximization test. Includes summary of clinical results of formulations containing Glycolic and Lactic Acid. Study dated February 8. Unpublished data submitted by CTFA (95-AHA-49). 18 pp.*
- CTFA. 1995k. Changes in UV transmittance. Section III (pp. 15–20) of α -hydroxy acids and the skin barrier. A presentation to the Cosmetic Ingredient Review; dated Dec. 12. Unpublished data submitted by industry. 6 pp.*
- CTFA. 1995l. Human comedogenic assay procedure. Includes summary of clinical results of formulations containing Glycolic and Lactic Acid. Study dated January 9. Unpublished data submitted by CTFA (95-AHA-51). 9 pp.*

- CTFA. 1995m. Memorandum from G. N. McEwen, CTFA, to F. A. Andersen, CIR, regarding the relative irritation potential of AHA moisturizers. Dated August 7. Unpublished data submitted by CTFA. 2 pp.*
- CTFA. 1996a. Memorandum from S. D. Gettings, CTFA, to F. A. Andersen, CIR, regarding the physical chemistry of AHA's in cosmetic formulations. Dated March 1. Unpublished data submitted by CTFA. 12 pp.*
- CTFA. 1996b. Sunburn cells in SLS treated skin. Unpublished data submitted by CTFA. 12 pp.*
- CTFA. (No date). Two-month chest use test results: AHA chest gel. Unpublished data submitted by CTFA (95-AHA-0021). 2 pp.*
- Craig, F. N. 1946. Renal tubular reabsorption, metabolic utilization and isomeric fractionation of Lactic Acid in the dog. *Am. J. Physiol.* 146: 146–159.
- D'Amour, F. E. 1934. Effects of feeding sodium bicarbonate or Lactic Acid upon the sex ratio in rats. *Science* 79(2038):61–62.
- De Leo, V. 1996. UV susceptibility of skin treated with 4% and 8% Glycolic Acid products. Unpublished data submitted by CTFA. 55 pp.*
- Demerec, M., Bertani, G., and Flint, J. 1951. A survey of chemicals for mutagenic action on *E. coli*. *Am. Naturalist* 85:119–136.
- Depocas, F., Minaire, Y., and Chatonnet, J. 1969. Rates of formation and oxidation of Lactic Acid in dogs at rest and during moderate exercise. *Can. J. Physiol. Pharmacol.* 47:603–610.
- Dermatech of Conn., Inc. 1993. Dermal safety: 10-day primary irritancy study of a mixed fruit acid. Unpublished data submitted by CTFA (95-AHA-0108). 5 pp.*
- Dial, W. F. 1990. Use of AHAs add new dimensions to chemical peeling. *Cosmet. Dermatol.* (May):32–34.
- Dies, F., Ramos, G., Avelar, E., and Lennhoff, M. 1969. Renal excretion of Lactic Acid in the dog. *Am. J. Physiol.* 216:106–111.
- DiNardo, J. C. 1994. The objective and subjective irritation potential of Glycolic Acid-based products. Unpublished data submitted by CTFA (95-AHA-0014). 2 pp.*
- DiNardo, J. C. 1995. Effect of pH and concentration on the cumulative irritation potential of Glycolic Acid-based products. Unpublished data submitted by CTFA. 4 pp.*
- DiNardo, J. C., Grove, G. L., and Moy, L. S. 1994. 12% Ammonium Lactate "vs" 8% Glycolic Acid. Unpublished data submitted by CTFA (95-AHA-0013). 2 pp.*
- DiNardo, J. C., Grove, G. L., and Lavker, R. M. 1996a. The effects of 30% Glycolic Acid chemical wash at various pH levels under exaggerated conditions of use on stratum corneum integrity. Unpublished data submitted by CTFA. 5 pp.*
- DiNardo, J. C., Grove, G. L., and Moy, L. S. 1996b. Clinical and histological effects of Glycolic Acid at different concentration and pH levels. *Dermatol. Surg.* 22:421–424.

- Ditre, C. M., Griffin, T. D., and Murphy, G. F., et al. 1996. Effects of α -hydroxy acids on photoaged skin: a pilot clinical, histologic, and ultrastructural study. *J. Am. Acad. Dermatol.* 34:187-195.
- Drury, D. R., and Wick, A. N. 1965. Chemistry and metabolism of L(+) and D(-) Lactic Acids. Symposium on chemistry and metabolism of L- and D-Lactate Acids, New York, 12-14 Nov., 1964. *Ann. NY Acad. Sci.* 119:1061-1069.
- DuPont. 1995. Technical information on DuPont Glycolic Acid. Wilmington, DE: DuPont Specialty Chemicals.
- DuPont Specialty Chemicals. 1995. Information included in correspondence, dated April 3, from D. L. Lohr, DuPont Specialty Chemicals, to G. N. McEwen, CTFA, subsequently submitted to CIR. A summary statement regarding DuPont's pilot developmental toxicity test using 70% technical grade Glycolic Acid. 1 p.*
- DuPont Specialty Chemicals. 1996. Letter dated February 5 from D. L. Lohr, DuPont, to G. N. McEwen, CTFA, stating that formaldehyde content in Glycolic Acid is measured in ppm and giving information as to how DuPont prevents the use of technical grade Glycolic Acid in cosmetic products. Unpublished data submitted by CTFA. 5 pp.*
- ECETOC. 1993. Monograph No. 20. Percutaneous absorption. Brussels, Belgium.
- Elder, R. L., ed. 1982. Final report on the safety assessment of Cetyl Lactate and Myristyl Lactate. *J. Am. Coll. Toxicol.* 1:97-107.
- Elder, R. L., ed. 1983. Final report on the safety assessment of triethanolamine, diethanolamine, and monoethanolamine. *J. Am. Coll. Toxicol.* 2:183-235.
- Elson, M. L. 1993. The molecular structure of Glycolic Acid and its importance in dermatology. *Cosmet. Dermatol.* 6:31-32.
- Environmental Safety Laboratory-Unilever Research (ESLUR). 1994a. Draft of Lactic Acid: safety assessment for use in skin care products. Document ref.: D94/003. Unpublished data submitted by CTFA (AHA-0051). 13 pp.*
- ESLUR. 1994b. Draft of Glycolic Acid: safety assessment for use in skin care products. Document ref.: D94/004. Unpublished data submitted by CTFA (AHA-0049). 13 pp.*
- Essex Testing Clinic, Inc. (ETC) 1994a. Final Report: Clinical safety evaluation of PXL Cream 536543-221165 containing ~0.5% Glycolic/Lactic Acid mix. Repeated insult patch test. ETC Entry No. 4294.01. Report dated March 24. Unpublished data submitted by CTFA (95-AHA-0098). 9 pp.*
- Essex Testing Clinic, Inc. (ETC) 1994b. Final Report: Clinical safety evaluation of moisturizer lotion #C94-2596-1614A containing 4% Glycolic Acid. Repeated insult patch test. ETC Entry No. 4294.01. Report dated December 20. Unpublished data submitted by CTFA (95-AHA-0085). 14 pp.*

- Essex Testing Clinic, Inc. (ETC) 1994c. Final Report: Clinical safety evaluation of moisturizer lotion #C94-2596-1614C containing 4% Glycolic Acid. Repeated insult patch test. ETC Entry No. 4294.03. Report dated December 20. Unpublished data submitted by CTFA (95-AHA-0087). 14 pp.*
- Essex Testing Clinic, Inc. (ETC) 1994d. Final Report: Clinical safety evaluation of moisturizer cream #C94-2596-1614G containing 4% Glycolic Acid. Repeated insult patch test. ETC Entry No. 4294.07. Report dated December 20. Unpublished data submitted by CTFA (95-AHA-0089). 14 pp.*
- Essex Testing Clinic, Inc. (ETC) 1994e. Final Report: Clinical safety evaluation of moisturizer cream #C94-2596-1614H containing 4% Glycolic Acid. Repeated insult patch test. ETC Entry No. 4294.08. Report dated December 20. Unpublished data submitted by CTFA (95-AHA-0090). 14 pp.*
- Essex Testing Clinic, Inc. (ETC) 1994f. Final Report: Clinical safety evaluation of moisturizer lotion #C94-2596-1614B containing 8% Glycolic Acid. Repeated insult patch test. ETC Entry No. 4294.02. Report dated December 20. Unpublished data submitted by CTFA (95-AHA-0086). 14 pp.*
- Essex Testing Clinic, Inc. (ETC) 1994g. Final Report: Clinical safety evaluation of moisturizer lotion #C94-2596-1614D containing 8% Glycolic Acid. Repeated insult patch test. ETC Entry No. 4294.04. Report dated December 20. Unpublished data submitted by CTFA (95-AHA-0088). 14 pp.*
- Essex Testing Clinic, Inc. (ETC) 1994h. Final Report: Clinical safety evaluation of moisturizer cream #C94-2596-1614I containing 8% Glycolic Acid. Repeated insult patch test. ETC Entry No. 4294.09. Report dated December 20. Unpublished data submitted by CTFA (95-AHA-0091). 14 pp.*
- Essex Testing Clinic, Inc. (ETC) 1994i. Final Report: Clinical safety evaluation of moisturizer cream #C94-2596-1614J containing 8% Glycolic Acid. Repeated insult patch test. ETC Entry No. 4294.10. Report dated December 20. Unpublished data submitted by CTFA (95-AHA-0092). 14 pp.*
- Essex Testing Clinic, Inc. (ETC) 1996. Effect of pH and concentration on the cumulative irritation potential of Lactic Acid-based products. Unpublished data submitted by CTFA. 4 pp.*
- Estee Lauder Research and Development. (No date). Use of low levels of alpha hydroxy acids in cosmetic products. Unpublished data submitted by CTFA (95-AHA-0006). 10 pp.*
- Esthetic Manufacturers/Distributors Alliance (EMDA). 1996a. EMDA guidelines for alphahydroxy professional use only product manufacturing and distribution. Unpublished data submitted by the American Beauty Association. 1 p.*

- EMDA. 1996b. EMDA professional guidelines for alpha hydroxy acid (AHA) cosmetic chemical exfoliation procedure. Unpublished data submitted by the American Beauty Association. 3 pp.*
- European Economic Community (EEC). 1995. EEC Cosmetics Directive 76/768/EEC, as amended, Annex III. Brussels: EEC.
- Evans, O. B. 1986. Lactic acidosis in childhood, II. *Pediatr. Neurol.* 2:5-12.
- FAO/WHO. 1967. Toxicological evaluation of some antimicrobials, antioxidants, emulsifiers, stabilizers, flour-treatment agents, acids and bases. FAO Nutrition mtgs. Rpt. Series No. 40A, B, C. WHO/Food Add./67.29. (Submitted by FDA in response to an FOI request.)
- Farinelli, M. P., and Richardson, K. E. 1983. Oxalate synthesis from [$^{14}\text{C}_1$]glycollate and [$^{14}\text{C}_1$]glyoxylate in the hepatectomized rat. *Biochim. Biophys. Acta* 757:8-14.
- Faust, E. S. 1910. *Cöthener Chem. Z.* 34:57.
- Food and Drug Administration (FDA). 1978. *Federal Register* 43(166).
- FDA. 1980. Lactic Acid and Calcium Lactate; Affirmation of GRAS status for Lactic Acid and Calcium Lactate for direct human food ingredients. 21 CFR Parts 182, 184. *Federal Register* 45(97):32324-32328.
- FDA. 1984. Cosmetic product formulation and frequency of use data. FDA computer printout. Washington, DC: FDA.
- FDA. 1988. FDA summary action review of the New Drug Application submitted by Bristol-Myers on Lac-Hydrin (Ammonium Lactate) 12% lotion. Washington, DC: FDA.
- FDA. 1992. Modification in voluntary filing of cosmetic product ingredient and cosmetic raw composition statements. *Federal Register* 57(18):3128-3130.
- FDA. 1995. Skin penetration data of Glycolic Acid at pH 3.0 and 7.0. Memo on AHA absorption/metabolism studies dated May 10 from Chief, Skin Absorption and Metabolism Section, HFS-128, to Act. Director, Office of Cosmetics and Colors, HFS-100, through the Director, Division of Science and Applied Technology, HFS-125. 2 pp.*
- FDA. 1996a. Adverse reaction data and survey of commercial and professional use only skin peeling products for composition and pH. Letter dated February 23 from J. E. Bailey, FDA, to F. A. Andersen, CIR. (Report dated February 15). 25 pp.*
- FDA. 1996b. pH of 12 AHA-containing commercial products. Report dated March 4.*
- FDA. 1996c. Percutaneous absorption of Glycolic Acid in two emulsion vehicles in vitro using human skin. Memo on summary of Glycolic Acid studies dated March 3 from Chief, Skin Absorption and Metabolism Section, HFS-128, to Acting Director, Office of Cosmetics and Colors (HFS-100). 7 pp.*
- FDA. 1996d. Letter from J. E. Bailey, FDA, to F. A. Andersen, CIR, dated May 10 amending Table 2 from the letter giving adverse reaction data

- and survey of commercial and professional use only skin peeling products for composition and pH [FDA, 1996a] because a named product did not contain AHAs. 2 pp.*
- FDA. 1997. Frequency of use of cosmetic ingredients. FDA computer printout. Washington, DC: FDA.
- Food and Drug Research Laboratories, Inc. 1976. Unpublished data. 1 p.*
- Forbath, N., Kenshole, A. B., and Hetenyi, G., Jr. 1967. Turnover of Lactic Acid in normal and diabetic dogs calculated by two tracer methods. *Am. J. Physiol.* 212:1179–1184.
- Fox, C., Tassoff, J. A., Rieger, M. M., and Deem, D. E. 1962. Modification of the water holding capacity of callus by pretreatment with additives. *J. Soc. Cosmet. Chem.* 13:263–279.
- Fraser, A. D., and MacNeil, W. 1993. Colorimetric and gas chromatographic procedures for Glycolic Acid in serum: the major toxic metabolite of ethylene glycol. *Clin. Toxicol.* 31:397–405.
- Frenning, B. 1972. Gastric absorption of L(+) and D(–) Lactic Acid and their effects on the transmucosal ion transport in innervated, nonsecreting cat stomachs. *Acta Physiol. Scand* 85:362–373.
- Frosch, P. J., and Kligman, A. M. 1977. A method for appraising the stinging capacity of topically applied substances. *J. Soc. Cosmet. Chem.* 28:197–28209.
- Frugoni, P., Pike, S. E., and Tosato, G. 1993. A mechanism of T cell regulation of Epstein–Barr virus latency. *Cell. Immunol.* 147:256–147266.
- Fry, D. W., and Richardson, K. E. 1979. Isolation and characterization of Glycolic Acid dehydrogenase from human liver. *Biochim. Biophys. Acta* 567:482–491.
- Gennaro, A. R., ed. 1990. *Remington's Pharmaceutical Sciences*, 18th ed., 1322. Easton, PA: Mack Publishing Company.
- Geraghty, J. T., and Rowntree, L. G. 1911. The phenolsulphonephthalein test for estimating renal function. *J. Am. Med. Assoc.* 57:811–816.
- Gibson, J. R., Stevens, V., and Leyden, J., et al. (Date unknown.) A double-blind parallel-group study of the efficacy and safety of Ammonium Lactate 12% lotion in the treatment of photodamaged skin. Unpublished data submitted by Unileverl. 1 p.*
- Giesecke, D., and Fabritius, A. 1974. Oxidation and excretion of D-Lactic Acid by rats. *Experientia* 30:1124–1125.
- Goldstein, M., and Brucks, R. 1994. Evaluation of Glycolic Acid permeation through skin. [Abstract] *Pharm. Res.* 11:S-180.
- Gosselin, R. E., Smith, R. P., and Hodge, H. C., eds. 1984. *Clinical Toxicology of Commercial Products*, 5th ed., II-102, 202, 205–206. Baltimore, MD: Williams & Wilkins.
- Granados, H., Glavind, J., and Dam, H. 1949. Observations on experimental dental caries, III: the effect of dietary Lactic Acid. *J. Dental Res.* 28:282–287.

- Grant, J., ed. 1972. *Hackh's Chemical Dictionary*, 4th ed., 39, 124, 303, 377, 619. New York: McGraw Hill Book Company.
- Green, B. G., and Bluth, J. 1995. Measuring the chemosensory irritability of human skin. *J. Toxicol.—Cut & Ocular Toxicol.* 14:23–48.
- Guillot, J. P., Martini, M. C., Giauffret, J. Y., Gonnet, J. F., and Guyot, J. Y. 1982a. Safety evaluation of some humectants and moisturizers used in cosmetic formulations. *Int. J. Cosmet. Sci.* 4:67–79.
- Guillot, J. P., Gonnet, J. F., Clement, C., Caillard, L., and Truhart, R. 1982b. Evaluation of the ocular-irritation potential of 56 compounds. *Fd. Cosmet. Toxicol.* 20:573–582.
- Hackney, J. M., and Hensley, P. 1987. Use of an enzyme assay to detect glycolate in aquatic systems. *Aquatic Botany* 27:395–402.
- Hall, K. J., and Hill, J. C. 1986. The skin plasticisation effect of 2-hydroxyoctanoic acid, I: the use of potentiators. *J. Soc. Cosmet. Chem.* 37:397–407.
- Harris, K. S., and Richardson, K. E. 1980. Glycolate in the diet and its conversion to urinary oxalate in the rat. *Invest. Urol.* 18:106–109.
- Harris, R. A., Cornell, N. W., Straight, C., and Veech, R. L. 1982. Mechanism responsible for aminooxyacetate and glycolate stimulation of ethanol oxidation by isolated hepatocytes. *Arch. Biochem. Biophys.* 213:414–425.
- Harrison Research Laboratories, Inc. [HRL]. 1994a. Final Report: Photoallergy test on PEX cream 536543-221165 containing ~0.5% Glycolic/Lactic Acid mix. Report dated April 7. Unpublished data submitted by CTFA (95-AHA-0099). 18 pp.*
- HRL. 1994b. Final Report: Phototoxicity test on PEX cream 536543-221165 containing ~0.5% Glycolic/Lactic Acid mix. Report dated February 17. Unpublished data submitted by CTFA (95-AHA-0101). 9 pp.*
- Haskell Laboratory. 1990. Haskell Laboratory review of published and unpublished data on Glycolic Acid toxicity. Unpublished data submitted by CTFA (AHA-0052). 20 pp.*
- Haskell Laboratory. 1995. Pilot developmental toxicity study of 70% Glycolic Acid technical solution in rats. Haskell Laboratory Report No. 96-95. Unpublished data submitted by CTFA. 146 pp.*
- Haskell Laboratory. 1996. Summary of a developmental toxicity study on Glypure[®] 99% high-purity Glycolic Acid -crystalline using rats. Unpublished data submitted by CTFA. 4 pp.*
- Hazardous Substances Database (HSDB). 1994. Computer printout from the HSDB. Bethesda, MD: National Library of Medicine.
- Herkel, W., and Koch, K. 1936. *Deut. Arch. Klin. Med.* 178:511–537.
- Hill, J. C., White, R. H., Barratt, M. D., and Mignini, E. 1988. The skin plasticization effect of a medium chain 2-hydroxy acid and the use of potentiators. *J. Appl. Cosmetol.* 6:53–68.
- Hill Top Research. 1994a. Report of a human skin test of cumulative irritation. File No. 2594. Study dated October 14; summary dated

- December 4. Unpublished data submitted by CTFA (95-AHA-0094). 8 pp.*
- Hill Top Research. 1994b. Report of a human skin test of cumulative irritation. File No. 2595. Study and summary dated December 7. Unpublished data submitted by CTFA (95-AHA-0095). 7 pp.*
- Hill Top Research. 1995. Report of a human skin test of cumulative irritation for a product containing 8% Glycolic Acid. File No. 2660. Report dated April 3. Unpublished data submitted by CTFA (95-AHA-0093). 7 pp.*
- Hill Top Research, Inc. 1996. Investigation of the influence of topical application of Glycolic Acid on the percutaneous penetration of model penetrants through human skin. HTR Ref. No. 96-1077-70. Report dated Dec 12. Unpublished data submitted by CTFA. 113 pp.*
- Hood, H. L., Robl, M. G., Kraeling, M. E. K., and Bronaugh, R. L. 1996. In vitro percutaneous absorption of cosmetic ingredients after repeated application of an alpha hydroxy acid in vivo. Unpublished data submitted to CIR by FDA. 22 pp.*
- Huff, J. W. 1990. Effects of Sodium Lactate on isolated rabbit corneas. *Invest. Ophthalmol. Vis. Sci.* 31:942-947.
- Hurd, R. E., and Freeman, D. 1991. Proton editing and imaging of lactate. *NMR Biomed.* 4:73-80.
- Informatics, Inc. 1975. Scientific literature reviews on generally recognized as safe (GRAS) food ingredients: Lactic Acid. Sponsored by FDA. National Technical Information Service (NTIS) report PB-241 958.
- Ishidate M., Jr., Harnois MC, Sofuni T. (1988) A comparative analysis of data on the clastogenicity of 951 chemical substances tested in mammalian cell cultures. *Mutat. Res.* 195:151-213.
- Ishidate, M., Jr., Sofuni, T., and Yoshikawa, K., et al. 1984. Primary mutagenicity screening of food additives currently used in Japan. *Fd. Chem. Toxicol.* 22:623-636.
- Jackson, E. M. 1993. AHA-type products proliferate in 1993. *Cosmet. Dermatol.* 6:22-26.
- Jackson, E. M. 1994. Do AHA products really work? *Cosmet. Dermatol.* (Oct Suppl):21-22.
- Jansen, L. H., Hojyo-Tooko, M. T., and Kligman, A. M. 1974. Improved fluorescence staining technique for estimating turnover of the human stratum corneum. *Br. J. Dermatol.* 90:9-12.
- Jenkins, G. L. 1938. Stable supersaturated solution of Calcium Gluconate. *J. Am. Pharm. Assoc.* 27:484-487.
- Jensen, J. C., Buresh, C., and Norton, J. A. 1990. Lactic acidosis increases tumor necrosis factor secretion and transcription in vitro. *J. Surg. Res.* 49:350-353.
- Johansson, S., and Tabova, R. 1974. Determination of oxalic and Glycolic Acid with isotope dilution methods and studies on the determination of glyoxylic acid. *Biochem. Med.* 11:1-9.

- Johnson, A. W. 1997. Six-month test of commercial AHA products shows no thinning of the stratum corneum and no increase in sensitivity to UV. Unpublished data submitted to CIR. 21 pp.*
- Joint FAO/WHO Expert Committee on Food Additives (JECFA). 1974. Toxicological evaluation of certain food additives. *Report of the 17th meeting of JECFA, WHO*.
- Kageyama, K., Onoyama, Y., and Nakajima, T., et al. 1992. Rapid and simple gas chromatographic measurement of Lactic Acid in red blood cells, plasma, and tumor cells after hyperthermia. *Life Sci.* 51:407–410.
- Kavanaugh, E. E. 1994. Correspondence from E. E. Kavanaugh, President-CTFA, to FR Shank, Director, Center for Food Safety and Applied Nutrition, FDA, regarding the use of alpha hydroxy acids as ingredients in retail cosmetic products. Dated May 20. 19 pp.*
- Kay, J. H., and Calandra, J. C. 1962. Interpretation of eye irritation tests. *J. Soc. Cosmet. Chem.* 13:281.
- Kershaw, G. F., et al. 1966. *Vet. Rec.* 79:276.
- KGL, Inc. 1995. Effect of 4% Glycolic Acid on skin barrier integrity. Unpublished data submitted by industry. 15 pp.*
- KGL, Inc. 1996a. An investigation of the short-term effects of topical treatments on the sensitivity of human skin to UVR. KGL Protocol #3800. Final report dated Dec 11. Unpublished data submitted by CTFA. 34 pp.*
- KGL, Inc. 1996b. A study to investigate the effects of several topical treatments on the sensitivity of human skin to UVR. Protocol #3813. Final report dated Dec 11. Unpublished data submitted by CTFA. 42 pp.*
- KGL, Inc. 1996c. Dose–response relationship between UVR and sunburn cell production in human skin. Protocol #3929. Final report dated Dec 10. Unpublished data submitted by CTFA. 18 pp.*
- KGL Skin Study Center. 1995a. Seasonal variation of minimal erythema dose (MED): influence of skin dryness/roughness. Unpublished data submitted by industry. 10 pp.*
- KGL Skin Study Center. 1995b. Effect of 4% Glycolic Acid (GA) on skin dryness, roughness, and minimal erythema dose (MED). Unpublished data submitted by industry. 13 pp.*
- Klein, M. E. 1994. Clinical observation remains essential in evaluating the cosmetic effectiveness of glycolic formulations. *Cosmet. Dermatol.* (Oct. Suppl.):35–36.
- Kligman, A. M. 1976a. Report to RIFM, May 6.
- Kligman, A. M. 1976b. Report to RIFM, December 6.
- Kligman, A. 1993. Results of a pilot study evaluating the compatibility of topical tretinoin in combination with Glycolic Acid. *Cosmet. Dermatol.* 6:28–32.
- Kligman, A. M., and Epstein, W. 1975. *Contact Derm.* 1:231–239.

- Kohri, N., Matsuda, T., Umeniwa, K., Miyazaki, K., and Arita, T. 1982. Development of assay method in biological fluids and biological fate of triethanolamine. *Yakuzaigaku* 42:342-348. [Abstract.]
- Kopsidas, G., and MacPhee, D. G. 1994. Mutagenesis by 9-aminoacridine in *Salmonella typhimurium*: inhibition by glucose and other PTS class A carbon sources. *Mutat. Res.* 306:111-117.
- Kornreich, C., Zheng, Z. S., Xue, G. Z., and Prystowsky, J. H. 1996. A simple method to predict whether topical agents will interfere with phototherapy. *Cutis* 57:113-118.
- Kraeling, M. E. K., and Bronaugh, R. L. 1996. In vitro percutaneous absorption of alpha hydroxy acids in human skin. Unpublished data submitted to CIR by FDA. 20 pp.*
- Kreisberg, R. A. 1972. Glucose-lactate interrelations in man. *N. Engl. J. Med.* 287:132-137.
- Kreisberg, R. A., Pennington, L. F., and Boshell, B. R. 1970. Lactate turnover and gluconeogenesis in normal and obese humans: effect of starvation. *Diabetes* 19:53-63.
- Kreisberg, R. A., Siegal, A. M., and Owen, W. C. 1971. Glucose-lactate interrelationships: effect of ethanol. *J. Clin. Invest.* 50:175-185.
- Krop, S., and Gold, H. 1944. On the toxicity of hydroxyacetic acid after prolonged administration: comparison with its sodium salt and citric and tartaric acids. *J. Am. Pharm. Assn.* 34:86-89.
- Kubinski, H., Gutzke, G. E., and Kubinski, Z. O. 1981. DNA-cell-binding (DCB) assay for suspected carcinogens and mutagens. *Mutat. Res.* 89:95-136.
- Kumar, A., Kiefer, J., Schneider, E., and Crompton, N. E. A. 1985. Inhibition of recovery from potentially lethal damage by chemicals in Chinese hamster V79 cells. *Radiat. Environ. Biophys.* 24:89-98.
- Lahti, A. 1980. Non-immunologic contact urticaria. *Acta Dermato-Venerol. Suppl.* 60:1-41.
- Lamb, A. R., and Evvard, M. 1919. *J. Biol. Chem. Toxicol.* 20:193.
- Lamothe, C., et al. 1971a. *Agressologie* 12:213-216.
- Lamothe, C., Thuret, F., and Laborit, H. 1971b. The action of glyoxylic acid, Glycolic Acid and glycolaldehyde, in vivo and in vitro on some phases of energy metabolism in cerebral cortex, liver, and myocardial slices of the rat. *Agressologie* 12:233-240.
- Latven, A. R., and Molitor, H. 1939. Comparison of the toxic, hypnotic and irritating properties of eight organic solvents. *J. Pharmacol. Exp. Ther.* 65:89-94.
- Lavker, R. M., Kaidbey, K., and Leyden, J. J. 1992. Effects of topical Ammonium Lactate on cutaneous atrophy resulting from a potent corticosteroid. *J. Am. Acad. Dermatol.* 26:535-544.
- Lewis, R. J., Sr. 1993a. *Hawley's Condensed Chemical Dictionary*, 12th ed., 187, 203, 495, 619, 679, 1058, 1060. New York: Van Nostrand Reinhold Company.

- Lewis, R. J., Sr. 1993b. *Hazardous Chemicals Desk Reference*, 3rd ed., 219-20; 754-755. New York: Van Nostrand Reinhold Company.
- Liao, L. L., and Richardson, K. E. 1972. The metabolism of oxalate precursors in isolated perfused rat livers. *Arch. Biochem. Biophys.* 153:438-448.
- Lide, D. R., ed. 1993. *CRC Handbook of Chemistry and Physics*, 74th ed., 3-287. Boca Raton, FL: CRC Press.
- Life Sciences Research Office. 1978. Evaluation of health aspects of Lactic Acid and Calcium Lactate as food ingredients. (NTIS Report #PB-241958/8.)
- Litton Bionetics, Inc. 1976. Mutagenic evaluation of compound FDA 75-19, MX8012-21-3, Lactic Acid USP. LBI Project No. 2468. (Submitted by FDA in response to an FOI request.)
- Lorimer, G. H. 1977. Determination of Glycolic Acid by the Eegriwe (Calkins) method. *Anal. Biochem.* 83:785-787.
- Maekawa, A., Matsushima, Y., Onodera, H., et al. 1991. Long-term toxicity/carcinogenicity study of Calcium Lactate in F344 rats. *Fd. Chem. Toxicol.* 29:589-594.
- Matsushima, Y., Onodera, H., Nagaoka, T., et al. 1989. Subchronic oral toxicity study of Calcium Lactate in F344 rats. *Eisei Shikenjo Hokoku* 107:78-83.
- MB Research Laboratories, Inc. 1977. Unpublished data. 1 p.*
- McCallion, R., and Li Wan Po, A. 1995. In vivo evaluation of the effects of moisturisers on transepidermal water loss using factorial designs. *Int. J. Pharmaceutics* 113:247-255.
- McChesney, E. W., Goldberg, L., and Harris, E. S. 1972. Reappraisal of the toxicology of ethylene glycol, IV: the metabolism of labelled Glycolic and Glyoxylic Acids in the rhesus monkey. *Fd. Cosmet. Toxicol.* 10:655-670.
- McClung, H. J., Sloan, H. R., Powers, P., et al. 1990. Early changes in the permeability of the blood-brain barrier produced by toxins associated with liver failure. *Pediatr. Res.* 28:227-231.
- Microbiological Associates, Inc. 1994a. Final report: Salmonella plate incorporation mutagenicity assay (Ames test) of test article RI3343. Study No. G94AT72.501. Unpublished data submitted by CTFA (95-AHA-41). 38 pp.*
- Microbiological Associates, Inc. 1994b. Final report: Chromosome aberrations in Chinese hamster ovary (CHO) cells with test article RI3343. Study No. G94AT72.330. Unpublished data submitted by CTFA (95-AHA-42). 30 pp.*
- Middleton, J. D. 1974. Development of a skin cream designed to reduce dry and flaky skin. *J. Soc. Cosmet. Chem.* 25:519-534.
- Middleton, J. D. 1978. Sodium Lactate as a moisturizer. *Cosmet. Toilet.* 93:85-86.

- Mills, O. H., and Kligman, A. M. 1982. A human model for assessing comedogenic substances. *Arch. Dermatol.* 118:903-905.
- Milmark Research, Inc. 1994. Determination of the safety and efficacy of the micropeel: a comparison study. Unpublished data submitted by CTFA (95-AHA-0001). 43 pp.*
- Moley, K. H., Vaughn, W. K., and Diamond, M. P. 1994. Manifestations of diabetes mellitus on mouse preimplantation development: effect of elevated concentration of metabolic intermediates. *Human Reprod.* 9:113-121.
- Monteiro-Riviere, N. A. 1991. In: Hobson, D. W., ed., *Dermal and Ocular Toxicology: Fundamentals and Methods*, 18-19. Boca Raton, FL: CRC Press.
- Morganti, P., Randazzo, S. D., Palombo, P., and Bruno, C. 1994a. Topical gelatin-glycine and alpha-hydroxy acids for photoaged skin. *J. Appl. Cosmetol.* 12:1-10.
- Morganti, P., Persechino, S., and Bruno, C. 1994b. Effects of topical alpha-hydroxy acids on skin xerosis. *J. Appl. Cosmetol.* 12:85-90.
- Morganti, P., Randazzo, S. D., Fabrizi, G., and Bruno, C. 1996a. Decreasing the stinging capacity and improving the antiaging activity of AHAs. *J. Appl. Cosmetol.* 17:79-91.
- Morganti, P., Bruno, C., and Randazzo, S. D. 1996b. Stratum corneum "turnover time" in aged skin: the effect of topical Ammonium/Amino-acid Lactate. In press. *J. Appl. Cosmetol.* 14.
- Morita, T., Takeda, K., and Okumura, K. 1990. Evaluation of clastogenicity of formic acid, acetic acid, and Lactic Acid on cultured mammalian cells. *Mutat. Res.* 240:195-202.
- Morotomi, M., Sakai, K., Yazawa, K., Suegara, N., Kawai, Y., and Mutai, M. 1981. Effect and fate of orally administered Lactic Acid in rats. *J. Nutr. Sci. Vitaminol.* 27:117-128.
- Moy, L. S., Peace, S., and Moy, R. L. 1996a. Comparison of the effect of various chemical peeling agents in a mini-pig model. *Dermatol. Surg.* 22:429-432.
- Moy, L. S., Howe, K., and Moy, R. L. 1996b. Glycolic Acid modulation of collagen production in human skin fibroblast cultures in vitro. *Dermatol. Surg.* 22:439-441.
- Murad, H., and Shamban, A. T. 1994a. Various combinations of peeling agents improve results. *Cosmet. Dermatol.* (Oct Suppl):29-32.
- Murad, H., and Shamban, A. T. 1994b. Alternative uses of Glycolic Acid. *Cosmet. Dermatol.* (Oct Suppl):32-35.
- Murthy, M. S. R., Talwar, H. S., Thind, S. K., and Nath, R. 1983. Effects of Sodium Glycolate and sodium pyruvate on oxalic acid biosynthesizing enzymes in rat liver and kidney. *Ann. Nutr. Metab.* 27:355-360.
- National Academy of Sciences. 1981. *Food Chemicals Codex*, 3rd ed., 159. Washington, DC: National Academy Press.

- Natura Bissé. 1996. Dermal irritation testing using rabbits of products containing Glycolic Acid. Unpublished data submitted by CTFA. 9 pp.*
- Newman, N., Newman, A., and Moy, L. S., et al. 1996. Clinical improvement of photoaged skin with 50% Glycolic Acid. A double-blind vehicle-controlled study. *Dermatol. Surg.* 22:455–460.
- Niederwieser, A., Matasovic, A., and Leumann, E. P. 1978. Glycolic Acid in urine: a colorimetric method with values in normal adult controls and in patients with primary hyperoxaluria. *Clin. Chim. Acta.* 89:13–23.
- Ogawa, Y., Yamaguchi, K., and Morozumi, M. 1990. Effects of magnesium salts in preventing experimental oxalate urolithiasis in rats. *J. Urol.* 144:385–389.
- Ogawa, Y., Yamaguchi, K., Tanaka, T., and Morozumi, M. 1986. Effects of pyruvate salts, pyruvic acid, and bicarbonate salts in preventing experimental oxalate urolithiasis in rats. *J. Urol.* 135:1057–1060.
- Ohta, M., Ramachandran, C., and Weiner, N. D. 1996. Influence of formulation type on the deposition of Glycolic Acid and glycerol in hairless mouse skin following topical in vivo application. *J. Soc. Cosmet. Chem.* 47:97–107.
- Opdyke, D. L. J. 1979. Fragrance raw material monographs: Butyl Lactate. *Fd. Cosmet. Toxicol.* 17(Suppl.):727.
- Opdyke, D. L. J., and Letizia, C. 1982. Fragrance raw material monographs: Ethyl Lactate. *Food Chem. Toxicol.* 20(Suppl.):677–678.
- Ovrebo, S., Jacobsen, D., and Sejersted, O. M. 1987. Determination of ionic metabolites from ethylene glycol in human blood by isotachopheresis. *J. Chromatogr.* 416:111–117.
- Patty, F. A., Fassett, D. W., and Irish, D. D., eds. 1963. *Industrial Hygiene and Toxicology, Volume II: Toxicology*, 2nd ed., 1803–1804. New York: Interscience Publishers.
- Perier, C., Frey, C., and Auboyer, C., et al. 1988. Accumulation of Glycolic Acid and glyoxylic acid in serum in cases of transient hyperglycinemia after transurethral surgery. *Clin. Chem.* 34:1471–1473.
- Perricone, N. V., and DiNardo, J. C. 1996. Photoprotective and anti-inflammatory effects of topical Glycolic Acid. *Dermatol. Surg.* 22:435–437.
- Piacquadio, D., Dobry, M., Hunt, S., Andree, C., Grove, G., and Hollenbach, K. A. 1996. Short contact 70% Glycolic Acid peels as a treatment for photodamaged skin: pilot study. *Dermatol. Surg.* 22:449–452.
- Pike, S. E., Markey, S. P., Ijames, C., Jones, K. D., and Tosato, G. 1991. The role of Lactic Acid in autocrine B-cell growth stimulation. *Proc. Natl. Acad. Sci. USA* 88:11081–11085.
- Premo, P. S. 1995. Understanding chemical peels and their complications. *Les Nouvelles Esthetiques* 11:67–71.

- Registry of Toxic Effects of Chemical Substances (RTECS). 1994. Online print-out from the RTECS database. Bethesda, MD: National Library of Medicine.
- RTECS. 1995. Online print-out from the RTECS database. Bethesda, MD: National Library of Medicine.
- Rempe, J. M., and Santucci, L. G. 1997. *CTFA List of Japanese Cosmetic Ingredients*, 3rd ed., 15, 18, 43, 56, 58, 68, 114. Washington, DC: CTFA.
- Richardson, K. E. 1965. Endogenous oxalate synthesis in male and female rats. *Toxicol. Appl. Pharmacol.* 7:507-515.
- Richardson, K. E. 1967. Effects of vitamin B₆, Glycolic Acid, testosterone, and castration on the synthesis, deposition, and excretion of oxalic acid in rats. *Toxicol. Appl. Pharmacol.* 10:40-53.
- Richardson, K. E. 1973. The effect of partial hepatectomy on the toxicity of ethylene glycol, Glycolic Acid, glyoxylic acid, and glycine. *Toxicol. Appl. Pharmacol.* 24:530-538.
- Richardson, K. E., and Tolbert, N. E. 1961. Oxidation of glyoxylic acid to oxalic acid by Glycolic Acid oxidase. *J. Biol. Chem.* 236:1280-1284.
- Recherche e Technologie Cosmetologique (RTC). 1996. Repeat insult patch test for contact sensitization of a Glycolic Acid cyclosystem complex 50%. Study No. RTC/001/V. Study dated May. Unpublished data submitted to CIR. 21 p.*
- Ridge, J. M., Siegle, R. J., and Zuckerman, J. 1990. Use of α -hydroxy acids in the therapy for "photoaged" skin. *J. Am. Acad. Dermatol.* (Vol. unknown): 932-933.
- Riker, W. F., and Gold, H. 1942. The pharmacology of sodium hydroxyacetate with observations on the toxicity of glycine. *J. Am. Pharm. Assn.* 31:306-312.
- Rogers, R. S., III, Callen, J., Wehr, R., and Krochmal, L. 1989. Comparative efficacy of 12% Ammonium Lactate lotion and 5% Lactic Acid lotion in the treatment of moderate to severe xerosis. *J. Am. Acad. Dermatol.* 21:714-716.
- Rosan, A. M. 1994. The chemistry of alpha-hydroxy acids. *Cosmet. Dermatol.* (Oct Suppl):4-11.
- Rothschild, D. L., Jr. 1990. *The Food Chemical News Guide to the Current Status of Food and Color Additives*. Washington, DC.
- Sah, A., Mukherjee, S., and Wickett, R. R. 1996. An in vitro study of the effects of formulation variables and product structure on the delivery of AHA (Lactic Acid) to dermal tissues. Poster presented at the Society of Cosmetic Chemists, May 9-10, Boston, MA. Submitted to CIR by CTFA.*
- Sanderson, D. M. 1959. A note on glycerol formal as a solvent in toxicity testing. *J. Pharm. Pharmacol.* 11:150-155.
- Sax, N. I. 1979. *Dangerous Properties of Industrial Materials*, 5th ed., 447-8, 463, 668, 707, 756, 762, 824. New York, NY: Van Nostrand Reinhold Company.

- Sayre, R. M., Desrochers, D. L., Wilson, C. J., and Marlowe, E. 1981. Skin type, minimal erythema dose (MED), and sunlight acclimatization. *Am. Acad. Dermatol.* 5:439-443.
- Scatina, J., Abdel-Rahman, M. S., Gerges, S. E., Khan, M. Y., and Gona, O. 1984. Pharmacodynamics of alcide, a new antimicrobial compound, in rat and rabbit. *Fundam. Appl. Toxicol.* 4:478-484.
- Schwartz, L., Tulipan, L., and Birmingham, D. J. 1948. Dermatoses caused by inorganic acids and organic acids. In: Lea & Febiger, Eds. *A Textbook of Occupational Diseases of the Skin*, 3rd ed., 234-244. Philadelphia, PA.
- Searle, G. L., and Cavalieri, R. R. 1972. Determination of lactate kinetics in the human: analysis of data from single injection vs. continuous infusion methods. *Proc. Soc. Exp. Biol. Med.* 139:1002-1006.
- Selvam, G. S., Subha, K., and Varalakshmi, P. 1992. Effect of L(+)-tartrate on some biochemical and enzymatic parameters in normal and glycolate treated rats. *Pharmacol. Res.* 26:385-394.
- Shelef, L. A. 1994. Antimicrobial effects of lactates: a review. *J. Food Protection* 57:445-450.
- Shubik, P., and Hartwell, J. L. 1957. Survey of compounds which have been tested for carcinogenic activity. Suppl. 1. U.S. Dept. of Hlth., Ed., and Welfare. (Submitted by FDA in response to an FOI request.)
- Silbergeld, S. 1960. Observations on the accumulation of oxalate in kidney following the oral administration of Glycolic Acid. *Toxicol. Appl. Pharmacol.* 2:220-224.
- Silbergeld, S., and Carter, H. E. 1959. Toxicity of Glycolic Acid in male and female rats. *Arch. Biochem. Biophys.* 84:183-187.
- Smith, W. P. 1994. Hydroxy acids and skin aging. *Cosmet. Toilet* 109:41-48.
- Smith, W. P. 1996. Comparative effectiveness of α -hydroxy acids on skin properties. *Int. J. Cosmet. Sci.* 18:75-83.
- Smyth, H. F., Jr., Seaton, J., and Fischer, L. 1941. The single dose toxicity of some glycols and derivatives. *J. Indiv. Hyg. Toxicol.* 23:259-268.
- Stauffer Chemical Co. 1971. Acute oral and dermal and ocular irritation studies performed for ICI Americas, Inc. (Submitted by FDA in response to an FOI request.)
- Stephens and Associates. 1992. Human repeated insult patch test of a 100% neutralized cream containing 1.0% Sodium Lactate [test material:92-152(0312-2)]. Study No. C2-0025. Unpublished data submitted by CTFA (95-AHA-0016). 28 pp.*
- Stillier, M. J., Bartolone, J., and Stern, R., et al. 1996. Topical 8% Glycolic Acid and 8% L-Lactic Acid creams for the treatment of photodamaged skin. *Arch. Dermatol.* 132:631-636.
- Tabar, A. I., Muro, M. D., Quirce, S., and Olaguibel, J. M. 1993. Contact dermatitis due to sensitization to Lactic Acid and castor oil in a wart remover solution. *Contact Dermatol.* 28:49-50.

- Takahashi, M., Machida, Y., and Tsuda, Y. 1985. The influence of hydroxy acids on the rheological properties of the stratum corneum. *J. Soc. Cosmet. Chem.* 36:177-187.
- Talwar, H. S., and Murthy, M. S. R., Thind, S. K., and Nath, R. 1984. Sodium Glycolate absorption in rat intestine. *Biochem. Med.* 31:311-318.
- Talwar, H. S., Makiraju, V. S., Murthy, S. R., Nath, R., and Thind, S. K. 1985. Normalization of urinary oxalate by taurine in glycolate-fed rats. *Metabolism* 34:97-100.
- 3M Health Care. 1997. Comments on the CIR Tentative Report on Glycolic and Lactic Acid, their common salts and their simple esters. Unpublished data. 10 pp.*
- TKL Research, Inc. 1994a. A clinical safety evaluation of an AHA-containing facial lotion containing approximately 1.5% Glycolic Acid. TKL Study No. 939253. Report dated January 21. Unpublished data submitted by CTFA (95-AHA-0106). 59 pp.*
- TKL Research, Inc. 1994b. A clinical safety evaluation of an AHA-containing facial cream containing approximately 0.5% of a Glycolic/Lactic Acid. TKL Study No. 940101. Report dated May 11. Unpublished data submitted by CTFA (95-AHA-0100). 58 pp.*
- TKL Research. 1995a. Effect of emollients on the minimal erythema dose (MED). Unpublished data submitted by industry. 12 pp.*
- TKL Research. 1995b. Effect of mechanical exfoliation on the minimal erythema dose (MED) response. Unpublished data submitted by industry. 8 pp.*
- Tox Monitor Laboratories, Inc. (TML) 1994a. Primary eye irritation study (TMHC/02) of a lotion containing 4% Glycolic Acid. TM Study No. 94-275. Final report dated November 3. Unpublished data submitted by CTFA (95-AHA-0073). 13 pp.*
- TML. 1994b. Primary eye irritation study (TMHC/02) of a lotion containing 4% Glycolic Acid. TM Study No. 94-277. Final report dated November 3. Unpublished data submitted by CTFA (95-AHA-0079). 13 pp.*
- TML. 1994c. Primary eye irritation study (TMHC/02) of a cream containing 4% Glycolic Acid. TM Study No. 94-281. Final report dated November 3. Unpublished data submitted by CTFA (95-AHA-0076). 13 pp.*
- TML. 1994d. Primary eye irritation study (TMHC/02) of a cream containing 4% Glycolic Acid. TM Study No. 94-282. Final report dated November 3. Unpublished data submitted by CTFA (95-AHA-0077). 13 pp.*
- TML. 1994e. Primary eye irritation study (TMHC/02) of a lotion containing 8% Glycolic Acid. TM Study No. 94-276. Final report dated November 3. Unpublished data submitted by CTFA (95-AHA-0074). 13 pp.*
- TML. 1994f. Primary eye irritation study (TMHC/02) of a lotion containing 8% Glycolic Acid. TM Study No. 94-278. Final report dated November 3. Unpublished data submitted by CTFA (95-AHA-0075). 13 pp.*

- TML. 1994g. Primary eye irritation study (TMHC/02) of a cream containing 8% Glycolic Acid. TM Study No. 94-283. Final report dated November 3. Unpublished data submitted by CTFA (95-AHA-0080). 13 pp.*
- TML. 1994h. Primary eye irritation study (TMHC/02) of a cream containing 8% Glycolic Acid. TM Study No. 94-284. Final report dated November 3. Unpublished data submitted by CTFA (95-AHA-0078). 13 pp.*
- TML. 1994i. Primary eye irritation study (TMHC/01) of a lotion containing 8% Glycolic Acid. TM Study No. 94-276A. Final report dated November 23. Unpublished data submitted by CTFA (95-AHA-0081). 13 pp.*
- TML. 1994j. Primary eye irritation study (TMHC/01) of a lotion containing 8% Glycolic Acid. TM Study No. 94-278A. Final report dated November 23. Unpublished data submitted by CTFA (95-AHA-0084). 13 pp.*
- TML. 1994k. Primary eye irritation study (TMHC/01) of a cream containing 8% Glycolic Acid. TM Study No. 94-283A. Final report dated November 23. Unpublished data submitted by CTFA (95-AHA-0082). 13 pp.*
- TML. 1994l. Primary eye irritation study (TMHC/01) of a cream containing 8% Glycolic Acid. TM Study No. 94-284A. Final report dated November 23. Unpublished data submitted by CTFA (95-AHA-0083). 13 pp.*
- TML. 1995. Primary eye irritation study (TMHC/02) of a lotion containing 8% Glycolic Acid. TM Study No. 94-337. Final report dated January 5. Unpublished data submitted by CTFA (95-AHA-0071). 13 pp.*
- Unilever Research U.S., Inc. 1995. A double-blind, vehicle-controlled, randomized study to evaluate the efficacy and safety of 8% L-Lactic Acid and 8% Glycolic Acid in the cosmetic improvement of the signs of photodamaged skin (URUS-93-MG-1). Part 3: Evaluations of results on the safety parameters. Report dated March 15. Unpublished data submitted by CTFA (95-AHA-0018). 271 pp.* (Includes addendum giving pH information dated Feb. 29, 1996.)
- Unilever Research U.S. 1996. A double-blind, vehicle controlled, randomized study to evaluate the efficacy and safety of 8% L-Lactic Acid and 8% Glycolic Acid in the cosmetic improvement of the signs of photodamaged skin. (URUS-93-MG-1). Part 7: Evaluation of sunburn cell formation. Unpublished data submitted by CTFA. 21 pp.*
- United States Pharmacopeia (USP). 1994. Vol. XXIII, 868. Taunton, MA: Rand McNally.
- Van Scott, E. J., and Yu, R. J. 1974. Control of keratinization with " α -hydroxy acids and related compounds, I: topical treatment of ichthyotic disorders. *Arch. Dermatol.* 110:586-590.
- Van Scott, E. J., and Yu, R. J. 1977. Modulation of keratinization with

- “-hydroxy acids and related compounds. In: *Recent Advances in Dermatopharmacology*, 211–217. Spectrum Publications.
- Van Scott, E. J., and Yu, R. J. 1984. Hyperkeratinization, corneocyte adhesion, and alpha hydroxy acids. *J. Am. Acad. Dermatol.* 11:867–879.
- Van Scott, E. J., and Yu, R. J. 1989a. Alpha hydroxy acids: procedures for use in clinical practice. *Cutis* 43:222–228.
- Van Scott, E. J., and Yu, R. J. 1989b. Alpha hydroxyacids: therapeutic potentials. *Can. J. Dermatol.* 1:108–112.
- Varalakshmi, P., and Richardson, K. E. 1983. The effects of vitamin B₆ deficiency and hepatectomy on the synthesis of oxalate from glycolate in the rat. *Biochim. Biophys. Acta* 757:1–7.
- Vilaplana, J., Coll, J., Trullás, C., Azón, A., and Pelejero, C. 1992. Clinical and noninvasive evaluation of 12% Ammonium Lactate emulsion for the treatment of dry skin in atopic and non-atopic subjects. *Acta Dermatol. Venereol. (Stockh.)* 72:28–33.
- Wandzilak, T. R., Hagen, L. E., Hughes, H., Sutton, R. A. L., Smith, L. H., and Williams, H. E. 1991. Quantitation of glycolate in urine by ion-chromatography. *Kidney. Intl.* 39:765–770.
- Wehr, R. F., Kantor, I., Jones, E. L., McPhee, M. E., and Krochmal, L. 1991. A controlled comparative efficacy study of 5% Ammonium Lactate lotion versus an emollient control lotion in the treatment of moderate xerosis. *J. Am. Acad. Dermatol.* 5:849–851.
- Weinhouse, S., and Friedmann, B. 1951. Metabolism of labeled 2-carbon acids in the intact rat. *J. Biol. Chem.* 191:707–717.
- Wenninger, J. A., and McEwen, G. N., Jr., eds. 1995a. *International Cosmetic Ingredient Handbook*, 3rd ed., 39, 91, 119, 310, 381, 394, 443, 587, 669, 725. Washington, DC: CTFA.
- Wenninger, J. A., and McEwen, G. N., Jr., eds. 1995b. *International Cosmetic Ingredient Dictionary*, 6th ed., Vol. 1, 48, 126, 166, 417, 518, 538, 609–610, 810. Washington, DC: CTFA.
- Wenninger, J. A., and McEwen, G. N., Jr., eds. 1995c. *International Cosmetic Ingredient Dictionary*, 6th ed., Vol. 2. Washington, DC: CTFA.
- White, C. W., Jr., and Stutzman, J. W. 1950. The protective effects of glycine, glycolic, and acetic acids and their salts against cyclopropane-epinephrin ventricular arrhythmias. *Arch. Int. Pharmacodyn.* 82:416–424.
- Wilkinson, J., and Moore, R., eds. 1982. *Harry's Cosmeticology*, 7th ed., 74–75. New York: Chemical Publishing.
- Wysokinska, Z. 1952. A comparison of the effects of lactic and acetic acid on the rat organism. *Roczniki Panstwowego Zakladu Hig.* 3:273–292.
- Yamaguchi, T., and Nakagawa, K. 1983. Mutagenicity of and formation of oxygen radicals by trioses and glyoxal derivatives. *Agric. Biol. Chem.* 47:2461–2465.

REFERENCES


241

- Yanagawa, M., Maeda-Nakai, E., and Yamakawa, K., et al. 1990. The formation of oxalate from glycolate in rat and human liver. *Biochim. Biophys. Acta* 1036:24–33.
- Yu, R. J., and Van Scott, E. J. 1994. Alpha-hydroxy acids: science and therapeutic use. *Cosmet. Dermatol.* (Oct. Suppl.):12–20.
- Yu, R. J., and Van Scott, E. J. 1996. Bioavailability of Alpha Hydroxy-acid in topical formulations. (Submitted for publication.) Unpublished data submitted by R. J. Yu. 14 pp.*
- Zatz, J. L. 1994. Enhancing skin penetration of actives with the vehicle. *Cosmet. Toilet.* 109:27–36.

*Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Washington, DC 20036, USA.



TO: Lillian Gill, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel 

DATE: September 12, 2013

SUBJECT: Concentration of Use by FDA Product Category: Glycolic and Lactic Acids and their salts and esters

Concentration of Use by FDA Product Category

Glycolic Acid
 Ammonium Glycolate
 Sodium Glycolate
 Butyl Glycolate
 Lactic Acid
 Ammonium Lactate
 Calcium Lactate
 Potassium Lactate

Sodium Lactate
 TEA-Lactate
 Methyl Lactate
 Ethyl Lactate
 Butyl Lactate
 Lauryl Lactate
 Myristyl Lactate
 Cetyl Lactate

Ingredient	FDA Code†	Product Category	Maximum Concentration of Use
Glycolic Acid	03D	Eye lotion	0.035-0.49%
Glycolic Acid	05A	Hair conditioners	3.5-4.5%
Glycolic Acid	05B	Hair sprays aerosol pump spray	0.0005% 0.05%
Glycolic Acid	05E	Rinses (noncoloring)	0.0062%
Glycolic Acid	05F	Shampoos (noncoloring)	0.04-0.5%
Glycolic Acid	05G	Tonics, dressings and other hair grooming aids	0.6%
Glycolic Acid	06B	Hair tints	4%
Glycolic Acid	06H	Other hair coloring preparations	0.0008%
Glycolic Acid	07C	Foundations	0.012-4%
Glycolic Acid	08C	Nail creams and lotions	4.1%
Glycolic Acid	10A	Bath soaps and detergents	0.06%
Glycolic Acid	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.14-50%
Glycolic Acid	12B	Depilatories	3.7%
Glycolic Acid	12C	Face and neck products not spray	0.035-50%
Glycolic Acid	12D	Body and hand products not spray	0.35-10%
Glycolic Acid	12F	Moisturizing products foot cream	2.1%
Glycolic Acid	12G	Night products not spray	4-4.1%
Glycolic Acid	12H	Paste masks and mud packs	0.099-6.1%

Glycolic Acid	12I	Skin fresheners	0.12%
Glycolic Acid	12J	Other skin care preparations	4.1%
Sodium Glycolate	02D	Other bath preparations	1.9%
Sodium Glycolate	05C	Hair straighteners	0.25%
Sodium Glycolate	05F	Shampoos (noncoloring)	0.005%
Sodium Glycolate	05G	Tonics, dressings and other hair grooming aids	0.0002%
Sodium Glycolate	10D	Feminine hygiene deodorants	0.01%
Sodium Glycolate	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.11%
Lactic Acid	02C	Bath capsules	30%
Lactic Acid	02D	Other bath preparations	0.085-0.088%
Lactic Acid	03A	Eyebrow pencil	0.00023-0.07%
Lactic Acid	03B	Eye liner	0.000023%
Lactic Acid	03C	Eye shadow	0.00023%
Lactic Acid	03D	Eye lotion	0.01-0.1%
Lactic Acid	03F	Mascara	0.000023-0.0018%
Lactic Acid	03G	Other eye makeup preparations	0.2%
Lactic Acid	04A	Colognes and toilet waters	0.00063%
Lactic Acid	04B	Perfumes	0.21%
Lactic Acid	04C	Powders (dusting and talcum)	0.002%
Lactic Acid	05A	Hair conditioners	0.0088-5%
Lactic Acid	05B	Hair sprays aerosol pump spray	0.0002% 0.17-0.99%
Lactic Acid	05D	Permanent waves	4.9%
Lactic Acid	05E	Rinses (noncoloring)	0.09-0.99%
Lactic Acid	05F	Shampoos (noncoloring)	0.000081-4.4%
Lactic Acid	05G	Tonics, dressings and other hair grooming aids pump spray	0.0088-0.66% 5.8%
Lactic Acid	05H	Wave sets	0.018-0.023%
Lactic Acid	05I	Other hair preparations (noncoloring)	0.016%

Lactic Acid	06A	Hair dyes and colors (all types requiring caution statement and patch test)	0.65-1.3%
Lactic Acid	06B	Hair tints	0.9-5%
Lactic Acid	06G	Hair bleaches	0.014%
Lactic Acid	06H	Other hair coloring preparations	0.64%
Lactic Acid	07B	Face powders	0.000023%
Lactic Acid	07C	Foundations	0.0023-0.16%
Lactic Acid	07E	Lipstick	0.0023-0.085%
Lactic Acid	07F	Makeup bases	0.04-0.35%
Lactic Acid	07G	Rouges	0.081%
Lactic Acid	08B	Cuticle softeners	10.1%
Lactic Acid	08C	Nail creams and lotions	0.0006%
Lactic Acid	08G	Other manicuring preparations	1.8%
Lactic Acid	09A	Dentifrices (aerosol, liquid, pastes and powders)	0.03%
Lactic Acid	10A	Bath soaps and detergents	0.001-1%
Lactic Acid	10B	Deodorants not spray	0.05-1.7%
Lactic Acid	10D	Feminine hygiene deodorants	0.0032-0.21%
Lactic Acid	10E	Other personal cleanliness products	0.009-0.3%
Lactic Acid	11A	Aftershave lotions	0.00045-0.05%
Lactic Acid	11E	Shaving cream (aerosol, brushless and lather)	0.01%
Lactic Acid	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.01-6%
Lactic Acid	12B	Depilatories	6.1%
Lactic Acid	12C	Face and neck products not spray	0.00072-10%
Lactic Acid	12D	Body and hand products not spray	0.003-9.23%
Lactic Acid	12F	Moisturizing products not spray	0.01-0.36%
Lactic Acid	12G	Night products not spray	0.00045-0.01%

Lactic Acid	12H	Paste masks and mud packs	0.039-3.1%
Lactic Acid	12I	Skin fresheners	0.01%
Lactic Acid	12J	Other skin care preparations	0.01-1%
Lactic Acid	13B	Indoor tanning preparations	1.1%
Ammonium Lactate	05A	Hair conditioners	0.032%
Ammonium Lactate	05B	Hair sprays pump spray	0.0064%
Ammonium Lactate	05E	Rinses (noncoloring)	0.023%
Ammonium Lactate	05F	Shampoos (noncoloring)	0.0064%
Ammonium Lactate	05G	Tonics, dressings and other hair grooming aids	0.023%
Ammonium Lactate	05I	Other hair preparations (noncoloring)	0.0064%
Ammonium Lactate	07E	Lipstick	0.0003%
Ammonium Lactate	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0004%
Ammonium Lactate	12C	Face and neck products not spray	0.0096-0.06%
Ammonium Lactate	12F	Moisturizing products not spray	0.06%
Ammonium Lactate	12I	Skin fresheners	0.06%
Calcium Lactate	07E	Lipstick	1%
Calcium Lactate	09A	Dentifrices (aerosol, liquid, pastes and powders)	1.5%
Calcium Lactate	09B	Mouthwashes and breath fresheners (liquids and sprays)	0.3%
Calcium Lactate	12C	Face and neck products not spray	0.072%
Potassium Lactate	11E	Shaving cream (aerosol, brushless and lather)	0.0004%
Potassium Lactate	12D	Body and hand products not spray	0.92%
Sodium Lactate	03D	Eye lotion	0.1-0.6%
Sodium Lactate	03E	Eye makeup remover	0.02%
Sodium Lactate	04A	Colognes and toilet waters	1.3%
Sodium Lactate	04B	Perfumes	0.075%

Sodium Lactate	04C	Powders (dusting and talcum)	0.03%
Sodium Lactate	05A	Hair conditioners	0.0075-0.12%
Sodium Lactate	05B	Hair sprays aerosol pump spray	0.012-0.013% 0.035-0.06%
Sodium Lactate	05D	Permanent waves	0.13%
Sodium Lactate	05E	Rinses (noncoloring)	0.01-0.044%
Sodium Lactate	05F	Shampoos (noncoloring)	0.0002-0.3%
Sodium Lactate	05G	Tonics, dressings and other hair grooming aids	0.012-0.5%
Sodium Lactate	06B	Hair tints	0.07%
Sodium Lactate	07C	Foundations	0.0009-0.6%
Sodium Lactate	07E	Lipstick	0.0018%
Sodium Lactate	07F	Makeup bases	0.25%
Sodium Lactate	07H	Makeup fixatives	0.006-0.6%
Sodium Lactate	09A	Dentifrices (aerosol, liquid, pastes and powders)	0.1%
Sodium Lactate	10A	Bath soaps and detergents	0.0002%
Sodium Lactate	10B	Deodorants (underarm) not spray	0.01-0.075%
Sodium Lactate	10D	Feminine hygiene deodorants	0.63%
Sodium Lactate	10E	Other personal cleanliness products	1.2%
Sodium Lactate	11A	Aftershave lotions	0.2%
Sodium Lactate	11E	Shaving cream (aerosol, brushless and lather)	0.2%
Sodium Lactate	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.0002-0.26%
Sodium Lactate	12C	Face and neck products not spray	0.02-2.7%
Sodium Lactate	12D	Body and hand products not spray	0.05-8%
Sodium Lactate	12F	Moisturizing products not spray	0.6-1%
Sodium Lactate	12H	Paste masks and mud packs	0.03-7.6%
Sodium Lactate	12J	Other skin care preparations	0.06-2%

Sodium Lactate	13A	Suntan products not spray	0.0002%
Sodium Lactate	13B	Indoor tanning products	0.0002%
Sodium Lactate	13C	Other suntan products	0.015%
TEA-Lactate	12C	Face and neck products not spray	0.07%
TEA-Lactate	12J	Other skin care products	0.06%
Methyl Lactate	10B	Deodorants (underarm) aerosol	0.038%
Methyl Lactate	11A	Aftershave lotions	0.75%
Ethyl Lactate	08F	Nail polish and enamel removers	50%
Ethyl Lactate	08G	Other manicuring preparations	95%
Ethyl Lactate	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.15%
Butyl Lactate	08E	Nail polish and enamel	1%
Lauryl Lactate	03D	Eye lotion	1%
Lauryl Lactate	05G	Tonics, dressings and other hair grooming aids	0.14%
Lauryl Lactate	07C	Foundations	1.7%
Lauryl Lactate	07E	Lipstick	1%
Lauryl Lactate	08B	Cuticle softeners	1%
Lauryl Lactate	08C	Nail creams and lotions	1%
Lauryl Lactate	10A	Bath soaps and detergents	0.5%
Lauryl Lactate	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.5-1%
Lauryl Lactate	12C	Face and neck products not spray	1-10%
Lauryl Lactate	12D	Body and hand products not spray	2%
Lauryl Lactate	12G	Night products not spray	1.1%
Lauryl Lactate	12I	Skin fresheners	2%
Myristyl Lactate	03A	Eyebrow pencil	5.1-7.2%
Myristyl Lactate	03B	Eye liner	3.5-4%

Myristyl Lactate	03C	Eye shadow	5-6.5%
Myristyl Lactate	07A	Blushers (all types)	1%
Myristyl Lactate	07E	Lipstick	6.3-13.2%
Myristyl Lactate	07F	Makeup bases	3.9%
Myristyl Lactate	07I	Other makeup preparations	0.01%
Myristyl Lactate	11E	Shaving cream (aerosol, brushless and lather)	1%
Myristyl Lactate	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.79-11.2%
Myristyl Lactate	12C	Face and neck products not spray	1.2%
Myristyl Lactate	12G	Night products not spray	1.5%
Myristyl Lactate	12J	Other skin care preparations	5.7%
Myristyl Lactate	13B	Indoor tanning preparations	1.5%
Cetyl Lactate	03D	Eye lotion	1.5-10%
Cetyl Lactate	05A	Hair conditioners	0.015%
Cetyl Lactate	07C	Foundations	5%
Cetyl Lactate	07E	Lipstick	2-9%
Cetyl Lactate	10E	Other personal cleanliness products	0.55-1.2%
Cetyl Lactate	11A	Aftershave lotions	0.5%
Cetyl Lactate	11E	Shaving cream (aerosol, brushless and later)	1%
Cetyl Lactate	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	1%
Cetyl Lactate	12C	Face and neck products not spray	1%
Cetyl Lactate	12D	Body and hand products not spray	2%
Cetyl Lactate	12F	Moisturizing products not spray	2%
Cetyl Lactate	12J	Other skin care preparations	10.2%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

†Product category codes used by FDA

Information collected in 2013
Table prepared: September 12, 2013