NICNAS

National Industrial Chemicals Notification and Assessment Scheme

Glycolic Acid

Priority Existing Chemical Assessment Report No. 12

April 2000

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Preface

This assessment was carried out under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals.

NICNAS assessments are carried out in conjunction with Environment Australia and the Therapeutic Goods Administration, which carry out the environmental and public health assessments, respectively.

NICNAS has two major programs: the assessment of the health and environmental effects of new industrial chemicals prior to importation or manufacture; and the other focussing on the assessment of chemicals already in use in Australia in response to specific concerns about their health/or environmental effects.

There is an established mechanism within NICNAS for prioritising and assessing the many thousands of existing chemicals in use in Australia. Chemicals selected for assessment are referred to as Priority Existing Chemicals.

This preliminary assessment report has been prepared by the Director (Chemicals Notification and Assessment) in accordance with Section 60A of the Act. Under the Act manufacturers and importers of Priority Existing Chemicals are required to apply for assessment. Applicants for assessment are given a draft copy of the report and 28 days to advise the Director of any errors. Following the correction of any errors, the Director provides applicants and other interested parties with a copy of the draft assessment report for consideration. This is a period of public comment lasting for 28 days during which requests for variation of the report may be made. Where variations are requested the Director's decision concerning each request is made available to each respondent and to other interested parties (for a further period of 28 days). Notices in relation to public comment and decisions made appear in the *Commonwealth Chemical Gazette*.

In accordance with the Act, publication of this report revokes the declaration of this chemical as a Priority Existing Chemical, therefore manufacturers and importers wishing to introduce this chemical in the future need not apply for assessment. However, manufacturers and importers need to be aware of their duty to provide any new information to NICNAS, as required under section 64 of the Act.

For the purposes of Section 78(1) of the Act, copies of assessment reports for New and Existing Chemical assessments may be inspected by the public at the Library, NOHSC, 92-94 Parramatta Road, Camperdown, Sydney, NSW 2050 (between 10 am and 12 noon and 2 pm and 4 pm each weekday). Summary reports are published in the *Commonwealth Chemical Gazette*, which are also available to the public at the above address.

Copies of this and other assessment reports are available from NICNAS either by using the prescribed application form at the back of this report, or directly from the following address:

GPO Box 58

Sydney

NSW 2001

AUSTRALIA

Tel: +61 (02) 8577 8800

Fax: +61 (02) 8577 8888

Other information about NICNAS (also available on request) includes:

- NICNAS Service Charter;
- information sheets on NICNAS Company Registration;
- information sheets on Priority Existing Chemical and New Chemical assessment programs;
- subscription details for the NICNAS Handbook for Notifiers; and
- subscription details for the Commonwealth Chemical Gazette.

Information on NICNAS, together with other information on the management of workplace chemicals can be found on the NOHSC Web site:

http://www.nohsc.gov.au

Overview

Glycolic acid (CAS No. 79-14-1) was declared a Priority Existing Chemical for preliminary assessment on 7 April 1998. The reason for the declaration was concern about the health effects of the chemical following consumer complaints that some cosmetic products containing glycolic acid caused irritation of the skin. The declaration applied to cosmetic uses of the chemical.

Glycolic acid is prepared by chemical synthesis or extraction from plants and has both industrial and domestic applications that utilise its acidity and ability to dissolve encrustations.

In Australia, annual imports for cosmetic purposes amount to 5.7 metric tonnes per year, of which about 2/3 is imported in finished cosmetic products and the remainder as raw materials used by local formulators. Cosmetic grade raw materials include crystalline glycolic acid, 70% aqueous solutions and plant extracts containing 2.5-17% glycolic acid. An industry survey identified 180 cosmetic products on the Australian market that contain glycolic acid, of which 25 are used in beauty salons and 155 are sold to consumers for use at home. Apart from 11 consumer hair care products, all products are intended for application to the skin. Salon products contain from 4-60% glycolic acid at pH 1.5-4.5. Consumer products contain 0.01-20% glycolic acid at pH 3.0-6.6.

Glycolic acid is absorbed by ingestion, inhalation and through the skin. In humans, it is mainly excreted unchanged in the urine while smaller amounts are metabolised to glyoxylic and oxalic acids, which are also excreted in the urine. The kinetics and metabolism are qualitatively similar in rats and humans; however, rats metabolise a greater proportion to carbon dioxide and eliminate the chemical faster than humans.

In laboratory animals, glycolic acid is harmful by single-dose ingestion or inhalation of high doses. Depending on concentration and pH, it may be corrosive or irritating to the skin, eyes and respiratory system. It is toxic to the kidneys by repeated oral administration. When glycolic acid is given to pregnant rats by mouth on a daily basis, it induces malformations at high, maternally toxic doses. In two studies, there was an 8-9% reduction in foetal body weight and a substantial increase in minor skeletal abnormalities at dose levels associated with mild maternal toxicity. In another study, a marginal increase in foetal abnormalities was seen at a dose associated with marginal maternal toxicity, with no effects on foetal development seen at lower doses. Glycolic acid is not mutagenic. It does not impair fertility or neonatal growth during lactation. There are no animal studies of systemic or developmental toxicity from dermal exposure and no carcinogenicity studies.

Glycolic acid is a metabolite of ethylene glycol and is the immediate cause of the metabolic acidosis and kidney failure associated with ethylene glycol poisoning in humans. Cosmetic formulations with glycolic acid have been extensively tested in human tolerability studies. There is no evidence of contact sensitisation; however, glycolic acid causes stinging and skin irritation in a dose- and/or pH-dependent manner. In use studies of products with 0.5-50% glycolic acid at pH 1.2-5.5, 13% of subjects had signs of skin irritation and 10% complained of stinging. In one study glycolic acid increased the sensitivity of human skin to sunburn by up to 50% in some individuals.

Occupational exposure to glycolic acid in the cosmetic industry is predominantly through skin contact as the chemical is practically non-volatile and the formation of aerosols (mists) is likely to be insignificant during formulation and beauty salon use of cosmetic products. Occupational control measures such as isolation, engineering controls and/or the use of personal protective equipment are in place in most formulation plants. Control measures in beauty salons include the substitution of solutions with gels or creams to minimise dispersion and the use of gloves to reduce hand exposure. Current MSDS and labels are satisfactory for synthetic raw materials. In the case of plant extracts and salon-only products, MSDS and labels generally do not comply with the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances*.

The public is exposed to skin contact with a variety of cosmetic products that contain the chemical. Under the *Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations*, consumer cosmetics must be labelled with their ingredients. Ten of 66 labels assessed (15%) did not comply with the ingredient labelling requirements and 18 (27%) did not explicitly disclose the presence of glycolic acid in the formulation.

The no observed adverse effect level (NOAEL) based on a 3-month oral rat toxicity test and on maternal and developmental toxicity in pregnant rats is 150 mg/kg/day.

External exposures obtained from reasonable worst-case workplace scenarios are estimated at 1.7 mg/kg/day in beauty salon workers and 6.3 mg/kg/day in formulation workers. As such, the known uses of glycolic acid in the cosmetic formulation and beauty salon industries are considered unlikely to present a significant risk to occupational health in Australia if exposure is appropriately controlled.

External exposures obtained from reasonable worst-case consumer scenarios are estimated at 10 mg/kg/treatment for skin peels of large areas of the body and at 28 mg/kg/day from at-home use of glycolic acid cosmetics. Based on the same scenarios, the estimated internal exposure level is 4.7 mg/kg/day on the day of a salon treatment and 3.4 mg/kg/day for use at home. Compared with the NOAEL determined in rats, this represents a margin of exposure below the recommended level for chemicals which are widely used by the general population. However, considerations relating to the route and frequency of exposure, the blood levels known to be associated with systemic toxicity in humans and the pH of commercial formulations relative to the test materials used in animal studies justify the conclusion that the use of glycolic acid in salon and consumer cosmetics is unlikely to pose a significant risk to the general public, although skin and eye irritation may occur at high concentrations and low pH values.

Based on the assessment findings and the NOHSC *Approved Criteria for Classifying Workplace Hazardous Substances*, it is recommended that glycolic acid for use at work be classified as 'Harmful by inhalation and if swallowed' (Risk phrase R20/22), 'Causes burns' (R34), 'Risk of serious damage to eyes' (R41), 'Irritating to eye and skin' (R36/38), and 'Irritating to respiratory system' (R37).

It is recommended that glycolic acid be included in the NOHSC *List of Designated Hazardous Substances* with the above classification. The reference cut-off levels for mixtures are given in section 15.1 of the main report.

Suppliers of the chemical for workplace use should update their MSDS and labels in accordance with the recommended hazard classification. As with other hazardous workplace chemicals, employers should conduct a risk assessment of their individual workplace and, where necessary, implement appropriate control measures.

Glycolic acid in cosmetic products used by the general public may cause skin and eye irritation when present at high concentrations and low pH values. As such, it is recommended that glycolic acid be considered for listing in the Standard for the Uniform Scheduling of Drugs and Poisons. In addition, manufacturers, importers and suppliers of consumer products should inform consumers that the use of skin exfoliant cosmetic products may result in an enhanced sensitivity to sunburn, and that use of sunscreen protection is advised.

On the basis of the assessed hazard, exposure information and current controls, NICNAS does not recommend a full (risk) assessment of glycolic acid in cosmetic products at this time.

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Abbreviations and Acronyms

ADG	Australian Dangerous Goods
AHA	alpha-hydroxy acid
ALD	approximate lethal dose
ALT	alanine aminotransferase
AS	Australian Standard
AS/NZS	Australian/New Zealand Standard
ASCC	Australian Society of Cosmetic Chemists
AST	aspartate aminotransferase
CAS	Chemical Abstracts Service
CIR	Cosmetic Ingredient Review
cm	centimeter
cm^2	square centimeter
CTFA	Cosmetic, Toiletry, and Fragrance Association
DNA	deoxyribonucleic acid
EASE	Estimation and Assessment of Substances Exposure
EINECS	European Inventory of Existing Chemical Substances
FDA	Food and Drug Administration
FXIIIa(+)	Factor XIIIa positive
g	gram
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
h	hour
HPLC	high-pressure liquid chromatography
IUPAC	International Union for Pure and Applied Chemistry
kg	kilogram
K_m	Michaelis-Menten constant
L	litre
LOAEL	lowest observed adverse effect level
M	molar (moles/L)
m^3	cubic meter
MED	minimal erythemal dose
mg	milligram
min	minute
mL	millilitre
mm	millimeter
mM	millimolar
mRNA	messenger RNA
MSDS	material safety data sheet
NDPSC	National Drugs and Poisons Schedule Committee
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
nm	nanometer
NOAEL	no observed adverse effect level
NOHSC	National Occupational Health and Safety Commission
OECD	Organisation for Economic Co-Operation and Development
Pa	Pascal (0.0075 mm Hg)
PPE	personal protective equipment
ppm	parts per million
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances

s	second
SPF	sun protection factor
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
t	metric tonne
TAFE	Technical and Further Education
TEWL	trans-epidermal water loss
TGA	Therapeutic Goods Administration
TNF-α	tumour necrosis factor alpha
TWA	time-weighted average
UN	United Nations
UV	ultraviolet
V_{max}	maximum velocity
y	year
$Å^3$	cubic angstrom
µg	microgram
µm	micrometer
µM	micromolar
µmole	micromole

1. Introduction

1.1 Declaration

The chemical glycolic acid (CAS No. 79-14-1) was declared a Priority Existing Chemical for preliminary assessment under the *Industrial Chemicals (Notification and Assessment) Act 1989* on 7 April 1998. The declaration applied to the cosmetic uses of glycolic acid. The reason for the declaration was concern about the health effects of the chemical following consumer complaints that some cosmetic products containing glycolic acid caused irritation of the skin.

1.2 Scope of the assessment

The *Industrial Chemicals (Notification and Assessment) Act 1989* prescribes which matters may be taken into account and addressed in a preliminary assessment. Risk assessment and risk management are not covered in preliminary assessments. However, as an outcome of a preliminary assessment, the Act requires the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) to determine the significance of the assessment findings for risk. This consideration may be facilitated by undertaking a reasonable worst-case risk estimate for adverse effects resulting from the importation, manufacture, use, storage, handling or disposal of the chemical. If the findings indicate that there may be a significant risk of adverse health or environmental effects, then a full (risk) assessment may be recommended.

The declaration of glycolic acid as a Priority Existing Chemical for preliminary assessment applied to the cosmetic uses of the chemical. As such, the scope of the assessment was limited to potential adverse health effects of glycolic acid resulting from the manufacture, handling and use of 'cosmetic products' as defined in the *Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations* (Statutory Rules 1991 No. 327, as amended). The use of glycolic acid for therapeutic purposes by, or as directed by, members of the medical profession was excluded from the assessment, as were the potential effects of glycolic acid on the environment.

1.3 Objectives

The objectives of this assessment were to:

- critically review the available scientific data with regard to the properties of glycolic acid, particularly data of relevance to toxicity;
- characterise the intrinsic capacity of glycolic acid to cause adverse health effects;
- determine the likely uses of glycolic acid in cosmetics in Australia;
- determine the extent of occupational and public exposure to glycolic acid resulting from its use in the cosmetics industry; and
- determine whether or not the significance for risk is such that a full (risk) assessment should be undertaken.

1.4 Sources of information

Relevant scientific data were submitted by applicants and notifiers, obtained from a comprehensive literature survey, or retrieved from other sources. In particular, a large number of unpublished reports were obtained from the Cosmetic Ingredient Review (CIR), which is a self-regulatory program sponsored by the US industry association, the Cosmetic, Toiletry, and Fragrance Association (CTFA). In these reports, references to the identity, composition and pH of experimental or commercial products were often blacked out for reasons of confidentiality. However, information about the type of formulation, glycolic acid content and pH was usually included in the CIR's published review of the studies (CIR, 1998).

Information on product specifications, labelling and use patterns and on occupational exposure and control measures was made available by applicants and notifiers. Information on the training and work practices of beauty therapists was obtained through telephone interviews and correspondence with a small sample of beauty therapy teachers and practitioners.

1.5 Peer review

During all stages of preparation, the report has been subject to internal peer review by NICNAS and the Therapeutic Goods Administration (TGA). Sections of the report relating to cosmetic technologies were also peer reviewed by Richard J.E. Williams, Technical Manager, Vetsearch International & Medical Research Pty Ltd. Sections of the report relating to the developmental toxicity of glycolic acid were also peer reviewed by Dr William S. Webster of the Department of Anatomy and Histology at the University of Sydney. Dr David Cutler of the University of Sydney's Department of Pharmacology calculated estimated blood levels of glycolic acid in animals and humans exposed to the chemical.

2. Background

2.1 International perspective

The use of glycolic acid in cosmetic products is believed to have derived from so-called 'chemical peels' that dermatologists and plastic surgeons have been using for years to remove undesirable signs of skin ageing, such as discolouration, roughness and wrinkling (Kurtzweil, 1998). The peels, typically trichloroacetic acid, phenol, resorcinol, and salicylic acid, cause the skin to lose its outermost layer, revealing a fresher-looking layer of skin. Also known as 'chemical exfoliation', the procedure is performed in doctors' surgeries under close supervision to avoid deep skin burns from the highly acidic solutions.

In the late 1980s, cosmetic manufacturers in USA began to market similar but milder versions of chemical peels containing alpha-hydroxy acids (AHAs) for salon use by cosmetologists and beauticians. These products quickly caught on and led to the introduction of AHA-containing cosmetics for the consumer market, such as face creams and body lotions. A dermatologist, Dr Van Scott, and a pharmacologist, Dr Yu, were instrumental in promoting this development. They published the first clinical paper on the use of AHAs to control keratinisation (Van Scott & Yu, 1974), took out a number of US and European patents relating to the use and formulation of AHA preparations and founded a pharmaceutical and cosmetics company to commercialise their invention.

AHAs comprise several chemicals, all of which are natural carboxylic acids with a hydroxy group at the two, or alpha, position. They are mostly manufactured by chemical synthesis or fermentation, but because of their abundance in sources such as citrus fruits, apricots, apples, grapes and sugar cane, they are sometimes referred to as 'fruit acids' rather than AHAs. With only two carbon atoms, glycolic acid is the smallest molecule within the homologous series of AHAs. It is commercially available at low cost and is used in a wide range of cosmetic products.

In 1992, the US Food and Drug Administration (FDA) cautioned consumers about possible hazards associated with the use of AHA-based skin peeling products. The warning was issued after FDA received reports of several injuries caused by skin peeling procedures done by non-medical professionals. At the same time, FDA announced its intention to commission a review of all products marketed with a skin peeling claim. The review concluded that additional scientific investigation was needed to establish the safety of cosmetic products containing AHAs and in particular to address concerns that AHAs might sensitise the skin to ultraviolet (UV) rays (KRA, 1996). Consequently, the National Toxicology Program of the US National Institute of Environmental Science accepted FDA's proposal to conduct a long-term study in hairless mice to investigate the effect of AHAs on the risk of cancer associated with sunlight and UV radiation. This study is scheduled to commence in 1999 and will take 3 years to complete.

Meanwhile, the Cosmetic Ingredient Review (CIR) Panel of the CTFA conducted a separate review of the safety of AHAs. The final report was released in 1997

and published in 1998 (CIR, 1998). CIR concluded that glycolic acid and lactic acid and their common salts and esters are safe for use in cosmetic products at concentrations ≤10%, at final formulation pH values ≥3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection. For salon use products, CIR considered the same ingredients safe at concentrations ≤30%, at final formulation pH values ≥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.

2.2 Australian perspective

The first lines of salon and consumer cosmetics containing glycolic acid were launched in Australia in the early 1990s.

In Australia, specific legislation concerning cosmetic products is limited to the *Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations* which came into effect on 31 October 1993. The information standard deals with requirements concerning ingredient labelling information. It defines 'cosmetic product' as a substance or preparation intended for placement in contact with any external part of the body, with a view to:

- altering the odours of the body;
- changing its appearance;
- cleansing it;
- maintaining it in good condition;
- perfuming it; or
- protecting it.

Chemicals contained in cosmetic products are considered industrial chemicals and are subject to the *Industrial Chemicals (Notification and Assessment) Act. The Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations* as well as the *Industrial Chemicals (Notification and Assessment) Act* specifically exempt products which are therapeutic goods in the meaning of the *Therapeutic Goods Act* 1989, that is, products intended to treat or prevent disease or modify a physiological process in humans. Therapeutic goods are subject to pre-market review and approval by TGA and are required to be included in the Australian Register of Therapeutic Goods; cosmetics are not. In some cases, the classification of a product as cosmetic or therapeutic depends on subtle differences in the wording of the actions and benefits the product is claimed to provide (NCCTG, 1997).

2.3 Assessment by other national or international bodies

Except for the FDA-sponsored review referred to in section 2.1, glycolic acid has not been assessed by other national agencies or international organisations involved in reviewing or evaluating data pertaining to health hazards posed by chemicals.

3. Applicants

Following the declaration of glycolic acid as a PEC, 38 companies importing glycolic acid into Australia for cosmetic or other uses applied for assessment of the chemical. The applicants supplied information on the properties, import quantities and cosmetic uses of the chemical. In accordance with the *Industrial Chemicals (Notification and Assessment) Act 1989*, NICNAS provided the applicants with a draft copy of the report for comments during the corrections/variation phase of the assessment. Data for the assessment were also provided by 22 notifiers, that is, companies which purchase glycolic acid in Australia and formulate it into various products.

The applicants were, as follows:

Advanced Skin Technology Pty Ltd
1606 High St
Glen Iris VIC 3143

Allergan Australia Pty Ltd
22 Rodborough Rd
Frenchs Forest NSW 2086

Amway of Australia
46 Carrington Rd
Castle Hill NSW 2154

Beiersdorf Australia Ltd
4 Khartoum Rd
North Ryde NSW 2113

Bio Scientific Pty Ltd
28 Munroe Ave
Kirrawee NSW 2232

Bioscor International Pty Ltd
184 Huntingdale Rd
Oakleigh East VIC 3166

Bronson & Jacobs Pty Ltd
Parkview Drv Australia Cntr
Homebush NSW 2140

Clariant (Australia) Pty Ltd
675 Warrigal Rd
Chadstone VIC 3148

Clinical Skincare & Equipment Pty

ICN Biomedicals Australasia
12/167 Prospect Hwy
Seven Hills NSW 2147

Internatio-Müller Australia/New Zealand Pty Ltd
64 Trenerry Cr
Abbotsford VIC 3067

International Beauty Supplies Pty Ltd
6 Narrabang Way
Belrose NSW 2085

Johnson & Johnson Pacific Pty Ltd
Stephen Rd
Botany NSW 2019

Kandas International Australia Pty Ltd
Level 2, 762 George Street
Haymarket NSW 2000

Lever J H & Co Pty Ltd
6 Bond St
Richmond SA 5033

Lever Rexona
219 North Rocks Rd
North Rocks NSW 2151

3M Australia Pty Ltd
950 Pacific Hwy
Pymble NSW 2073

Merck Pty Ltd

Ltd
PO Box 649
Alderley QLD 4051

Cosmetic Products Pty Ltd
1 Wella Way
Sommersby NSW 2250

Crampton RVB
29 Antlia St
Regents Park QLD 4118

Crown Scientific Pty Ltd
144 Moorebank Ave
Moorebank NSW 2170

Cussons Pty Ltd
282 Hammond Rd
Dandenong VIC 3175

Doctors Formula Pty Ltd
1/182 Euston Rd
Alexandria NSW 2015

Du Pont (Australia) Ltd
168 Walker St
North Sydney NSW 2060

Eckstein Australia Pty Ltd
66c Maryborough St
Fyshwick ACT 2609

Goldwell Cosmetics (Australia) Pty Ltd
103 Yerrick Rd
Lakemba NSW 2195

Hamilton Laboratories
217 Flinders St
Adelaide SA 5000

Heavenly Beauty
12/300B Burns Bay Rd
Lane Cove NSW 2066

207 Colchester Rd
Kilsyth VIC 3137

Montcove Pty Ltd
101 Allambi Ave
Florida Gardens QLD 4218

Nutri-Metics International (Australia) Pty Ltd
102 Elliott St
Balmain NSW 2041

Salon Marketing Services Pty Ltd
Unit 6/165 Rookwood Rd
Bankstown NSW 2200

Sanofi Beaute Australia Pty Ltd
166 Epping Rd
Lane Cove NSW 2066

Scental Pacific Pty Ltd
53 Jersey Rd
Bayswater VIC 3153

Sigma Aldrich Pty Ltd
14 Anella Ave
Castle Hill NSW 2154

Specialty Supply Australia Pty Ltd
9/10-12 Yalgar Rd
Kirrawee NSW 2232

Universal Aesthetics Pty Ltd
1/14 Roseberry St
Balgowlah NSW 2093

Victor Paul Direct Marketing Pty Ltd
561 Botany Rd
Waterloo NSW 2017

Yves Rocher
46 South St
Rydalmere NSW 2116

4. Chemical Identity and Composition

4.1 Chemical name (IUPAC)

Hydroxyethanoic acid

4.2 Registry numbers

Glycolic acid is listed on the Australian Inventory of Chemical Substances (AICS) as *hydroxyethanoic acid*.

CAS number	79-14-1
EINECS number	201-180-5
RTECS number	MC5250000

4.3 Other names

Acetic acid, hydroxy-

Alpha-hydroxyacetic acid

Gluco-hydroxy-acid

Glycollic acid (Approved Australian Name)

Hydroxyacetic acid

2-Hydroxyacetic acid

4.4 Trade names of cosmetic raw materials

4.4.1 Pure substance

Glycolic acid

Glypure®

4.4.2 AHA blends

α-HydroxyAcids 'AHA'

Amidroxy Apple

Amidroxy Sugar Cane

Fruitlange

Multifruit BSC

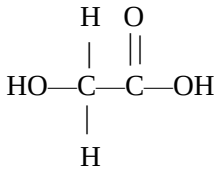
NAB Apricot Extract

Sugar Cane AHA

4.5 Molecular formula

$C_2H_4O_3$

4.6 Structural formula



4.7 Molecular weight

76.05

4.8 Concentration units

It is customary to state the concentration of glycolic acid in cosmetic products in % w/w. Thus, the concentration of glycolic acid in a 1% solution, gel, cream or lotion is 10 mg/g. A 1 M solution contains 7.6% or 76 mg/mL glycolic acid.

4.9 Composition

Glycolic acid is a naturally occurring substance formed during photosynthesis. Blends of glycolic acid and other AHAs are made by extraction of plant materials but may be standardised by the addition of man-made chemicals. It is made synthetically by treating formaldehyde with carbon monoxide and water or by hydrolysis of monochloroacetic acid with sodium hydroxide (Miltenberger, 1989). The composition of some raw materials is shown in Tables 4.1-4.2.

Compared with cosmetic grade glycolic acid, the technical quality has a higher content of process impurities such as formic acid, formaldehyde, diglycolic acid and methoxyacetic acid.

Table 4.1: Composition of technical and cosmetic grade glycolic acid (DuPont, 1995b)

	Technical grade	Cosmetic grade	
	70% solution	70% solution	99% crystalline
Total acid (%)	70.0-72.2	69.7-72.0	99.8-100.5
Heavy metals (ppm)	<4	<4	<4
Sulfates (ppm)	<150	<25	<100
Formic acid (ppm)	<3800	<150	<10
Formaldehyde (ppm)	<750	<15	<3.5
Iron (ppm)	<7.0	<1.0	<1.0
Chloride (ppm)	<1.7	<1.0	<1.0
Sodium (ppm)	<32	<2.5	<10
Ammonia (ppm)	<110	<3.9	<5.0
Diglycolic acid	<1.1%	<140 ppm	<115 ppm
Methoxyacetic acid	<1.9%	<190 ppm	<170 ppm
Free acid (%)	62.8-65.2	64.0-67.0	>95.0
pH	<0.5	<0.5	-

Table 4.2: Composition of some AHA blends for cosmetic use (Bronson & Jacobs, 1999; Lever, 1998; Sohume, 1998; Specialty Supply, 1999)

	α-Hydroxy Acids 'AHA'	Fruitlange	Multifruit BSC	NAB Apricot Extract	Sugar Cane AHA
Glycolic acid (%)	~2.5	≥10	12-17	10-15	~15
Lactic acid (%)	~23.5	≥13	28-32	13-18	~5
Malic acid (%)	~2.5	≥4	<1	1-3	~2.5
Tartaric acid (%)	~0.1	≥4	<1	<1	-
Citric acid (%)	~5.0	≥13	2-6	1-3	~2.5
Pyroglutamic acid (%)	~5.0	-	-	-	-
Pyruvic acid (%)	~0.2	-	-	-	-
Glycerol (%)	~6.0	-	-	-	-
Propylene glycol (%)	-	-	-	-	30-40
Water (%)	51-56	52-60	~40	~69	30-40
pH	3.4-4.6	3.5-4.5	4-5	~2	1-2

5. Physical and Chemical Properties

5.1 Physical state

Glycolic acid is a crystalline, colourless, odourless, somewhat hygroscopic solid (Budavari, 1996).

Conversion factors (at 25°C): 1 mg/m^3 = 0.32 ppm; 1 ppm = 3.1 mg/m^3.

5.2 Physical properties

Table 5.1: Physical properties

Property	Value	Reference
Boiling point	100°C (decomposes)	Miltenberger (1989)
	112°C (70% solution)	DuPont (1998e)
Melting point	78-80°C	Miltenberger (1989)
Partition coefficient ($logP_{o/w}$)	-1.38	Barratt (1996)
	-1.11	Hansch & Leo (1987)
Density	1.49 g/mL (at 25°C)	Miltenberger (1989)
	1.27 g/mL (70% solution at 15.6°C)	DuPont (1998e)
Vapour pressure		
• solid form	Nil (at 25°C)	DuPont (1999b)
	143 Pa (at 91°C)	DuPont (1999b)
	779 Pa (at 119°C)	DuPont (1999b)
• 70% aqueous solution	1.92 Pa (at 45°C)	DuPont (1999b)
Dissociation constant (pK_a)	3.83 (at 25°C)	Budavari (1996)
Molecular volume	55$Å^3$	Barratt (1996)
Flammability limits	Non-flammable	DuPont (1999b)

5.3 Chemical properties

Glycolic acid is freely soluble in water, methanol, ethanol, acetone, ethyl acetate, ether and acetic acid (Budavari, 1996; Miltenberger, 1989).

The pH of unbuffered solutions of glycolic acid in water is illustrated in Figure 5.1.

Glycolic acid contains acid as well as primary alcohol functional groups. It undergoes typical oxidation reactions to give glyoxylic acid and oxalic acid and reduction reactions with active metals to form acetic acid. As an acid it forms salts, esters, amides etc. As an alcohol it forms esters, acetals and ethers. It uses both functional groups to form complexes with polyvalent metal ions. In acid environments, glycolic acid can undergo self-esterification to form cyclic and

linear polymers known as glycolides. There are no readily hydrolysable groups in glycolic acid.

Glycolic acid is non-flammable. Its combustion products include formaldehyde, formic acid, carbon monoxide and carbon dioxide.

Crystalline glycolic acid begins to lose water and polymerise at temperatures above 50ºC (DuPont, 1998e). When heated to its melting point, the chemical emits acrid smoke and irritating fumes (Lewis, 1996). Concentrated aqueous solutions of glycolic acid are chemically stable at normal temperatures (DuPont, 1998e).

5.4 Concentration of undissociated acid in cosmetic formulations

Glycolic acid is a moderately strong acid and in aqueous environments dissociates into glycolate and hydrogen ions:

$$HOCH_2COOH \leftrightarrow HOCH_2COO^- + H^+$$

The relative concentrations of undissociated acid and glycolate ion depend on the pH of the solution and are governed by the following equation:

$$[\text{undissociated acid}]/[\text{glycolate}] = [H^+]/ K_a$$

where [molecule] denotes the molar concentration of the molecule and K_a is the dissociation constant of glycolic acid (1.48×10^{-4} (Budavari, 1996)).

Thus, in an unbuffered 10% (100 mg/mL) solution of glycolic acid with a pH of 1.73 (Budavari, 1996), the ratio [undissociated acid]/[glycolate] is 126/1 and the concentration of undissociated glycolic acid is >9.9% (>99 mg/mL). If the pH is increased by the addition of a base, then the concentration of undissociated glycolic acid decreases, as shown in Figure 5.2.

Most formulations of glycolic acid are not aqueous solutions but oil-in-water emulsions such as creams and lotions. In emulsions, undissociated glycolic acid molecules distribute to the oil phase, decreasing the concentration of undissociated glycolic acid, glycolate ion and hydrogen ion in the aqueous phase.

In this case, the concentration of undissociated acid in the aqueous phase can be calculated from the following equation (CIR, 1998):

$$[\text{undissociated acid}]_w = \frac{C}{K_{o/a} \times q + 1 + K_a/[H^+]_w}$$

where C is the total concentration of glycolic acid in the formulation, $K_{o/a}$ is the oil/water partition coefficient of glycolic acid, q is the volume ratio of the oil and water phases, K_a is the dissociation constant of glycolic acid and $[H^+]_w$ is the hydrogen ion concentration in the aqueous phase.

No information was available on the $K_{o/a}$ of glycolic acid for cosmetic oil phase ingredients. However, the octanol/water partition coefficient is known (Table 5.1). A graph constructed from data from a series of octanol-in-water emulsions at pH 2 and 4 shows that the concentration of undissociated glycolic acid in the aqueous phase of a given product is much more susceptible to changes in pH than to variations in the oil/water phase ratio (Figure 5.3).

Figure 5.1: pH of aqueous solutions of glycolic acid (Budavari, 1996; Yu & Van Scott, 1994)

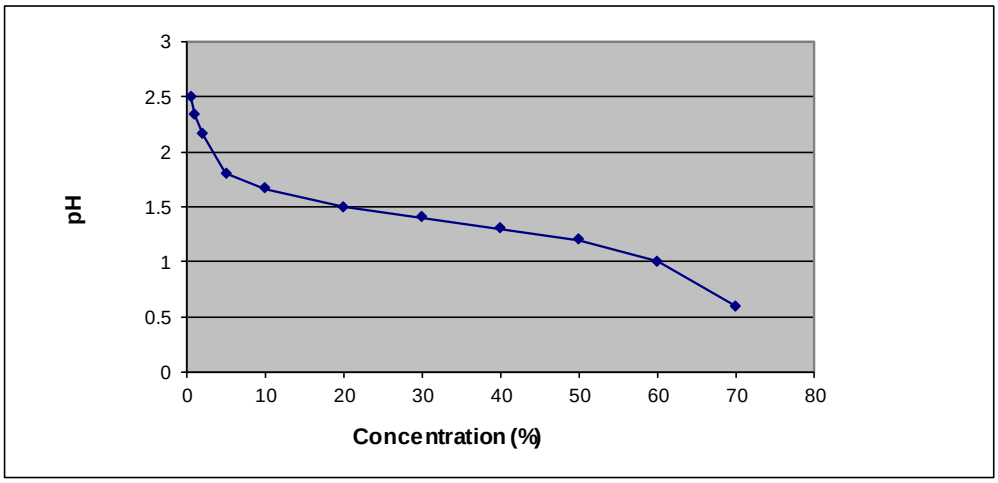


Figure 5.2: Undissociated glycolic acid in % of total concentration in aqueous solutions at pH 2-6

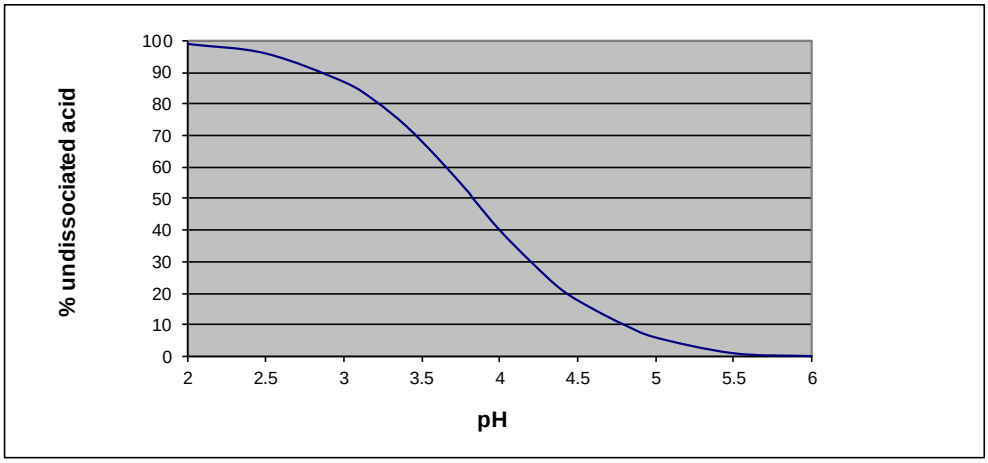
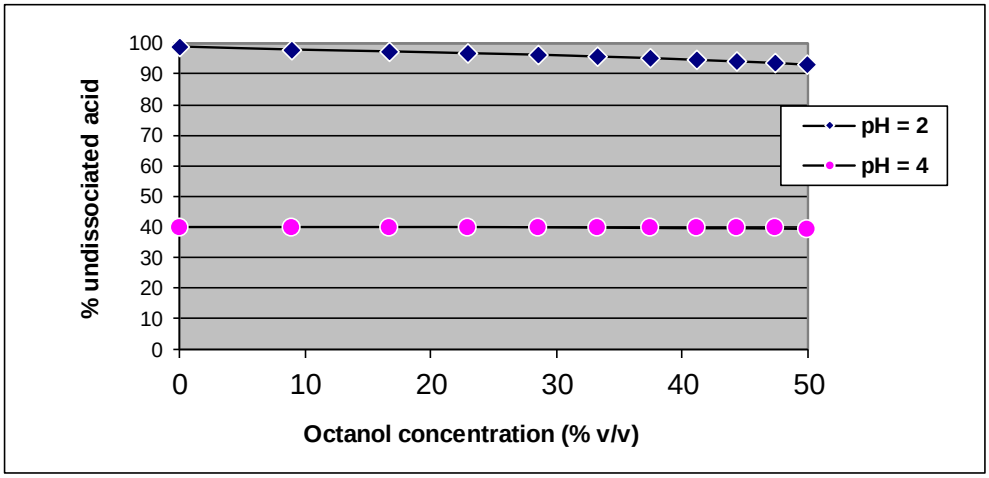


Figure 5.3: Undissociated glycolic acid in the aqueous phase of octanol-in-water emulsions at pH 2 and pH 4 in % of total concentration in the product



6. Methods of Detection and Analysis

6.1 Identification

Glycolic acid can be characterised by nuclear magnetic resonance, infrared and mass spectroscopy. The chemical may be detected qualitatively in a spot test with 2,7-dihydroxynaphtalene in concentrated sulphuric acid (Eegriwe, 1932, as cited in Miltenberger, 1989).

6.2 Quantitative analysis

6.2.1 General methods

Quantitative determination of glycolic acid can be performed by acidimetric titration or a variety of spectroscopic and chromatographic methods. A frequently employed assay utilises the Eegriwe colour reaction described above, followed by measurement of the absorbance of the solution at 540 nm (Calkins, 1943, as cited in Hackney & Hensley, 1987). The Calkins method has a detection limit of approximately 1 μM (76 μg/L) but its specificity is low because of interference by formaldehyde, ammonium and nitrate ions, carbohydrates and other naturally occurring substances. A less sensitive (about 4 μM) but more specific assay employs glycolate oxidase to catalyse the conversion of glycolic acid to glyoxylic acid, which then reacts with phenylhydrazine to form a coloured derivative with an absorbance peak at 324 nm (Hackney & Hensley, 1987). The most sensitive method developed to date uses extraction with ethyl acetate, derivatisation with bis-trimethylsilyl trifluoroacetamide and quantification by gas chromatography-mass spectrometry (Leboulanger et al., 1998). This method has a limit of detection below 0.05 μM (4 μg/L) glycolic acid.

6.2.2 Raw materials

Blake et al. (1987) have developed a method for the quantitative analysis of organic acids in sugar cane juice which allows the simultaneous determination of glycolic, lactic, malic, tartaric, citric, pyroglutamic, pyruvic and other commonly occurring 'fruit acids'. The acids in the sample are passed through a cation-exchange column, isolated on an anion-exchange column and eluted with dilute sulphuric acid. After filtration of the eluate, the acids are separated by high-pressure liquid chromatography (HPLC) on 2 cation-exchange columns connected in series and equilibrated at 35°C and 85°C respectively and quantified by refractive index monitoring. The system is calibrated using external standards and has a detection limit of about 50 mg/L.

6.2.3 Cosmetic products

A method has been developed for routine analysis of commercial cosmetics such as creams and lotions (Scalia et al., 1998). A sample of the product is dispersed in tetrahydrofuran-water by sonication, purified by solid-phase extraction on a silica-based, strong anion-exchange cartridge and directly analysed by HPLC

using an UV detector set at 210 nm. The sensitivity of the assay was determined at 15 μg/mL, which corresponds to a concentration of 0.4% glycolic acid in the cosmetic product. The peaks representing glycolic, lactic, malic, tartaric and citric acid were well separated and the average recovery of glycolic acid was 92-96%.

6.2.4 Biological monitoring

Blood glycolic acid may be measured by high-performance ion chromatography of a plasma or serum ultrafiltrate, using monitoring of the column eluant with a conductivity cell and an external standard (Hagen et al., 1993). The ion-exchange method can be automated and has a high degree of sensitivity (approximately 3 μM), precision and specificity. It can also be applied to urine (Wandzilak et al., 1991).

Fraser & MacNeil (1993) have developed colourimetric and gas chromatographic procedures for the measurement of glycolic acid in blood from ethylene glycol poisoned patients (see section 11.1.2). These assays are rapid and can be run on standard equipment, but have a much higher detection limit than the ion-chromatographic method (1.0 mM).

Serum and urine samples can also be analysed directly for glycolic acid content by proton magnetic resonance spectroscopy (Wahl et al., 1998).

7. Manufacture, Importation and Use

7.1 Manufacture of glycolic acid

Glycolic acid manufacture does not occur in Australia, but is reported in USA, Europe and Japan. Glycolic acid is on the OECD list of high production volume chemicals (OECD, 1997), which means that at least one OECD member state imports and/or produces more than 1000 metric tonnes per year (t/y) of the chemical. In the late 1980s, worldwide consumption (all grades and uses) was estimated at 2000-3000 t/y (Miltenberger, 1989). Manufacture of AHA blends by extraction of plant materials is on a much smaller scale, mainly in Europe and USA, and is not known to occur in Australia.

7.2 Overview of the Australian cosmetic industry

As shown in Figure 7.1, the entities involved with cosmetic uses of glycolic acid in Australia are:

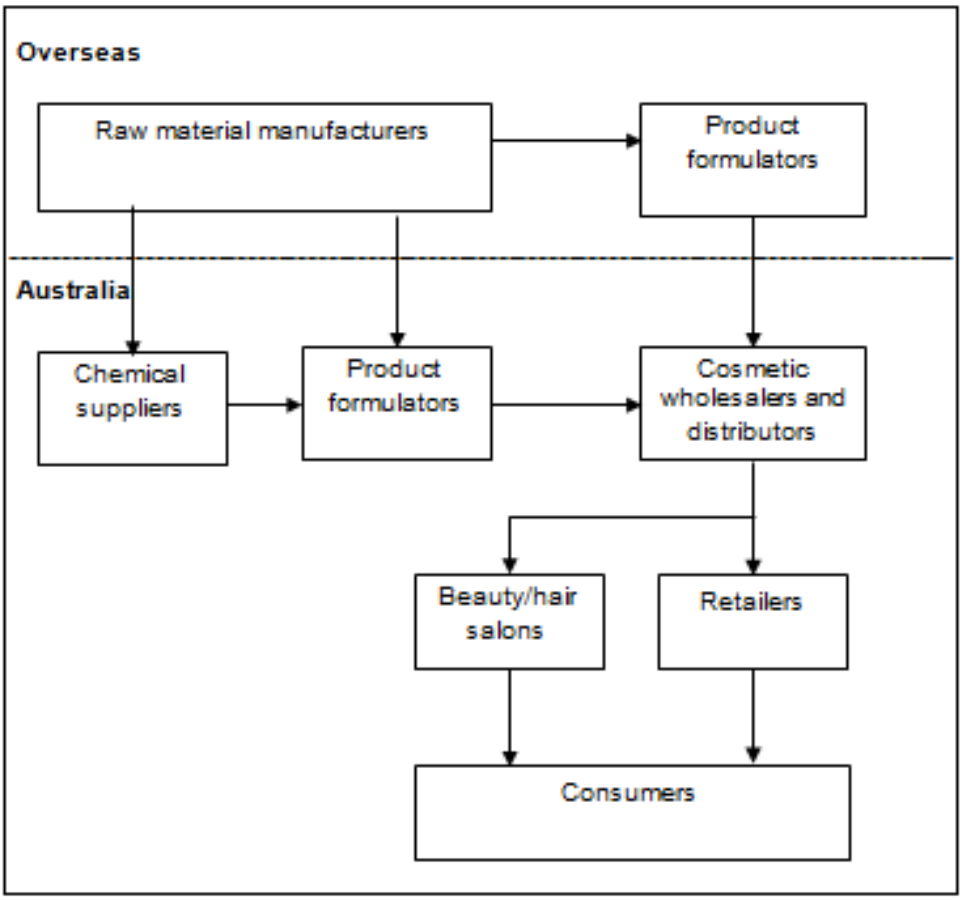
- chemical suppliers who purchase glycolic acid raw materials overseas and resell them to product formulators;
- product formulators who manufacture salon and consumer cosmetics and sell them to cosmetic wholesalers and distributors;
- cosmetic wholesalers and distributors who purchase products from overseas and/or domestic formulators and resell them to beauty and hair salons or retailers;
- beauty and hair salons who purchase products for in-salon end use or resale to clients;
- retailers such as pharmacies, supermarkets and department stores; and
- consumers.

Industry sources estimate that there are 2500-3000 full-service beauty salons and 12,000 hair salons in Australia. In addition, there are over 15,000 pharmacies, supermarkets and department stores (Australian Bureau of Statistics, 1993), most of which would stock one or more lines of glycolic acid consumer cosmetics.

Many businesses are both importers and formulators of finished goods and some also control the distribution and retailing of their products:

- Business A distributes a total of 29 glycolic acid containing cosmetic products, of which 23 are for the retail and 6 for the salon market. Twenty-eight of the products are manufactured in USA and imported in finished form. One product is manufactured in Australia by a contract manufacturer who purchases the raw material from a local chemical supplier.

Figure 7.1: Schematic representation of the flow of glycolic acid for cosmetic use from manufacturers through to end users



- Business B is the Australian subsidiary of a large multinational company specialising in beauty and related products which are sold and distributed directly to the consumer. The business imports most of its products in finished form, however 5 formulations containing glycolic acid are manufactured in Australia by a contract manufacturer from raw materials purchased from a local chemical supplier.

- Business C, which is owned by two physicians, makes and distributes 16 different glycolic acid products, which are sold to about 30 beauty salons where they are either consumed or resold to the public. The business also uses and retails the products in its own beauty salon. The finished products are manufactured in the business' own laboratory from raw materials purchased from a local chemical supplier.

- Business D, a pharmacy, retails a number of branded cosmetics containing glycolic acid but also manufactures two extemporaneous formulations, which are packaged in glass jars with typewritten labels and sold to the general public. The raw material is purchased from a local chemical supplier.

The industry comprises a large number of small formulators and importers of finished products that are not subscribers to the *Chemical Gazette* or members of the industry association (Cosmetic, Toiletry and Fragrance Association of Australia) and may not have been aware of the declaration of glycolic acid as a PEC. As such, the quantity of glycolic acid imported in finished form, the number of salon and consumer products marketed in Australia and the number of formulators and importers of finished products are likely to be higher than reported below.

7.3 Importation for cosmetic use

Cosmetic grade raw materials (synthetic and natural) were imported by 8 of the applicants for this assessment, whereas 17 imported the chemical as an ingredient in finished cosmetic products. Information submitted by the applicants indicates that glycolic acid is imported at annual levels ≥1500 kg in synthetic, cosmetic grade raw materials, ≥500 kg as an ingredient in natural raw materials (AHA blends) and ≥3700 kg as an ingredient in cosmetic products for salon or consumer use.

7.4 Types of cosmetic products containing glycolic acid

Based on information collected from applicants and notifiers, it is estimated that 180 different cosmetic products containing glycolic acid were marketed in Australia in 1998/99 (Table 7.1 and Appendix 1). This number does not include different pack sizes of the same brand, formulation, glycolic acid content, pH and recommended use. Also, 20 products which 3 importers distribute directly to physicians for use in their practice were not considered. Although the database is unlikely to be complete, it probably includes most, if not all, major brands and high volume products. As the cosmetics market is dynamic, some of the products may no longer be commercially available.

Table 7.1: Types of glycolic acid containing cosmetic products marketed in Australia in 1998/99

End users	Formulation	Number	Range of glycolic acid content (%)	Range of pH
Beauty salons	Cream	3	4-10	3.0-3.5
	Gel	8	10-60	2.0-3.5
	Lotion	2	10	3.5
	Solution	12	5-50	1.5-4.5
	Total	*25*	*4-60*	*1.5-4.5*
Consumers	Cream	56	0.06-20	3.0-6.6
	Gel	22	0.1-20	3.0-5.8
	Hair products	11	0.01-8	4.3-6.0
	Lotion	40	0.7-20	3.0-5.8
	Oil	1	5	3.5
	Scrub	9	0.3-15	3.0-6.0
	Solution	16	0.2-6.5	3.5-5.8
	Total	*155*	*0.01-20*	*3.0-6.6*
Grand total		***180***	***0.01-60***	***1.5-6.6***

By comparison, a FDA survey of the US cosmetics market conducted in 1997 identified 62 different formulations containing glycolic acid (CIR, 1998).

All cosmetics containing glycolic acid are used in the care of the skin and its appendages (hair and nails). According to their end users, they can be divided into salon products and consumer products. All salon and most consumer products are recommended for skin care, that, is application to the skin of the face, body, hands or feet as moisturising and exfoliating agents and to improve skin texture, smooth fine lines and wrinkles and reduce the appearance of age spots. All hair products are for consumer end use. They include shampoos, conditioners and intensive hair treatments, most of which contain very small

amounts of glycolic acid, either for the purposes of pH adjustment or to provide a 'fruit acid' marketing platform.

7.5 Non-cosmetic uses

In Australia, technical grade glycolic acid is used in household and industrial cleaners, paint strippers, textile finishing solutions and oil and water well flow enhancers. These uses are outside the scope of the present assessment.

7.6 Glycolic acid in foods

Glycolic acid is found in the fruit, leaf, stem and root portions of all plants. Commonly consumed fruits and vegetables are reported to contain from 0.45-7.4 mg glycolic acid per 100 g fresh wet weight (Harris & Richardson, 1980). Tea, coffee, fruit juice and other beverages derived from plant sources may contain 5-7 mg glycolic acid per 100 mL. Foods of animal origin are generally low in glycolic acid, with milk and beef reported to contain 0.06-0.12 mg per 100 g of the chemical.

8. Estimated Occupational and Public Exposure to Glycolic Acid Resulting from Cosmetic Uses

In Australia, exposure to glycolic acid resulting from its use in the cosmetics industry may occur to:

- workers handling glycolic acid raw materials during storage or transportation;
- workers involved with the manufacture of cosmetic products;
- workers handling finished cosmetic products during storage or transportation;
- workers in beauty salons;
- consumers treated with glycolic acid products in beauty salons; and
- consumers who use cosmetics with glycolic acid at home.

8.1 Methods of use

8.1.1 Formulation of cosmetic products

Of the 60 applicants and notifiers, 19 formulated skin or hair care products with glycolic acid in Australia or had such products formulated by local contract manufacturers.

The products are generally manufactured from liquid raw materials (70% glycolic acid solution or AHA blends) which are imported in polyethylene jerry cans, pails or drums containing 1-250 kg. The quantity of raw material required to formulate a batch is pre-weighed and decanted into smaller containers. Where the raw material is partially neutralised before final mixing, water is first weighed into a vessel to which the base (usually ammonium hydroxide) is slowly added. The raw material is then slowly poured into the basic solution and the premix is stirred for 10-15 min. Solutions and gels are manufactured by adding additional water and the remaining ingredients to the premix at room temperature whilst keeping the batch under slow/medium sweep blade mixing. Lotions and creams are manufactured by heating and homogenising the oil phase and aqueous phase ingredients together at 60-95°C. The batch is then cooled to 40-65°C and the raw material or partially neutralised premix is poured manually or pumped into the batch and mixed in. After further cooling, the batch is pumped or decanted into a storage tank from which it is dispensed into bottles, tubes or jars by gravity feed or pneumatic filling. The primary containers may be packaged into individual cartons. The finished product is stored and distributed in multiunit cardboard boxes or shrink-wrapped in plastic foil.

In a few cases, the starting material is crystalline glycolic acid which is imported in 20 kg disposable fibre drums. The solid raw material is weighed into a sealed

container, transferred to an open vessel and dissolved in water using a hand stirrer. The solution is then processed as above.

8.1.2 Application of cosmetic products

In salons, beauticians first cleanse and rinse the skin area to be treated and then apply the glycolic acid solution or gel with the fingertips or a cotton tip or brush. When treating the face, the solution/gel is left in place for 5-10 min and then washed off with gauze dipped in cold water. Occasionally, the solution/gel is applied a second time and left in place for another 5-10 min before being washed off. Hands, feet and other body parts are treated similarly. According to industry sources, products applied to body parts other than the face are usually washed off after about 15 min. The treatment is concluded with the application of a moisturising cream, which usually contains a sunscreen with a sun protection factor (SPF) ≥15. A typical treatment course includes 6-10 peels over a period of 4-6 weeks.

When used at home, skin care solutions, gels, lotions and creams are applied to the skin with the fingertips or a small cotton ball once or twice a day. Scrubs, which are lotions or creams that contain polishing granules, are rubbed into the skin with a cloth or a sponge and then rinsed off with water.

Hair products such as shampoos and conditioners are lathered into the hair, left on for a few minutes, and rinsed off with water. Intensive hair treatment products are usually applied to the hair and left in. In some cases, the manufacturer recommends to cover the head with plastic film or a towel for 15 min before rinsing out the product under the shower.

8.2 Occupational exposure

8.2.1 Methodology

Given the uses of glycolic acid in the cosmetics industry, workers are potentially exposed to the chemical by both skin contact and inhalation.

The theoretical external exposures by skin contact were estimated for reasonable worst-case scenarios, using occupational exposure parameters derived from the EASE (Estimation and Assessment of Substances Exposure) model developed by the UK Health and Safety Executive (EC, 1996). The assumptions and calculations used to arrive at these estimates are described in Appendix 2, section A2.1. The EASE model is designed to provide a conservative estimation of potential exposure.

Cosmetic products formulated in Australia contain a maximum of 40% glycolic acid and the most widely used raw material is a 70% solution of the chemical in water. For formulation plant workers, the EASE model predicted a maximum dermal exposure to glycolic acid assessed as external dose rate to predominantly the hands and forearms that varied between 140 mg/day for incidental exposure to a 70% solution and 800 mg/day for intermittent exposure to solutions containing 40% of the chemical.

During manual application of formulations of glycolic acid in beauty salons or skin clinics, the maximum external exposure predominantly to the hands and forearms predicted by the EASE model was 800 mg/day for application of a 40%

formulation in beauty salons and 1400 mg/day for a 70% formulation as used in skin clinics.

Data on airborne exposure were provided by a major manufacturer, based on air monitoring conducted at two US and three Australian sites handling various glycolic acid products (DuPont, 1999b). The air monitoring program also included a laboratory simulation of the blending of a commercial 70% glycolic acid solution in a 20 L gas-sparged, agitated, translucent open-air vessel equipped with baffles, a turbine propeller and a single-point sparging line and run with process parameters representing typical commercial-scale values. Aerosol formation was measured with an 11-stage cascade impactor placed 4-15 cm above the surface of the mixing liquid. There was visible splashing and churning in the vessel, but no mist could be seen with the naked eye. However, chemical analysis of the impactor filters identified the presence of very fine aerosol particles with a mean diameter of 0.4-1 μm in a quantity corresponding to an airborne concentration of glycolic acid ranging from 1.1-1.9 mg/m^3.

The measured air levels were comparable to estimates obtained by the EASE model as described in Appendix 2. The maximum exposure levels were estimated to equal the lowest rounded value encompassing all relevant UTL95%,95%[1] values and EASE estimates given in Table 8.1. A breathing zone concentration of 2 mg/m^3 was taken to be the maximum airborne exposure from the commercial 70% raw material, whereas a breathing zone concentration of 1 mg/m^3 was taken to be the maximum airborne exposure from formulated products containing ≤45% glycolic acid.

The maximum predicted dermal exposure is equivalent to the exposure resulting from the application of a standard amount (1-2 x 7.5 g; see Table 8.2) of a body lotion with 10% glycolic acid. The estimated maximum air concentrations of glycolic acid are 5-10 times lower than the workplace control level of 10 mg/m^3 (8- and 12-h TWA) established by one large manufacturer of the chemical (DuPont, 1999b).

8.2.2 Exposure during storage and transportation

Cosmetic raw materials and finished products containing glycolic acid are packaged into closed containers and as such the likelihood of occupational exposure during storage and transportation is negligible, except in case of accidental spills or leaks.

8.2.3 Exposure during formulation

Workers involved in the formulation of cosmetic products may be exposed to glycolic acid during pre-weighing of raw materials, during the preparation of premixes and final formulations, and during filling operations. As some formulators are small businesses with a limited number of staff, one worker could be involved in the entire formulation process. On the other hand, exposure is unlikely to occur repeatedly, as even the largest formulators do not manufacture glycolic acid containing cosmetics on a daily basis.

[1] Upper tolerance limit encompassing 95% of exposures with a certainty of 95%.

Table 8.1: Measured and predicted airborne concentrations of glycolic acid (mg/m³) in raw material and formulation manufacture facilities and a beauty salon in USA and Australia

Site	Process	Monitoring	Description	Duration (min)	Analytical results				EASE estimate	Average glycolic acid concentration in product handled
					N	Range	Median	UTL95%,95%*		
Belle, VA, USA	Manufacture	Personal	Operators	Full-shift**	10	<0.1-1.2	0.20	1.5	0-0.3	70%
	Purification	Personal	Operators	Full-shift	3	<0.1	<0.1	-	0-0.3	70%
	Road tanker loading	Personal	Operators	Full-shift	11	<0.1-1.4	0.20	1.6	Negligible	70%
	Drumming	Personal	Operators	Full-shift	19	<0.1-0.6	0.10	0.53	Negligible	70%
Wilmington, DE, USA	Simulated blending	Static	50 cm above tank at 45° angle	180-240	8	0.14-0.33	0.28	0.52	Negligible	70%
USA, not further specified	Cosmetic formulation manufacture	Static	15-45 cm from vessel surfaces	85-280	4	<0.1-0.15	0.085	0.60	0-0.2	40%
Tomago, NSW	Household cleaner formulation manufacture	Personal	Operator	300	1	<0.1	-	-	Negligible	5%
	Household cleaner formulation manufacture	Static	50 cm above open mixing vessel	270-280	2	<0.1	<0.1	-	Negligible	5%
Nowra, NSW	Industrial cleaner formulation manufacture and filling	Personal	Operator	240	1	<0.1	-	-	Negligible	45%
	Industrial cleaner formulation manufacture	Static	50 cm above open mixing vessel	240	1	0.15	-	-	Negligible	45%
	Industrial cleaner formulation filling	Static	Proximity of filling area	240	1	<0.1	-	-	Negligible	45%
Sydney, NSW	Beauty salon	Static	Inside cubicle	310	1	0.1	-	-	Negligible	20%

* Upper tolerance limit encompassing 95% of exposures with a certainty of 95% (calculated according to Mulhausen & Damiano (1998), with non-detectable results assigned a value of 0.7 times the detection limit)
** 12-hour shifts

In a reasonable worst-case scenario based on the manufacture of a 40% solution from a raw material containing 70% glycolic acid, one worker would spend 2 h at pre-weighing and mixing followed by 4 h at the filling line. As shown in Appendix 2, section A2.1.3, the estimated potential exposures are:

- inhalation: 0.1 mg/kg/day
- skin contact: 6.2 mg/kg/day
- total: 6.3 mg/kg/day.

8.2.4 Occupational exposure from salon use

Workers in beauty salons may be exposed to inhalation of vapours originating from and to intermittent skin contact with products containing glycolic acid. In a reasonable worst-case scenario, a beautician may perform 3 applications per day, each lasting 15-20 min, corresponding to a maximum of 1 h of exposure to the chemical. As shown in Appendix 2, section A2.1.3, this would result in the following potential exposures from a product containing 40% glycolic acid:

- inhalation: 0.02 mg/kg/day
- skin contact: 1.7 mg/kg/day
- total: 1.7 mg/kg/day.

8.3 Public exposure

8.3.1 Methodology

The public will be exposed to skin contact with a variety of cosmetic products such as face creams, body lotions and gels, scrubs, shampoos and conditioners. Inhalation may also occur, but vaporisation of glycolic acid from cosmetic formulations is expected to be negligible.

For a selection of relevant cosmetics, the typical use levels employed in the assessment of consumer exposure in Europe are shown in Table 8.2.

Table 8.2: Typical use levels of selected cosmetics (EC, 1996; ECETOC, 1993)

Product type	Amount/application (g)	Frequency of application
Non-rinse products		
• face cream	0.8	2/day
• general purpose cream	1*	1-2/day
• after-shave	1.2	1-2/day
• body lotion	7.5	1-2/day
• setting product	12	1-2/week
• make-up remover	2.5	1-2/day
• nail products	0.25	2-3/week
Rinse-off products		
• shower gel	10	1-4/week
• shampoo	12	1-7/week
• hair conditioner	14	1-3/week

* mg/cm^2

8.3.2 Exposure from personal use

In a reasonable worst-case scenario, home use of cosmetics with glycolic acid would imply 2 daily applications of a 10% leave-on face cream and a 10% leave-on body lotion (the highest concentration sold directly to consumers is 20%, but in general manufacturers do not recommend twice daily application for products containing >10% glycolic acid).

According to Table 8.2, this would result in the following external exposure for a 60 kg person: 10 x (0.8 + 7.5) x 2 x 1000 / 100 x 60 = 28 mg/kg/day.

8.3.3 Public exposure from salon use

Products used in salons for face peels contain up to 60% glycolic acid. However, as the surface area of the face is relatively small and it is customary to rinse off the product after a contact time of 5-10 min, face peels do not represent a reasonable worst-case scenario. As such, it is assumed that salon treatment involves 2 applications to the arms, legs and back of the hands and feet of a 40% formulation applied in a standard quantity of 1 mg/cm^2 (Table 8.2) and rinsed off. Assuming that 10% of the formulation is left on the skin after rinsing, this would result in the following external exposure for a person weighing 60 kg, in whom the surface area of the arms, legs and back of the hands and feet is approximately 7800 cm^2 (EPA, 1997): 40 x 7800 x 1 x 2 x 10 / 100 x 100 x 60 = 10 mg/kg/day.

8.4 Conclusions

In practice, workers involved with the manufacturing of cosmetic products would usually wear protective clothing in the form of long-sleeved overalls or coats and impervious gloves, which would minimise exposure to the hands and forearms. Workers in beauty salons may wear gloves, which would reduce skin exposure by about one-third.

Table 8.3: Potential external exposure of workers with and without gloves and/or long-sleeved protective clothing (GPC) and of consumers to glycolic acid resulting from cosmetic uses

Type of exposure	Scenario	Frequency of exposure	Total potential exposure (mg/kg/day)	
			Without GPC	With GPC*
Occupational	Formulation plant	Intermittent	6.3	2.1
	Beauty Salon	Repeated	1.7	1.1
Public	Salon skin peel	Intermittent	10	NA
	Home use	Repeated	28	NA

NA = not applicable

Table 8.3 above presents a summary of the estimated maximum external exposure of workers and consumers to glycolic acid as used in the cosmetics industry. The table also includes information on the likely frequency of exposure, which may be intermittent or repeated, that is, occur at intervals of several days to several weeks or on a daily or almost daily basis. The table may be used to estimate the impact of combined exposure scenarios. For example, a beautician who also consumes glycolic acid products at home could be subject to repeated exposures to the chemical at a level of 30 mg/kg/day.

Although physician use of glycolic acid falls outside the scope of this assessment, occupational exposure also occurs in clinical practice where nurses and other staff may handle and apply solutions containing up to 70% glycolic acid. As shown in Appendix 2, section A2.1.3, if such workers handle glycolic acid formulations manually for 1 h/day, their estimated maximal total exposure (repeated) would be 2.9 mg/kg/day without protective clothing. It would be 1.9 mg/kg/day if gloves are used and negligible if both gloves and long-sleeved coats are worn.

It should be emphasised that the above exposure estimates are conservative and do not include any form of absorption, which will be considered in the following section.

9. Kinetics and Metabolism

The toxicokinetics of glycolic acid has been well investigated in laboratory animals and humans. This is primarily because glycolic acid is both a precursor of oxalic acid, which is a common component of kidney stones, and the major toxic metabolite of ethylene glycol, which is an ingredient in antifreeze products and a frequent cause of poisoning by ingestion in many parts of the world. However, there are also studies of the absorption and metabolism of glycolic acid applied to the skin.

9.1 Absorption

9.1.1 Through the skin

Absorption is defined as the rate and extent to which a substance is taken up by the body when it is applied to a body surface. Dermal absorption *in vivo* may be determined indirectly by measuring radioactivity in excreta following topical application of the labelled substance. Alternatively, it is determined *in vitro* by mounting a piece of skin in a diffusion cell, adding labelled substance to the surface and measuring the amount of radioactivity which is taken up by the skin (the retention) or passes through the skin to the medium in the collection chamber (the penetration).

The available skin absorption data for glycolic acid are summarised in Table 9.1. As there are no differences in absorption between fresh (live) and frozen (dead) skin specimens, it is considered that dermal absorption of glycolic acid is a passive diffusion process (Jiang & Qureshi, 1998). As shown in Table 9.1, the absorption process is influenced by time, pH, concentration, type and composition of the formulation, and by the degree of occlusion of the site of application.

A graphic representation of the absorption rates determined by Jiang & Quareshi (1998) indicates that the most important factor in determining the rate of skin penetration is the concentration of undissociated glycolic acid in the test sample (Figure 9.1). The permeability coefficient (P) of glycolic acid can be calculated from the slope of the regression line through the linear portion of the penetration curve in Figure 9.1, after conversion of the unit of the abscissa (the concentration of undissociated glycolic acid) from % to mg/mL. In this case the result is approximately 3×10^{-4}cm/h.

The permeability coefficient through human skin of small non-electrolytes in aqueous solution can also be estimated from the following equation:

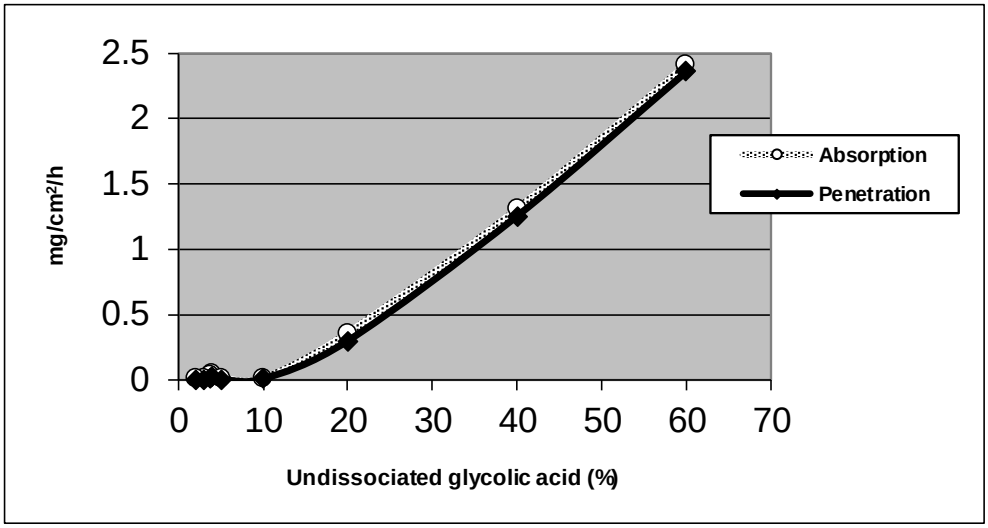
$$\log[P\ (cm/s)] = -6.36(\pm 0.18) + 0.74(\pm 0.07) \times \log P_{o/w} - 0.006(\pm 0.0006) \times MW$$

where $P_{o/w}$ is the octanol/water partition coefficient and MW the molecular weight (Guy, 1995).

Table 9.1: Summary of *in vivo* and *in vitro* studies of skin absorption of ^{14}C-labelled glycolic acid (GA) in animals and humans

Species	Study design	Test samples	Results	Comments	Reference
In vivo					
Hairless mice, SKH-hr-1, 5 males per group	Test samples rinsed off at 1 h. One animal per group killed at 1, 2, 3, 5 and 9 h. Skin, bladder and liver analysed for radioactivity.	250 μg/cm² GA in a 4% aqueous solution, 2 liposome formulations, 30% propylene glycol in water, an oil-in-water and a water-in-oil emulsion	At 1 h, 10-60% of the applied quantity was found on the skin surface, 30-70% in the stratum corneum, 1-3% in the living skin layers and <1% in the urine and liver. At 9 h, the corresponding values were 10-70, 20-50, 0.3-1 and 0.3-4%.	One liposome formulation had a significantly higher absorption than all other formulations	Ohta et al. (1996)
In vitro					
Hairless mice, SKH-hr-1, 3 males per group	Full thickness skin in static diffusion cell, no occlusion	565 μg/cm² GA in a 4% aqueous solution, 2 liposome formulations and 30% propylene glycol in water	After 16 h, the penetration was 3% for the aqueous solution, 13-20% for the liposome formulations and 10% for the propylene glycol/water mixture		Ohta et al. (1996)
Hairless mice	Full thickness skin in static diffusion cell ± occlusion	20 mg/cm² GA in a 10% aqueous solution, pH 3.8	Without occlusion, lag time was >15 min, penetration non-linear and 8-h penetration = 0.6-0.9%. With occlusion, lag time was <15 min, penetration linear and 8-h penetration = 1.8-2.3%.	Summary only	Goldstein & Brucks (1994)
Pigs	Separated epidermis in static diffusion cell ± occlusion	20 mg/cm² GA in a 10% aqueous solution, pH 3.8	Without occlusion, lag time was >15 min, penetration non-linear and 8-h penetration = 0.7-1.1%. With occlusion, lag time was <15 min, penetration linear and 8-h penetration = 0.8-1.8%.	Summary only	Goldstein & Brucks (1994)
Humans, 1 subject	Epidermal membranes from frozen abdominal skin in static diffusion cell, no occlusion	2 mg/cm² GA in a 10% aqueous solution, pH 3.7	At 24 h, total absorption was <1%.	Only 20 μL/cm² solution was applied and GA may have crystallised on the surface	An-eX (1994)
Humans, 3-5 subjects per group	Viable split thickness abdominal skin in flow-through diffusion cell, no occlusion	150 μg/cm² GA in 2 different 5% oil-in-water emulsions, pH 3.0 and 7.0	At 24 h, total absorption was 27-35%, retention 23-25% and penetration 3-12% at pH 3.0 and 2-3, 1-3 and <2% at pH 7.0	Study conducted by FDA	Kraeling & Bronaugh (1997)
Humans, 3-4 subjects per group	Fresh and frozen split thickness breast and abdominal skin in flow-through diffusion cell, no occlusion	4.4, 11.1 22.2 and 66.7 mg/cm² GA in 4, 10, 20 and 60% aqueous solutions at various pH levels	With a 20%, pH 1.9 solution, absorption was 12% at 6 h and 37% at 24 h. For solutions at their native pH (0.7-2.0), absorption was directly proportional to GA concentration. At pH 3.8 there was no difference in the total amount absorbed from a 4, 10 and 20% solution. At constant concentration (4%), absorption, retention and penetration were significantly higher at pH 2.0 and 2.6 than at pH 3.3 and 3.8.	Study conducted by Therapeutic Products Directorate, Health Canada	Jiang & Qureshi (1998)

Figure 9.1: Time-averaged skin absorption and penetration as a function of the concentration of undissociated glycolic acid in aqueous solutions (based on data from Jiang & Qureshi (1998) and Qureshi (1999))



For glycolic acid, whose MW = 76.05 and whose log $P_{o/w}$ is –1.38 to –1.11, the estimated permeability coefficient ranges from 3 x 10^{-5} to 2 x 10^{-4} cm/h, which is in reasonable agreement with the experimentally determined permeability coefficient of 3 x 10^{-4}cm/h. The slightly higher value of the measured coefficient could be due to glycolic acid inducing some loosening or thinning of the stratum corneum (see section 11.3), which would shorten the diffusion path across the skin.

The permeability coefficient can be used to estimate the absorption from aqueous solutions containing a practically infinite quantity of glycolic acid.

Kraeling & Bronaugh (1997) measured the *in vitro* penetration from two oil-in-water emulsions containing 5% glycolic acid at pH 3.0 and 7.0 which were applied in an amount equal to 3 mg/cm^2 to skin specimens from 5 human donors. The two formulations were the same, except that in Formulation B 1% ammonium laureth (or lauryl) sulfate, an ionic surfactant, replaced an equivalent quantity of Laureth-4 in Formulation A. The mean recovery of glycolic acid from the receptor fluid was 2.6% of the applied dose of Formulation A (pH 3.0), with a standard error of ±0.7% (corresponding to a 95% confidence interval of 1.2-4.0%), whereas the mean recovery from the receptor fluid was 12.2% of the applied dose of Formulation B (pH 3.0), with a standard error of ±5.2% (corresponding to a 95% confidence interval of 2.0-22.4%). At a formulation pH of 7.0, the mean recovery from Formulations A and B was 0.8% and 1.4% respectively. There was a high correlation (r^2 = 0.92) between glycolic acid and water absorption values. As water permeability is an indicator of the integrity of the skin, the authors speculated that the inter-individual variability in glycolic acid absorption was due to normal differences in the barrier function of the skin.

9.1.2 By inhalation

There were no quantitative studies of the rate or extent of uptake of glycolic acid from inhalation of vapours or aerosols of the chemical. However, the available

inhalation studies in laboratory animals indicate that glycolic acid is readily absorbed from the airways (see sections 10.1.3 and 10.4.2).

9.1.3 By ingestion

Absorption by ingestion has been determined in rats and Rhesus monkeys by measuring radioactivity in excreta after oral administration of ^{14}C-glycolic acid.

Groups of fasted and non-fasted male Wistar rats were dosed with 50-900 mg/kg ^{14}C-labelled sodium glycolate in an aqueous solution administered by gavage (Harris & Richardson, 1980). Urine, faeces and expired air were collected for 48 h, with food and water being withheld during the collection period. Only 2% of the radioactivity was recovered in faeces. At the lowest dose level, 50% of the administered dose was recovered as respiratory carbon dioxide and approximately 7% as glycolic, glyoxylic and oxalic acids in the urine. At the highest dose level, 22% of the administered dose was recovered as respiratory carbon dioxide, 51% as glycolic acid in the urine and 3% as glyoxylic and oxalic acids in the urine (see Table 9.2).

Two female Rhesus monkeys dosed orally with 500 mg/kg labelled glycolic acid in aqueous solution excreted around 3% of total radioactivity in faeces over a 72-96 h collection period (McChesney et al., 1972).

Intestinal absorption has also been studied *in vitro* using everted rat intestinal rings exposed to 0-10 mM (0-1.0 mg/mL) ^{14}C-labelled sodium glycolate (Talwar et al., 1984). Saturation kinetics was observed, with a K_m of 6.25 mM and a V_{max} of 11 μmoles/30 min/g wet weight. Absorption was not influenced by sulfhydryl binding agents or inhibitors of cellular respiration; however, it was competitively inhibited by glyoxylic and lactic, but not oxalic or pyruvic acids. The absorption rate was somewhat higher in specimens from the jejunum and ileum than from the duodenum and colon.

In conclusion, these findings indicate that glycolic acid is readily absorbed from the small intestine by a saturable carrier mechanism, which is shared by lactic acid and probably belongs to the family of monocarboxylate transporters referred to below.

9.2 Distribution

No experimental data were available about the distribution of glycolic acid to various organs and tissues following systemic administration or uptake.

Based on kinetic data from a reproductive toxicity study (Carney et al., 1997, 1999), the volume of distribution in pregnant rats can be determined at 0.66 L/kg.

In humans, blood contains glycolic acid of dietary origin, with plasma or serum levels having a reference interval of 1.4-7.5 μM (0.1-0.6 mg/L) (Hagen et al., 1993). The concentration is about 10 times higher in cerebrospinal fluid than in plasma, possibly due to formation of glycolic acid from certain neurotransmitters such as glycine and γ-aminobutyric acid (Hoffmann et al., 1993). Kinetic observations in 2 patients with ethylene glycol intoxication indicated a distribution volume of 0.56 L/kg, that is, glycolic acid is distributed in total body water (Jacobsen et al., 1988). This is expected since at physiological pH (7.4)

99.9% of the chemical is present as glycolate anion, which is miscible with water but insoluble in lipids.

Glycolic acid is taken up by rat liver cells by means of a monocarboxylate transporter which exchanges glycolate for inorganic anions (Jackson & Halestrap, 1996). Such transporters are found in many other mammalian organs and tissues, including the intestine, heart and skeletal muscle, the brain, the retina and red blood cells. Except for the liver and intestine, their function is to transport lactic acid into the extracellular fluid (Price et al., 1998).

9.3 Metabolism

The biotransformation of glycolic acid has been studied by oral or parental administration of glycolic acid labelled with ^{14}C at the 1 or 2 position to intact rats and monkeys followed by determination of labelled molecules in blood, urine and exhaled air. Exhaled air was found to contain labelled carbon dioxide (Harris & Richardson, 1980; Weinhouse & Friedman, 1951), whereas urine contained labelled glyoxylic acid, oxalic acid and hippuric acid as well as unmetabolised glycolic acid (Harris & Richardson, 1980; King & Lehner, 1971; McChesney et al., 1972; Weinhouse & Friedman, 1951). Hippuric acid is a conjugate of benzoic acid with the amino acid glycine which is formed from glyoxylic acid by transamination. Hepatectomy significantly altered the metabolism of labelled glycolic acid in the rat, reducing the formation of urinary metabolites and exhaled carbon dioxide by approximately 30-50% and 60-90% respectively (Farinelli & Richardson, 1983; Varalakshmi & Richardson, 1983).

In isolated perfused rat livers and rat liver homogenates, glycolic acid is oxidised to oxalic acid via glyoxylic acid (Richardson, 1973; Yanagawa, 1990). These reactions proceed at a rate which is twice as high in male as in female rats (Richardson, 1965; Runyan, 1971, Yoshihara et al., 1999). The oxidation of glycolic acid to glyoxylic acid is catalysed by glycolate oxidase, which is a hydrogen peroxide generating enzyme found in the peroxisome fraction of liver and kidney cells. Hydrogen peroxide is a co-substrate for catalase which catalyses the oxidation of formic acid to carbon dioxide. *In vitro,* glycolate oxidase also oxidises glyoxylic acid to oxalic acid; however, under physiological conditions, this reaction is more likely to be catalysed by lactate dehydrogenase (Poore et al., 1997).

When single doses of 1-4 g/kg of unlabelled or ^{14}C-labelled ethylene glycol was administered intraperitoneally to pigtail monkeys, the only detectable metabolite in blood and urine was glycolic acid (although the assay used would not have determined oxalic acid complexed with calcium) and the rate of CO_2 formation per h was $\leq 0.03\%$ of the ethylene glycol dose (Clay & Murphy, 1977).

Following intravenous administration of ^{14}C-glycolic acid to healthy human subjects, labelled glyoxylic and oxalic acids as well as unmetabolised glycolic acid were recovered from the urine (King, 1970). In human liver homogenates, labelled glycolic acid is metabolised to glyoxylic acid, oxalic acid and carbon dioxide (Dean et al., 1967; Richardson, 1965). There is no evidence of sex differences in the metabolic rate of glycolic acid in humans.

In various *in vitro* studies of human skin absorption, no metabolites of labelled glycolic acid were detected in the skin or the collecting fluid (FDA, 1996).

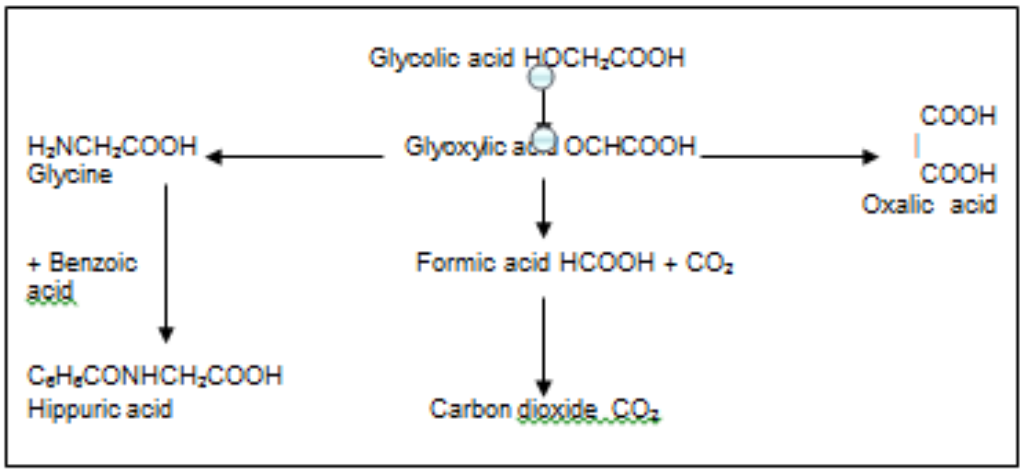
Table 9.2: Elimination of ^{14}C-labelled glycolic acid (GA) in animals and humans

Species	Dose and route	In urine (%)						Through the lungs (%)	Reference
		Total	Unchanged GA	Metabolites					
				Glyoxylic	Oxalic	Hippuric	Others		
Rat	50 mg/kg PO	ND	3	<1	3	ND	ND	50 (48 h)	Harris & Richardson (1980)
	900 mg/kg PO	ND	51	1	2	ND	ND	22 (48 h)	
Rat	380 mg/kg IV	67 (6 h)	61	1.2	3.5	ND	1.0	16 (6 h)	Varalakshmi & Richardson (1983)
Rat	10-110 mg/kg + 1mmole sodium benzoate IP	ND	ND	ND	0.8-1.1 (24 h)	7.2-12.5 (24 h)	ND	32-13 (5 h)	Weinhouse & Friedmann (1951)
Goat	Trace IV	ND	ND	ND	ND	ND	ND	40 (5 h)	Peters et al. (1971)
Cattle	Trace IV	11 (4 h)	ND	ND	ND	ND	ND	37 (4 h)	Peters et al. (1971)
Monkey	500 mg/kg PO	37-52 (72-96 h)	34-44	0.3-2.2	0.3-1.3	0.3	6	ND	McChesney et al. (1972)
Monkey	Trace IV	ND	61* (3 h)	12*	24*	-	3*	ND	King & Lehner (1971)
Human	Trace IV	9-14 (2 h)	5-10	1	3	-	-	ND	King (1970)

* % of count excreted in urine
IP = intraperitoneal administration
IV = intravenous administration
ND = not determined
PO = oral administration

In summary, glycolic acid metabolism is qualitatively similar in rats, non-human primates and humans and follows the pathways set out in Figure 9.2. Decarboxylation of glyoxylic acid to formic acid and CO_2 does not occur extensively in primates.

Figure 9.2: Metabolic pathways of glycolic acid



9.4 Elimination and excretion

The available studies of the elimination of ^{14}C-labelled glycolic acid in animals and humans are summarised in Table 9.2. Glycolic acid and its polar metabolites glyoxylic and oxalic acids are excreted in the urine, whereas the metabolite carbon dioxide is eliminated through the lungs. The amino acid glycine is normally preserved by the body but forms conjugates with aromatic acids such as benzoic acid that facilitate their excretion in the urine. This explains the high elimination as hippuric acid in the study in which glycolic acid was co-administered with sodium benzoate (Weinhouse & Friedmann, 1951). The data indicate that a substantial portion of glycolic acid is excreted unchanged in the urine, particularly at higher dose levels, where the metabolic processes tend to become saturated.

In pregnant rats, the elimination half-life of glycolic acid is 3 h (Carney et al., 1997, 1999).

In humans, the elimination half-life was determined at 7-10.5 h in a small number of patients with ethylene glycol intoxication (Jacobsen et al., 1988; Moreau et al., 1998). The reference interval for urinary excretion of glycolic acid in healthy men and women is in the order of 1-100 mg/24 h (Hagen et al., 1993; Wandzilak et al., 1991).

9.5 Comparative kinetics and metabolism

The key findings characterising the kinetics and metabolism of glycolic acid in rats, non-human primates and humans are summarised in Table 9.3.

Table 9.3: Summary of kinetics and metabolism in rats, non-human primates and humans

Parameter	Rats	Non-human primates	Humans
Absorption			
• ingestion	Almost complete	Almost complete	No data
• inhalation	No direct data	No data	No data
• through skin	No data	No data	Significant
Main metabolites	Glyoxylic acid Oxalic acid Carbon dioxide	Glyoxylic acid Oxalic acid	Glyoxylic acid Oxalic acid
Distribution volume	0.66 L/kg	No data	0.56 L/kg
Route of elimination	Kidney Lung (as carbon dioxide)	Kidney	Kidney
Elimination half-life	3 h (pregnant females)	No data	7-10.5 h
Sex differences	Rate of metabolism 2 times higher in males	No record	No record

10. Effects on Laboratory Mammals and Other Test Systems

Toxicology studies with glycolic acid have been conducted to characterise the general toxicity of the chemical, investigate the mechanisms of oxalate urolithiasis and of poisoning with ethylene glycol, or to determine the effects of the chemical on the skin. In this section, the emphasis is on studies which were conducted in accordance with Good Laboratory Practices (GLP) and employed internationally recognised methods such as OECD's Test Guidelines (OECD, 1981 as amended)[1]. Where such studies were not available, other test reports or published papers have been considered, provided they furnished enough scientific detail to permit a critical appraisal of their findings. Studies that were excluded from assessment because they did not meet the above criteria are listed in Appendix 3.

In some reports, dose levels were stated in mg/kg of commercially available solutions of glycolic acid. For purposes of comparison, these have been adjusted for concentration and expressed in mg/kg of 100% glycolic acid, unless otherwise indicated in the text.

10.1 Acute toxicity

10.1.1 Lethality

A number of acute lethality studies have been conducted with glycolic acid using different routes of administration and are summarised in Table 10.1. The rat studies were conducted in three different strains, namely Holzman (Bove, 1966), Sprague-Dawley (DuPont, 1963, 1998a*, 1998c*), and Wistar rats (Smyth et al., 1941).

10.1.2 Oral toxicity

The acute toxic effects from a single intragastric administration of glycolic acid or sodium glycolate included loss of appetite, weight loss, gastrointestinal irritation, kidney and liver damage and neuromuscular disturbances. Clinical signs comprised loss of appetite in all species, ataxia and flaccid paralysis in mice, lethargy, noisy breathing, ocular discharge and prostrate posture in rats, and vomiting, ataxia and convulsions in cats. Generally, the signs took about an hour to appear, progressed in intensity during the next 24 h, and either subsided gradually over several days or worsened and proved fatal (DuPont, 1998a*, 1998d*; Laborit et al., 1971; Riker & Gold, 1942).

The cat was the only species in which a no observed adverse effect level (NOAEL) was determined (Riker & Gold, 1942). Following oral administration of sodium glycolate by gavage, 5/5 animals dosed with 100 mg/kg showed no

[1] These studies are marked with an asterisk (*).

signs of intoxication, whereas 4/5 animals dosed with 250 mg/kg showed mild weakness, ataxia and anorexia. As such, the NOAEL was 100 mg/kg sodium glycolate corresponding to 78 mg/kg glycolic acid.

In rats dosed with 70% glycolic acid by gavage, there were signs of dose-related gastric irritation such as acute ulcerative and haemorrhagic gastritis (DuPont, 1963) or distended and discoloured stomachs lined with a black, unidentified fluid (DuPont, 1998a*). In one rat study, microscopic examination of the liver revealed hepatocyte necrosis in the paraportal region, increased mitosis and cytoplasmic eosinophilia (DuPont, 1963). In rats and guinea pigs, kidney weight was increased in surviving animals and microscopic examination revealed interstitial nephritis and calcium oxalate crystals in the tubules (Bove, 1966; DuPont, 1963; Smyth et al., 1941). In cats, tubular degeneration and increased blood urea nitrogen and creatinine were found (Riker & Gold, 1942).

Table 10.1: Summary of acute lethality studies

Route	Species	Results	Comments	Reference
Oral	Mouse (f)	ALD = 1120 mg/kg GA	70% technical grade by gavage	DuPont (1998d)*
	Mouse (m)	ALD = 840 mg/kg GA		
	Rat (f)	LD_{50} = 5000 mg/kg GA	25% analytical grade by gavage	Bove (1966)
	Rat (m)	LD_{50} = 2968 mg/kg GA	70% technical grade by gavage	DuPont (1963)
	Rat	LD_{50} = 1357 mg/kg GA	70% technical grade by gavage	DuPont (1998a)*
	Rat (m)	LD_{50} = 1950 mg/kg GA	5% commercial grade by gavage	Smyth et al. (1941)
	Guinea pig	LD_{50} = 1920 mg/kg GA	5% commercial grade by gavage	Smyth et al. (1941)
	Cat	ALD = 500 mg/kg NaG	9.8% solution by gavage	Riker & Gold (1942)
Dermal	No data			
Inhalation	Rat (f)	LC_{50} > 3640 mg/m^3 GA	Aerosolised 70% technical grade	DuPont (1998c)*
	Rat (m)	LC_{50} = 2520 mg/m^3 GA		
Intra-venous	Cat	ALD = 1000 mg/kg NaG	9.8% solution	Riker & Gold (1942)
Intra-peritoneal	Mouse	LD_{50} = 2000 mg/kg NaG	Unknown purity	Laborit et al. (1971)

ALD = approximate lethal dose (the lowest dose administered that causes mortality in at least one animal)
f = females only
GA = glycolic acid
LC_{50} = median lethal concentration
LD_{50} = median lethal dose
m = males only
NaG = sodium glycolate

10.1.3 Inhalation toxicity

Groups of 5 male and 5 female or 10 male Sprague-Dawley rats were exposed nose-only to aerosols of a 70% solution of technical grade glycolic acid for a single 4-h exposure period (DuPont, 1998c*). The aerosols provided exposure levels equal to 0, 420, 1470, 2660 and 3640 mg/m^3 glycolic acid. The animals were weighed and observed for clinical signs for 14-15 days before they were sacrificed for gross pathological examination and microscopy of the nose, larynx,

pharynx and lungs. Satellite groups of 5 male rats each were sacrificed approximately 24 h after exposure for microscopic examination of the same organs.

Time of death varied from 0-12 days post-exposure. Weight loss and clinical signs were evident at all dose levels and increased in severity with concentration. Immediately post-exposure, gasping, noisy breathing, hunched posture, and nasal and ocular discharges were observed. During the recovery period, in addition to the effects seen in the immediate post-exposure period, clinical signs included lethargy, sore eyes, sore nose, sore chin, vocalisation, hair loss, and stained and/or wet fur and/or perineum. No target organ gross changes were observed, whereas microscopic changes including dose-related degrees of ulceration and inflammation were observed in the mucosal membranes lining the larynx and the nose, with mild subacute-chronic inflammation of the lungs.

10.1.4 Intravenous toxicity

Intravenous administration of a solution of sodium glycolate to cats produced signs that were similar in type, strength and time course to those observed after oral administration of the same chemical (Riker & Gold, 1942).

10.2 Corrosivity and irritation

A number of *in vivo* skin and eye corrosivity and irritation studies have been conducted with glycolic acid in different formulations and are summarised in Table 10.2.

Table 10.2: Summary of *in vivo* corrosivity and irritation studies

Organ	Species	Test substance	Results	Reference
Skin	Rabbit	99% cosmetic grade	Corrosive	DuPont (1993a)*
	Rabbit	70% technical grade	Corrosive	DuPont (1993b)*
	Rabbit	70% cosmetic grade, adjusted to pH 7.0	Mild irritant	DuPont (1998f)
	Rabbit	10, 30 and 40% cosmetic grade, adjusted to pH 3.5	Mild to moderate irritant	DuPont (1994)*
	Rabbit	57% technical grade	Irritant	Hoechst (1984a)*
	Rabbit	15, 25 and 50% in cosmetic products, pH 4.5	Non-irritant	Natura Bissé (1996)
	Mini pig	50% cosmetic grade	Sloughing of the epidermis	Moy et al. (1996b)
		70% cosmetic grade	Epidermal and dermal necrosis	
Eye	Rabbit	64% technical grade	Corrosive	DuPont (1977)
	Rabbit	57% technical grade	Corrosive	Hoechst (1984b)*
	Rabbit	10% cosmetic grade	Moderate irritant	Ohno (1999)*
	Rabbit	4 and 8% in cosmetic products, pH 3.8-4.0	Non- or practically non-irritant (4%) Minimal to mild irritant (8%)	Tox Monitor Laboratories (1994a-h, 1995)*

10.2.1 Skin

Glycolic acid has been evaluated for skin corrosion/irritation potential in rabbits in several studies conducted according to OECD Guideline No. 404 or similar protocols (DuPont 1993a*, 1993b*, 1994*; 1998f; Hoechst, 1984a*). Crystalline glycolic acid and a solution containing 70% glycolic acid at its natural pH (<0.5) caused visible necrosis through the epidermis and into the dermis after a 1-h exposure and were classified as corrosive. Solutions containing 10%, 30% or 40% glycolic acid at pH 3.5, 57% glycolic acid at pH 1.8 or 70% glycolic acid at pH 7.0 caused slight to moderate erythema, no or slight oedema, and no or superficial sloughing and skin necrosis after a 4-h exposure. When tested in rabbits according to European guidelines, a commercial face cream and two peeling solutions containing 15, 25 and 50% glycolic acid at pH 4.5 produced some erythema but no oedema and were classified as non-irritant (Natura Bissé, 1996).

In mini pigs exposed to 50% and 70% glycolic acid, histological examination of the skin 8 h after application showed epidermal sloughing and epidermal and dermal necrosis respectively (Moy et al., 1996b).

Solutions of glycolic acid have also been evaluated for skin corrosion potential in a non-biological system using the InVitro International Corrositex™ assay[1] (DuPont, 1997a-b). Solutions containing 30%, 50% and 70% cosmetic grade glycolic acid at their natural pH and a 70% solution adjusted to pH 3 were assigned to Packing Group II (moderate corrosives), whereas a 70% solution adjusted to pH 11 was assigned to Packing Group I (severe corrosive).

10.2.2 Eyes

Pure glycolic acid has been evaluated for eye corrosion/irritation potential in rabbits in three studies conducted according to protocols consistent with OECD Guideline No. 405. A solution containing 64% glycolic acid (pH not reported) caused severe, irreversible effects including total blindness and was classified as corrosive (DuPont, 1977). A solution containing 57% glycolic acid at pH 1.8 caused irreversible opacity and vascularisation of the cornea in addition to reversible conjunctival erythema and oedema (Hoechst, 1984b*), whereas a 10% solution at pH 1.8 was classified as moderately irritating (Ohno, 1999*). A total of 12 commercial creams or lotions containing 4% or 8% glycolic acid at pH 3.8-4.0 were reported to be at worst mildly irritating, even when they were not rinsed off after the standard exposure time of 15 sec (Tox Monitor Laboratories, 1994a-h*, 1995*).

When tested in a non-biological system, several commercial cosmetics containing 2-10% glycolic acid at pH 3.5-5.5 produced readings similar to substances known to be mild to severe irritants to the eye (Avon Products, Inc., 1995).

[1] Corrositex™ is a rapid *in vitro* test that permits assignment of UN Packing Group classes to corrosive (class 8) substances. The method is accepted by several transport agencies, including the Federal Office of Road Safety.

10.3 Sensitisation

The potential of technical grade glycolic acid to induce contact skin sensitisation in guinea pigs was assessed by the modified Buehler method (White Eagle, 1998*). The chemical was dissolved in normal saline and applied repeatedly to clipped intact skin under occlusion. No delayed responses were observed.

10.4 Repeated dose toxicity

10.4.1 Oral toxicity

Subchronic toxicity with immunotoxicity and neurotoxicity evaluation

A 3-month oral gavage study was conducted in Sprague-Dawley rats given solutions containing technical grade glycolic acid at doses of 0, 150, 300 or 600 mg/kg/day of glycolic acid (DuPont, 1999a*). Each dosage group was divided into subchronic toxicity, immunotoxicity, neurotoxicity, and reproductive toxicity subsets (10 animals/sex/subset/dose level). The findings in the reproductive toxicity subset are reviewed in section 10.5.2.

Body weights and individual food consumption were determined weekly. Clinical observations were recorded at weighing and by daily cage-site examinations. Ophthalmoscopic examinations were conducted on all rats prior to the start of the study and on surviving subchronic toxicity rats on test day 86. Clinical pathology evaluations were performed on subchronic toxicity animals near the middle and the end of the study. In the immunotoxicity subset, humoral immune function was evaluated. Rats in the neurotoxicity subset underwent functional observation battery and motor activity assessments once prior to study start, then near the beginning, middle and end of the study. All rats were given a gross pathological examination and selected tissues were examined microscopically.

Table 10.3: Mean body weight, body weight gain, food consumption and food efficiency in rats given glycolic acid by mouth for 3 months (DuPont, 1999a*)

	Dose level (mg/kg/day)			
Parameter	**0**	**150**	**300**	**600**
Mean body weight (g)				
• male rats	553.3	539.6	510.6*	481.0*
• female rats	318.1	306.2	298.4*	284.1*
Overall body weight gain (g)				
• male rats	323.1	308.3	280.4*	252.5*
• female rats	153.7	140.0	131.6*	119.8*
Mean daily food consumption (g)				
• male rats	28.1	27.8	26.5*	25.2*
• female rats	20.6	20.0	19.5	18.7*
Mean food efficiency				
• male rats	0.126	0.121	0.116*	0.110*
• female rats	0.081	0.077	0.074*	0.070*

* Significantly different from controls ($p < 0.05$).

Mean body weight at day 92 and overall mean body weight gain, food consumption and food efficiency (weight gain divided by food consumption) over

days 1-92 are shown in Table 10.3. There were no clinical signs indicative of systemic toxicity, although irregular respiration or lung noise attributed to aspiration of glycolic acid occurred in all treatment groups. There were no treatment-related ophthalmological findings in any of the groups. In all subsets combined, there were 2 deaths from kidney lesions, both in high-dose males. Eight animals died as a result of dosing accidents and one from a disease that was unrelated to the substance.

In the subchronic toxicity subset, blood neutrophils were slightly increased in male rats treated with 300 and 600 mg/kg/day, that is, the groups with kidney lesions and the most severe cases of pulmonary inflammation. Increased serum urea nitrogen, creatinine and phosphorous and an increased volume of less concentrated urine, which are indicative of renal pathology, were also observed in male rats treated with 300 and 600 mg/kg/day.

In males, absolute/relative kidney weights were increased by 6/15% at 300 mg/kg/day and by 14/25% at 600 mg/kg/day. Gross and microscopic kidney lesions were observed in male rats at 300 or 600 mg/kg/day. These included dose-related increases in the incidence of dilatation of the renal pelvis, oxalate crystal nephrosis, unilateral hydronephrosis and hyperplasia of the transitional cell epithelium of the renal pelvis. In addition, there were microscopic lesions in the respiratory tract in both sexes in all treatment groups. These were compatible with broncho-pulmonary irritation and most likely the result of aspiration of glycolic acid.

In the immunotoxicity subset, the animals were inoculated with sheep red blood cells on day 23 and sacrificed on day 29. Serum was collected and tested for specific antibody formation and the spleen and thymus were weighed. There were no treatment-related changes in any of these parameters.

In the neurotoxicity subset, functional tests included forelimb and hindlimb grip strength, footsplay and a series of quantified observations of behaviour and motor activity. In addition, a histopathological examination was conducted on nervous system and skeletal muscle tissue specimens from 6 animals/sex from the control and high-dose groups that underwent whole body perfusion fixation at sacrifice. There were no substance-related microscopic observations or changes in the functional test parameters.

In conclusion, this study determined an overall NOAEL equal to 150 mg/kg/day, based on body weight, body weight gain, food consumption and food efficiency in both sexes and on kidney lesions in males. There was no indication of immunotoxicity or neurotoxicity in animals treated with up to 600 mg/kg/day for 4 and 13 weeks respectively.

Special studies

A number of feeding studies have investigated the effects of glycolic acid on the kidneys and the metabolism of lipids.

In male rats fed diets with 2-3% glycolic acid (approximately 200-300 mg/kg/day) for 3-6 weeks there was a significant increase in kidney weight and in kidney content and urinary excretion of oxalic acid, with deposition of calcium oxalate calculi in the renal tubules, pelvis and papilla, the ureters, and urinary bladder (Chow et al., 1975, 1978; Richardson, 1965, 1967). Rabbits and dogs

were considerably less sensitive to the nephrotoxic effects of the chemical (DuPont, 1940; Silbergeld, 1960).

In mice and rats fed diets with 1.3-3% glycolic acid (approximately 130-450 mg/kg/day) for 6-30 days there were significant changes in lipid metabolism in the liver and kidneys (Crane et al., 1980; Saravanan et al., 1995; Subha & Varalakshmi, 1993; Sumathi et al., 1993). The changes included increased catabolism of triglycerides, neutral lipids and phospholipids, increased levels of total and esterified cholesterol and increased lipid peroxidation. Glycolic acid also decreased the activity of the enzymes catalase, superoxide dismutase and gluthathione peroxidase and the content of reduced glutathione, total thiols and ascorbic acid. In addition, glycolic acid has been shown to stimulate the metabolism of ethanol in isolated rat hepatocytes as well as in intact rats (Harris et al., 1982; Oshino et al., 1975).

These metabolic effects may be related to the induction of peroxisomal enzymes and/or the generation of hydrogen peroxide from the oxidation of glycolic acid to glyoxylic acid by glycolic acid oxidase. Hydrogen peroxide can induce peroxidation of unsaturated fatty acids and is a co-substrate for catalase, which is one of three enzymes that catalyse the oxidation of ethanol to acetaldehyde.

10.4.2 Inhalation toxicity

Groups of 10 male Sprague-Dawley rats were exposed to nasal inhalation of aerosolised 70% technical grade glycolic acid at levels providing exposures equal to 0, 160, 510 and 1400 mg/m^3 glycolic acid for 6 h per day, 5 days per week for 2 weeks, with a 2-week recovery period for 3-5 animals per group (DuPont, 1983).

The highest level exposures were terminated after the 8th exposure. In the highest dose group, 7 rats were sacrificed *in extremis* 0-12 days after the 8th exposure. In the middle dose group, one animal died 13 days after the 10th exposure. In the 510 and 1400 mg/m^3 groups, findings included significant weight loss; decreased absolute liver, spleen, kidney and thymus weights; and dose-related clinical signs such as laboured breathing, noisy breathing, ruffled and discoloured fur, red and clear nasal and ocular discharges and general weakness. At 510 mg/m^3, urine volume was decreased and serum AST activity was increased. Serum protein, urine volume and pH were decreased and serum ALT and AST increased at 1400 mg/m^3. All of these clinical chemistry measurements reverted to normal at the end of the recovery period. At the end of the exposure period, the only gross pathological abnormality was a distended gastrointestinal tract and small spleen and thymus in the highest dose group. Microscopically, a very mild, diffuse liver cell degeneration was found in all dose groups. Atrophy and degeneration of the thymus were noted in the intermediate and high dose animals.

The only effect seen at 160 mg/m^3 was a very mild, diffuse hepatocellular degeneration in 1/10 animals by the end of the 2-week recovery period. Based on the steepness of the dose-response curve (disappearance of mortality, weight loss and clinical signs with concentration), 160 mg/m^3 was considered practically a no-effect level (DuPont, 1983). In a subsequent publication, this concentration was described as approaching and being essentially a NOAEL for exposure through inhalation (Kennedy & Burgess, 1997).

10.5 Developmental and reproductive toxicity

10.5.1 Developmental toxicity studies

The developmental toxicity of glycolic acid has been investigated in rats in two standard studies conducted by DuPont (1995a*, 1996*) and two special studies aimed at elucidating the mechanisms of the developmental toxicity of ethylene glycol conducted by researchers at Dow Chemical Company (Carney et al., 1996, 1997, 1999). All studies were conducted in compliance with GLP. In this section, structural abnormalities in the foetuses are described as malformations or variations in accordance with the terminology used in the source documents.

The DuPont studies

The DuPont studies comprised a pilot and a main study. In both studies the test substance was given to groups of pregnant Sprague-Dawley rats by gavage from day 7 to day 21 of gestation and the foetuses were examined on day 22.

In the pilot study, glycolic acid (70% technical solution) was administered to 5 groups of 8 pregnant rats at dose levels of 0, 125, 250, 500, or 1000 mg/kg/day. Chemical analysis of the gavage solutions showed these doses to be equivalent to 0, 77, 157, 332, and 697 mg/kg/day of the 100% chemical.

At 1000 mg/kg/day there was evidence of maternal toxicity, specifically lung noise, abnormal gait, stained and wet fur and increased salivation. Lung noise was also heard in two rats at the 500 mg/kg/day dose and there was also wet fur. In both groups maternal body weight decreased during the first few days (days 7-9) while in the other groups and controls there was increased weight. Final maternal body weight minus the weight of the products of conception was also decreased in the 1000 and 500 mg/kg/day groups. There were no remarkable post-mortem or clinical chemistry findings in any of the dams.

There was a significantly increased incidence of resorptions at 1000 mg/kg/day (1.5%) compared to controls (0.4%). At 1000 and 500 mg/kg/day mean foetal weight was significantly decreased by 18% and 9% respectively. At the 1000 mg/kg/day dose there were 6 litters containing 74 foetuses. Three of the foetuses had major malformations (1 septal defect (1.4%) and 2 cases of gastroschisis (2.7%)) and 4 (5.4%) had hydrocephaly. Twenty-two foetuses had skeletal malformations, mainly fused ribs and fused or hemi-vertebrae. At 500 mg/kg/day there were 69 foetuses from 5 litters. Only one foetus (1.4%) had hydrocephaly. The incidence of retarded ossification was significantly higher at 1000 and 500 mg/kg/day than in the controls (64% and 77% compared to 53%). At 250 and 125 mg/kg/day there were 87 and 122 foetuses respectively but no malformations and the incidence of retarded ossification was lower than in the controls. In the controls there were 102 foetuses, 5 of which had skeletal malformations similar to those seen at 1000 mg/kg/day. The study report did not provide historical control data for the DuPont laboratory. However, a collection of historical control data for the same strain (Sprague-Dawley CRL) obtained from a number of laboratories gives the incidence of septal defects, gastroschisis and hydrocephaly as 0.016, 0.01 and 0.02% respectively (Hood, 1997).

Overall, the pilot study showed that at 1000 mg/kg/day glycolic acid (70% technical solution) caused a significantly increased incidence of embryonic death, foetal growth retardation and congenital malformations. At 500 mg/kg/day

glycolic acid (70% technical solution) there was a significant reduction of mean foetal weight and a significant increase of retarded sternebral ossification, that is, signs of foetotoxicity but no teratogenic effects. As there was evidence of maternal toxicity at both these dose levels, the authors concluded that the maternal and developmental NOAEL was 250 mg/kg/day (70% technical solution) and that technical grade glycolic acid is unlikely to be uniquely toxic to the rat conceptus.

In the main study, groups of 25 pregnant rats were dosed with cosmetic grade glycolic acid (99.6%) at dose levels of 0, 75, 150, 300 or 600 mg/kg/day.

At 600 mg/kg/day, there was evidence of maternal toxicity with loss of maternal weight over the first few days of dosing and decreased food intake. Some of the high dose animals showed clinical signs of toxicity including lung noise, abnormal gait and irregular respiration. In the 300 mg/kg/day group 2 rats had noisy breathing. There were no remarkable post-mortem findings in any of the dams.

Mean foetal weight was significantly decreased at 600 mg/kg/day (by 13%) and the incidence of total malformations was significantly increased (10.6%) compared to controls (0.8%). There were 9 major malformations (heart septal defects (3), microphthalmia (1), absent kidney (1), cleft palate (1), gastroschisis (2) and omphalocoele(1)) in 352 high dose foetuses compared to 2 cases of septal defects in 366 control foetuses. There were also 5 foetuses (all from one litter) with distended brain ventricles and 3 foetuses with clubbed legs. Twenty-two of 351 foetuses examined had skeletal malformations mainly affecting the sternebrae and vertebrae. At the 300 mg/kg/day dose there was marginal evidence of an increase in the skeletal malformations of fused ribs and fused vertebrae. In the remaining treatment groups, the incidence of malformations was similar to the controls. The incidence of foetuses with retarded skeletal development was 31.5% in the controls, 41.8% at 75 mg/kg/day, 32.1% at 150 mg/kg/day, 42.0% at 300 mg/kg/day and 67.9% at 600 mg/kg/day. The study report did not provide historical control data for the DuPont laboratory. However, a collection of historical control data for the same strain (Sprague-Dawley CRL) obtained from a number of laboratories gives the incidence of septal defects, microphthalmia, absent kidney, gastroschisis and omphalocoele as 0.016, 0.027, 0.003, 0.01 and 0.01% respectively (Hood, 1997).

The main study indicated that at maternally toxic doses (600 mg/kg/day) glycolic acid caused an increased incidence of foetal growth retardation and skeletal malformations, mainly affecting the sternebrae and vertebrae. The dose of 300 mg/kg/day was not associated with foetal growth retardation or major soft tissue malformations, but there was a marginal ($p = 0.0555$) increase in the incidence of two skeletal malformations and marginal ($p = 0.0553$) evidence of maternal toxicity. The authors concluded that both the maternal and the developmental NOAEL was 150 mg/kg/day and that glycolic acid is unlikely to be uniquely toxic to the rat conceptus.

In a subsequent publication of key findings from the DuPont studies, the investigators stated that while this was a conservative interpretation, they believed that the marginally significant maternal and foetal effects observed at 300 mg/kg/day represented the bottom of the dose-response curve for the following reasons: (1) Noisy breathing or wheezing as a maternal observation is

rarely, if ever, seen in control group animals and was consistent with effects seen at 600 mg/kg/day; (2) lung noise/wheezing was statistically significantly increased at 500 mg/kg/day 70% solution and higher in the pilot study; (3) the skeletal malformations observed were consistent with malformations observed at 600 mg/kg/day; (4) skeletal effects were also observed at 500 mg/kg/day 70% solution and above in the pilot study (Munley et al., 1999).

Others have argued that the fused ribs and fused vertebrae observed in the 300 mg/kg/day dosage group in the main study were spontaneous in origin and unrelated to exposure to glycolic acid as the litter and foetal incidences were not significant and the pattern of effect was not dose-dependent (Christian, 1999).

For the purposes of this assessment, a NOAEL of 150 mg/kg/day is taken forward for assessment of the significance of risk to human health of exposure to glycolic acid.

The Dow studies

Ethylene glycol, which is metabolised to glycolic acid, is known to induce skeletal malformations when given orally in high doses to pregnant rats and mice (Carney, 1994).

Carney et al. (1996) used a Sprague-Dawley derived rat gestation day 10.5 whole embryo culture system to discriminate between the developmental effects of ethylene glycol, the metabolite glycolic acid acting indirectly via an acidic pH and a direct chemical toxicity of the glycolate anion. In one experiment, groups of 10 embryos were incubated at 37°C for 46 h in media containing 0.5, 2.5, 12.5, 25.0, or 50.0 mM ethylene glycol or glycolic acid (corresponding to 38-3800 mg/L glycolic acid) or 1.0 mM sodium valproate as a positive control. In another experiment, groups of 12 embryos were cultured under similar conditions in control media adjusted to pH 6.74 or 7.41, medium containing 12.5 mM (950 mg/L) glycolic acid at pH 6.74, or medium containing 12.5 mM sodium glycolate at pH 7.41. At the end of the incubation period, embryos were evaluated for viability, morphology (using an investigator-blind system), growth (by measurement of the visceral yolk sac diameter, crown-rump length and head length) and protein content in the body and visceral yolk sac.

In the first experiment, ethylene glycol at all concentrations and glycolic acid at 0.5 mM and 2.5 mM appeared to be without effect. Half the embryos in the 25 mM and all embryos in the 50 mM glycolic acid group were non-viable. In the 12.5 mM and 25 mM glycolic acid groups, somite number, crown-rump length, head length and embryo and visceral yolk sac protein content were significantly reduced in a concentration-dependent manner. Furthermore, the percentage of structurally abnormal embryos was significantly increased, with the most commonly observed alterations being a bilateral, cyst-like enlargement of the maxillary process and various abnormalities in the mid-facial region. In the second experiment, somite number, crown-rump length, head length and embryo and visceral yolk sac protein content were significantly reduced in the glycolic acid and sodium glycolate groups compared with the pH 7.41 controls. Head length and embryo and visceral yolk sac protein content were significantly reduced in the pH 6.74 control group compared with the pH 7.41 controls. The incidence and type of structural abnormalities in all groups are shown in Table 10.4.

Table 10.4: Summary of structural abnormalities in rat embryos exposed to glycolic acid or sodium glycolate *in vitro* (from Carney et al., 1996)

Treatment group	No. abnormal/ no. evaluated (%)	% of embryos with abnormality of[1]		
		Cranio-facial region	Yolk sac	Other
Control, pH 7.41	0/12 (0%)	0	0	0
Glycolic acid, 12.5 mM, pH 6.74	8/12 (67%)*	50	33	25
Sodium glycolate, 12.5 mM, pH 7.42	7/12 (58%)*	58	8	0
Control, pH 6.74	1/12 (8%)	8	0	0

[1] Some embryos had multiple abnormalities
* Statistically different from the pH 7.41 control group ($p < 0.05$)

The authors concluded that glycolic acid is the primary toxicant for ethylene glycol-induced developmental toxicity in rats and that the glycolic acid metabolite can act through an inherent toxicity of the glycolate anion as well as via induction of metabolic acidosis.

In pregnant Sprague-Dawley derived rats, single oral doses of 2500 mg/kg ethylene glycol or 650 mg/kg glycolic acid administered by gavage or 833 mg/kg sodium glycolate (pH 7.4) injected subcutaneously were shown to produce similar peak serum glycolate levels (8.4-8.8 mM, corresponding to approximately 650 mg/L glycolic acid) (Carney et al., 1997, 1999). Also, both ethylene glycol and glycolic acid induced a clear, but mild, metabolic acidosis. These treatments, or distilled water by gavage, were then given to 4 groups of 25 time-mated rats from day 6 to day 15 of gestation and the foetuses were examined on day 21.

In the glycolic acid group there was clear evidence of maternal toxicity. Several dams developed mouth breathing, noisy or deep respiration, facial soiling, salivation and/or nasal discharge and 3 of them were sacrificed because of their respiratory difficulties. A fourth dam was found dead on day 8 with no prior clinical symptoms observed. At necropsy, these dams had mucoid exudate in the nasal turbinates, blood-soiled face and nose regions, distended stomachs, congestion of the liver, lungs and kidneys and dilated renal pelvis, indicating that their respiratory problems might have been due to nasal reflux of small amounts of glycolic acid as a complication of oral gavage dosing. Maternal body weight gain was depressed compared with controls and relative kidney and absolute and relative liver weights were increased.

In the sodium glycolate-treated dams there was little evidence of maternal toxicity. There was no mortality, no treatment-related clinical symptoms, and maternal bodyweight gain and organ weights were not affected, except for an increase in absolute and relative liver weights.

In the glycolic acid group mean foetal body weight was significantly decreased (17%) compared to controls and the resorption rate was slightly increased (5.7%) compared to controls (2.5%) although within the historical range (3.5-14.1%). There were 264 foetuses of which 137 underwent visceral examination. There was a small number of major malformations including umbilical hernia (1), abnormal limb rotation (1), absent tail (1), diaphragmatic hernia (1) and hydroureter (1). Seven foetuses from 4 litters had dilated brain ventricles. In 128

foetuses examined for skeletal malformations, there were 30 foetuses with hemivertebrae, 16 with fused ribs and 30 with missing ribs and many of the foetuses had evidence of delayed ossification. Overall, there was a significant increase in the incidence of total malformations (23.5%) compared to controls (0.3%).

In the sodium glycolate group mean foetal body weight was significantly decreased (8%) compared to controls and the resorption rate was slightly increased (4.3%) compared to controls (2.5%) although within the historical range (3.5-14.1%). There were 314 foetuses of which 163 underwent visceral examination. There was a small number of external malformations including absent tail (1) and rudimentary tail (3), but no cases of dilated brain ventricles. In 151 foetuses examined for skeletal alterations, there was 1 foetus with hemivertebrae, none with fused ribs, 20 with wavy ribs, 1 with missing and 4 with calloused ribs and many of the foetuses had evidence of delayed ossification. Overall, there was a small, but significant increase in the incidence of total malformations (3.8% versus 0.3% in controls), whereas the incidence of delayed ossification of the skull, vertebrae and ribs and irregular pattern of ossification of the sternebrae was markedly increased (23.8, 92.7, 39.7 and 5.3% respectively) compared to controls (8.6, 32.2, 2.0 and 0.7% respectively).

According to the authors, these findings clearly showed that some of the well-known developmental effects of ethylene glycol can be induced by the glycolate anion in the absence of maternal metabolic acidosis. However, as the incidence and severity of skeletal abnormalities were considerably greater in the glycolic acid than in the sodium glycolate group, they concluded that metabolic acidosis is a major contributing factor in the developmental toxicity of large oral doses of ethylene glycol.

10.5.2 Reproductive toxicity studies

The subchronic oral toxicity study in rats described in section 10.4.1 included a subset of 10 animals/sex/dose level given 0, 150, 300 or 600 mg/kg/day of glycolic acid for 18-22 weeks (DuPont, 1999a*). These animals were mated on or after day 97. Pups in each litter were counted and weighed as soon as possible after delivery and on days 7, 14 and 21, when they were sacrificed and underwent gross pathological evaluation. Parental rats were sacrificed on day 131 (males) or on days 142 through 153 (females) and subjected to gross pathological examination. The testes of each male rat were weighed and the uteri of female rats examined for the presence and number of implantation sites.

There were no dose-related differences in mating, fecundity, or gestation indices, implantation efficiency, or gestation length in rats at any dose level compared to controls. In the males, an increase in the relative testis weight was observed in all dose groups, but attributed to the decrease in body weight at all dose levels. Four high-dose males had gross and microscopic kidney lesions.

Compared to controls, the number of pups born per litter was 106% at 150 mg/kg/day, 92% at 300 mg/kg/day and 88% at 600 mg/kg/day, resulting in a statistically significant trend being assigned to the 300 and 600 mg/kg/day groups. The mean pup weight was not adversely affected at any time during lactation. There were no dose-related differences in the incidences of any clinical signs among the litters or in mortality or gross observations in the pups.

As such, there was no indication of impaired fertility or of retarded neonatal growth during lactation in animals treated with up to 600 mg/kg/day of glycolic acid for 18-22 weeks.

10.6 Genetic toxicity

10.6.1 *In vitro*

Gene mutation assays

At concentrations varying from 1-10,000 μg per plate, glycolic acid was not mutagenic in *Salmonella typhimurium* strains TA97a, TA98, TA100, TA1535, TA1537 and TA 1538 or in *Escherichia coli* strain WP2 *uvrA* (pKM101) with and without metabolic activation (DuPont, 1998b*; Hoechst, 1993*; Microbiological Associates, 1994b*).

Technical grade glycolic acid was tested for induction of forward mutation at the TK locus of L5178Y mouse lymphoma cells (Covance, 1998*). There were no increases in mutant frequency at or below concentrations of 10mM (760 mg/L), whereas concentrations from 32.9-65.8 mM (2500-5000 mg/L) produced increases in mutant frequency in the presence of metabolic activation.

Assay for chromosomal aberration

When tested in Chinese hamster ovary cells at concentrations ranging from 625-5000 mg/L at pH 6.5, toxicity (mitotic inhibition) at the highest concentration level was <10% with and 43% without metabolic activation (Microbiological Associates, 1994a*). The percentage of cells with chromosomal aberrations in the test groups, both with and without metabolic activation, was not statistically increased compared to the solvent control. Clastogenic responses to mitomycin C and cyclophosphamide confirmed the sensitivity of the assay.

10.6.2 *In vivo*

Bone marrow micronucleus test

Groups of Crl:CD-1 (ICR) BR mice were given glycolic acid (70% technical grade diluted in water) by gavage at dose levels of 0, 210, 420, or 840 mg/kg (males), or 0, 280, 560, or 1120 mg/kg (females) (DuPont, 1998d*). Bone marrow smears were prepared from 5 mice/sex from the control and all treatment groups 24 h post-dosing and from the control and high-dose treatment groups 48 h post-dosing. Two thousand polychromatic erythrocytes per animal were evaluated for micronuclei. There were no statistically significant increases in micronucleated polychromatic erythrocytes in any of the exposed groups at either time point.

Five/15 males and 3/13 females from the highest dose groups were found dead 1-2 days post-dosing. Treatment-related clinical signs included lethargy, moribundity and/or abnormal gait and persisted for up to 2 days post-dosing. At the 48-h time point, there was an 18-25% reduction in the proportion of polychromatic erythrocytes per 1000 erythrocytes in smears from high-dose males and females respectively. Although the differences were not statistically

significant, the authors concluded that the finding might be indicative of bone marrow toxicity.

10.7 Carcinogenicity

No carcinogenicity studies with glycolic acid were available for assessment.

10.8 Other test systems

Bruschi & Bull (1993) assessed the cytotoxicity of glycolic acid by measuring the proportion of total lactate dehydrogenase activity released into the medium from isolated hepatocytes exposed to the chemical. When added to cultured hepatocytes from B6C3F1 mice or Sprague-Dawley rats in a pH 7.4 solution, glycolic acid had no effect at a concentration of 1.0 mM (76 mg/L) but produced significant release of the enzyme at 5.0 mM (380 mg/L). Glycolic acid also produced a dose-related depletion of intracellular reduced glutathione. In hepatocytes from animals pre-treated with clofibrate to induce peroxisome proliferation, there was a significant increase in cytotoxicity, which was paralleled by an increased depletion of reduced glutathione and a dose-dependent increase in intracellular formation of oxidised glutathione. As the conversion of reduced glutathione to oxidised glutathione requires hydrogen peroxide, these findings indicate that the cytotoxicity of glycolic acid to isolated liver cells is associated with the production of hydrogen peroxide that occurs concomitantly with its oxidation (see section 9.3). It has subsequently been demonstrated that clofibrate-induced peroxisome proliferation stimulates the oxidation of glycolic acid to oxalic acid and the urinary excretion of oxalate in rats *in vivo* (Sharma & Schwille, 1997).

10.9 Special skin investigations

10.9.1 Effects on the epidermis

Hood et al. (1996, 1999) studied the effect of two oil-in-water emulsions containing 5% or 10% glycolic acid at pH 3.0 on stratum corneum turnover time, epidermal thickness and percutaneous absorption of water, hydroquinone and musk xylol in hairless guinea pigs.

The emulsions, or a commercial moisturising lotion, were applied to the backs of 3 groups of 2-3 animals once daily 6 days per week. After 2 weeks, the stratum corneum was labelled with fluorescent dansyl chloride by a standard technique (Jansen et al., 1974). The clearance of the fluorescence was examined daily under UV illumination and treatment continued until all fluorescence had disappeared. Stratum corneum turnover time was defined as the time in days between staining and fluorescence disappearance. Compared to the vaseline-treated controls, stratum corneum turnover time was reduced by 36% and 39% in the animals exposed to 5% and 10% glycolic acid respectively.

In a subsequent study, 3 mg/cm^2 of the 5% emulsion, 10% emulsion, or moisturising lotion was applied to the backs of 3 groups of animals once daily 6 days per week for 3 weeks, with a 4th group of animals used as untreated controls. At the end of the treatment period, the skin was examined visually and skin specimens collected for microscopic examination and *in vitro* determination of percutaneous absorption of ^{3}H-labelled water or ^{14}C-labelled hydroquinone or

musk xylol. Compared with the control lotion and untreated skin, both glycolic acid emulsions produced some erythema and/or flaking of the skin as well as a 4-fold increase in viable epidermal thickness and a 2-fold increase in the number of epidermal cell layers. No significant differences in the absorption of any of the test compounds were found for skin treated with the glycolic acid formulations or the moisturising lotion.

In a small number of SKH-hairless-1 (albino) female mice treated once daily 5 days a week for 6 months with a 30% solution of glycolic acid in water (pH not specified), microscopic examination of the exposed skin revealed marked cellular atypia and intercellular oedema of the epidermis, with a dense lymphocytic infiltrate in the dermis accompanied by an increased amount of fine, curled elastic fibres (Kligman & Kligman, 1998).

10.9.2 Effects on the skin barrier

Two experimental oil-in-water emulsions containing 5% glycolic acid at pH 3 or 7 and two commercial products containing 5% or 10% glycolic acid at pH 2.5 and 3.5 respectively were compared for their effects on the barrier properties of hairless guinea pig skin (FDA, 1996). Steady-state ^{3}H-water absorption through the skin was measured *in vitro* following 24-h *in vivo* exposure to the test substances and the permeability constant was calculated. The average permeability constant for all formulations was determined at 7.5 x 10^{-4} cm/h, which was significantly higher that the permeability constant of 4.6 x 10^{-4} cm/h in untreated controls.

10.9.3 Effects on the dermis

Solutions of 50% and 70% glycolic acid at their natural pH (and other peeling agents) were applied to separate sites of the shaved back skin of 2 mini pigs after the skin had been cleansed by scrubbing it for 15 min with acetone-soaked cotton swabs (Moy et al., 1996b). The quantity applied is not reported and there was no negative (vehicle) control. Skin biopsies were taken from each site at 8 h, 7 days and 21 days after application and examined microscopically. At 8 h, there was some epidermolysis (small blebs in the epidermis) at both glycolic acid sites. In addition, there was sloughing of the epidermis at the 50% site and epidermal and dermal necrosis and a slight inflammatory infiltrate at the 70% site. At 7 and 21 days, both sites showed thickening of the granular layer of the epidermis, markedly thickened collagen fibres in the upper dermis and a slight inflammatory infiltrate. Compared with other peeling agents included in the test (phenol and trichloroacetic acid), 70% glycolic acid was reported to have induced a comparable amount of collagen deposition with less inflammation of the skin.

Twelve hairless mice (Hr+/kud) were treated twice daily for 14 days on the back area with 200 µL of a solution of 10% glycolic acid (pH 3.9), 10% lactic acid (pH 6.0), or a vehicle control (Kim et al., 1998). Twenty-four hours after the final application, skin specimens were taken for microscopic examination and RNA extraction. Microscopically, the glycolic and lactic acid sites had a thinner epidermis and a thicker dermis and appeared to contain more collagen than the control sites. RNA analysis revealed 2 pro α-1 (I) collagen mRNA transcripts, which appeared to be expressed at a higher level in skin from glycolic acid sites compared with the lactic acid and vehicle control sites. No statistical analysis was reported.

Three studies were conducted in SKH-hairless-1 (albino) mice which were irradiated thrice weekly for 10 weeks with UV light to photoage the skin and then treated with various glycolic acid formulations. A commercial glycolic acid lotion (10%, pH 3.8) applied once daily 5 days a week for 10 weeks did not induce any statistically significant deposition of new subepidermal collagen or type III procollagen and did not increase skin content of soluble or insoluble hydroxyproline (Kligman et al., 1996). Treatment with a 15% glycolic acid oil-in-water emulsion (pH not specified) once daily for 10 weeks resulted in a significant increase of about 60% in the thickness of the upper dermis and in collagen synthesis as measured by incubating homogenised skin specimens with ^{3}H-proline *in vitro* (Moon et al., 1999). Five fortnightly treatments with a highly acidic solution containing 50% or 70% glycolic acid produced concentration-related epidermal thickening and moderate inflammation of the dermis characterised by moderate to severe fibrosis and the presence of dense mats of fine elastic fibres (Kligman et al., 1999).

10.10 Summary of toxicological data

Table 10.5 summarises the results of all assessed studies.

Table 10.5: Summary of toxicological data

Type of study	Route	Test species and system	Effects and effect levels	Section
Acute toxicity				
Lethality	Oral	Mouse (f)	ALD = 1120 mg/kg GA	10.1.2
		Mouse (m)	ALD = 840 mg/kg GA	
		Rat	LD_{50} = 1357 mg/kg GA	
		Guinea pig	LD_{50} = 1920 mg/kg GA	
		Cat	ALD = 500 mg/kg NaG	
	Inhalation	Rat (f)	$LC_{50\ (4hr)}$ > 3640 mg/m^3 GA	10.1.3
		Rat (m)	$LC_{50\ (4hr)}$ = 2520 mg/m^3 GA	
	Intra-peritoneal	Mouse	LD_{50} = 2000 mg/kg NaG	10.1.2
	Intra-venous	Cat	ALD = 1000 mg/kg NaG	10.1.4
Irritation	Skin	Rabbit	Corrosive (70% GA)	10.2.1
		Mini pig	Corrosive (70% GA)	
	Eye	Rabbit	Corrosive (57% GA)	10.2.2
Sensitisation	Skin	Guinea pig	Negative	10.3
Repeated dose toxicity				
Subacute	Inhalation	Rat (m)	NOAEL = 160 mg/m^3 GA	10.4.2
Subchronic	Oral	Rat	NOAEL = 150 mg/kg/day GA	10.4.1
Reproductive effects				
Development	Oral	Rat	NOAEL = 150 mg/kg/day GA	10.5.1
	In vitro	Rat embryo	NOAEL = 190 mg/L GA	10.5.1
Fertility	Oral	Rat	NOAEL = 600 mg/kg/day GA	10.5.2
Lactation	Oral	Rat	NOAEL = 600 mg/kg/day GA	10.5.2
Genetic toxicity				
Gene mutation	*In vitro*	*S. typhi-murium*	Negative	10.6.1
		E. coli	Negative	
		Mouse lymphoma cells	Negative	
Chromosomal aberration	*In vitro*	Chinese hamster ovary cells	Negative	10.6.1
Bone marrow micronucleus test	Oral	Rat	Negative	10.6.2

ALD = approximate lethal dose
f = females only
GA = glycolic acid
LC_{50} = median lethal concentration
LD_{50} = median lethal dose
m = males only
NaG = sodium glycolate
NOAEL = no observed effect level

11. Human Health Effects

The commercial success of glycolic acid as a cosmetic ingredient has stimulated much research into the effects of the chemical on human skin. This section contains a critical review of all human studies that provide meaningful data on the nature, incidence and/or causes of adverse health effects of glycolic acid. It is beyond the scope of this assessment to review data on the desired effects of the chemical. In consequence, use studies that exclusively address the cosmetic or therapeutic efficacy of glycolic acid have not been considered, but are listed in Appendix 3 for easy reference. The citation or listing of a use study in this report does not constitute an endorsement of its quality or results. Indeed, very few of them are well-controlled trials conducted in accordance with Good Clinical Practices and published in peer-reviewed scientific journals.

The available data on human health effects resulting from systemic exposure to glycolic acid are limited to two studies conducted some 60 years ago. However, clinical observations from cases of ethylene glycol poisoning provide well-documented information on the potential toxic effects of glycolic acid in humans.

11.1 Systemic effects

11.1.1 From oral administration

For 4-5 consecutive days, 190-450 mg/kg/day of glycolic acid was added to the diet of 4 patients with progressive muscular dystrophy in whom the ingestion of glycine was followed by a definite increase in the urinary excretion of creatinine (Milhorat & Toscani, 1936). The treatment induced a modest increase in the output of creatinine, indicating that only a small fraction of glycolic acid was converted to glycine (see section 9.3). When measured in 2 of the patients, glycolic acid had no effect on urinary output of oxalic acid. There was no record of other effects of the exposure.

In a study aimed at determining the safety of a baking powder containing partially polymerised glycolic acid, 10 healthy volunteers ingested an average dose equivalent to 38 mg/kg/day of the chemical for 12 (2 females and 3 males) or 36 weeks (3 females and 2 males) (DuPont, 1940). Physical examinations were done pre-treatment and at 12 and 36 weeks; fasting urine and blood samples were collected at regular intervals. No treatment-related signs were observed. There were no significant changes in urine albumin, sugar, occult blood, casts, epithelial cells, red or white blood cells, or pH, and no excessive excretion of oxalate crystals. Blood counts and haemoglobin levels were normal throughout, and plasma carbon dioxide combining power (which is diminished in metabolic acidosis) stayed within the normal range.

11.1.2 From ethylene glycol intoxication

The systemic toxic effects of ethylene glycol poisoning include cardiopulmonary and renal effects that correlate directly with blood levels of glycolic acid (Brent et al., 1999; Davis et al., 1997; Jacobsen & McMartin, 1986; Keyes, 1998). The cardiopulmonary effects include increased heart rate and ventilation and may

progress to cyanosis and coma caused by pulmonary oedema and congestive heart failure attributed to metabolic acidosis and hypocalcaemia induced by glycolic acid and its metabolites. At plasma glycolate levels exceeding approximately 10 mM (760 mg/L), kidney failure ensues. Urine production decreases and the urine is of low specific gravity and contains protein, blood cells, and cylinders and/or calcium oxalate crystals. Blood urea nitrogen and creatinine are increased and kidney biopsies show cortical necrosis, diffuse oedema, dilated proximal tubules, degeneration of tubular epithelium, and intra-tubular casts. These effects may occur in the absence of calcium oxalate precipitation and it therefore appears that glycolic acid itself, or its metabolic products other than calcium oxalate, may have a direct toxic action on the kidneys. In most cases, the kidney lesions are reversible, but full recovery may take 45 days or longer.

11.2 Skin effects

11.2.1 Stinging tests

Cosmetic products may elicit subjective sensations of stinging, burning or tingling shortly after their application, particularly to the face, as a result of a direct stimulation of sensory nerves in the skin. The stinging response is transient, not associated with visible alterations of the skin and is not predictive of a positive irritation test to the same chemical (Frosch, 1992).

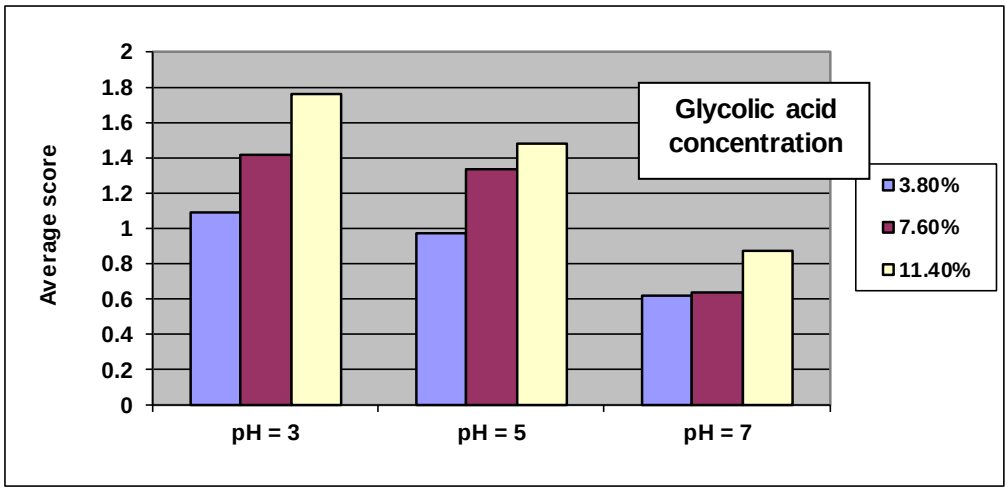
The standard test for stinging is performed on a panel of 10-20 'stingers', that is, healthy subjects who consistently experience acute discomfort from a 5-10% aqueous solution of lactic acid. With a cotton wool bud, a small amount of test substance is applied to one nasolabial fold and distilled water to the other. The panellists then record any sensory effects on a 3-point self-rating scale every 1-2½ min for 5-15 min after the application. A product is classified as non-stinging, or mildly, moderately, or severely stinging if the average score is <0.4, 0.4-1.0, 1.1-2.0, or 2.1-3.0 respectively.

Smith (1996) examined the stinging potential of 9 formulations that employed the same vehicle (water, ethanol, ethoxydiglycol and butylene glycol) but differed in glycolic acid content and pH. As shown in Figure 11.1, although all 9 formulations were classified as mildly to moderately stinging, the stinging potential was clearly a function of the concentration and pH of the formulation[1].

In tests of 50 commercial creams and lotions containing 2-10% glycolic acid at pH 3.25-5.5, about 42% of the products were classified as mildly and 18% as moderately stinging (Consumer Product Testing Co., 1993b; CTFA, 1995b; DiNardo, 1994; Morganti et al., 1996). Although there was a tendency for the higher concentrations to cause more stinging, there were also examples of sets of creams or lotions that differed considerably in stinging potential in spite of identical concentrations of glycolic acid and similar pH values. Thus, the nature and concentration of excipients also have an impact on the likelihood that a product causes stinging.

[1] Smith used a 4-point rating scale. For purposes of comparison, the average score has been converted to correspond to the more conventional 3-point scale.

Figure 11.1: Stinging potential of a glycolic acid lotion at various concentrations and pH values (data from Smith (1996))



11.2.2 Contact irritation tests

Cumulative irritation tests

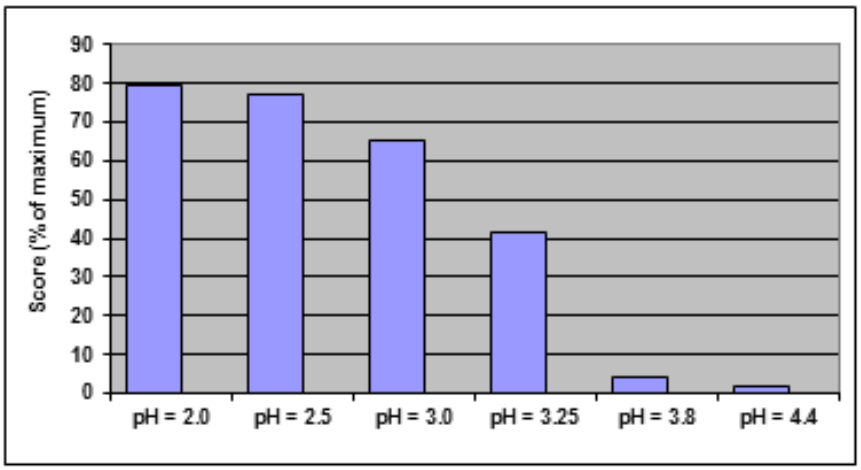
The cumulative irritation test is a common method for testing the potential of a cosmetic product to produce skin irritation (KRA, 1996). The test substance is applied to the back of 10-25 healthy subjects, under either an occluded or semi-occluded patch, and the patches are reapplied to the same site daily, usually for 14-21 consecutive days. Each site is examined visually before patch reapplication and signs of irritation are scored on a 6-point scale. Patches are occluded until a score of 1 (minimal erythema) is reached whereupon semi-occluded patches are used. When a score of 3 (definite erythema and papules) is reached, the site is no longer treated and the score of 3 is recorded for the remainder of the test. The irritation score is calculated by adding all the scores for the product over the duration of the test and comparing them to a maximum possible score if the product had produced maximum irritation (score 3) at all readings. Sodium lauryl sulphate and normal saline may be used as positive and negative controls. The overall score, expressed in % of the theoretical maximum, is usually interpreted, as follows: <8% = non-irritant/mild; 8-32% = probably mild in normal use; 33-71% = possibly mild in normal use; 72-92% = experimental cumulative irritant; >92% experimental primary irritant (Hill Top Research, 1995).

Hilltop Research (1994, 1995) conducted three separate 21-day tests on various creams and lotions containing 4% (4 products) or 8% (10 products) glycolic acid (pH not specified). All 4% products were classified as probably mild in normal use. Three 8% products were classified as probably mild and the remaining 7 as possibly mild in normal use.

In a 14-day test, in which semi-occluded patches were used throughout, the irritation score of a 10% glycolic acid formulation was shown to be inversely correlated with the pH of the formulation (Figure 11.2), whereas the scores of 3 formulations containing 10%, 15% or 20% glycolic acid at pH 3.8 were very low with little difference between them (DiNardo, 1995, 1996). Of 12 commercial creams and lotions, 5 products containing 5-10% glycolic acid at pH 2.4-3.6 were classified as probably or possibly mild in normal use, whereas 7 products

containing 8-13% glycolic acid at pH 3.8-4.4 were classified as non-irritant/mild (DiNardo, 1995). As such, the author concluded that a product's pH appears to contribute more to its cumulative irritation potential than its glycolic acid content.

Figure 11.2: Irritation potential of a 10 % glycolic acid lotion at various formulation pH values (data from DiNardo (1995, 1996))



Alfieri (1996) conducted a 14-day test on two commercial face lotions of identical glycolic acid concentration (8.4%) and similar pH (3.3 and 4.0). One was an oil-in-water suspension whereas the other used a non-phospholipid liposome delivery system. Both products were found to be possibly mild in normal use and there was little difference between them.

In the so-called mini-cumulative test, the product is applied for 4 consecutive days only. Treatment is discontinued if a reading produces a score ≥2 (definite erythema). Scoring is done 5 h after removal of the last patch. The overall score, expressed in % of the theoretical maximum, is usually interpreted, as follows: <15% = non-irritating; 15-25% = slightly irritating; 26-40% = mildly irritating; 41-75% = moderately irritating; >75% = severely irritating (CTFA, 1995e). In a mini-cumulative test in 19-20 subjects of 41 commercial creams and lotions containing 2-10% glycolic acid at pH 3.7-4.0, about 12% of the products were rated as slightly irritating, 22% as mildly irritating, 29% as moderately irritating, and 5% as severely irritating (CTFA, 1995e). There appeared to be no correlation between irritation score and glycolic acid concentration or type of formulation.

Follicular irritation chest tests

The potential of a commercial gel containing 2% or 4% glycolic acid at pH 3.9 to cause folliculitis (inflammation of the hair follicles) was tested by applying the products or a vehicle control to the chest of groups of healthy subjects once or twice daily for 7-14 days (CTFA, 1991c). Throughout the test period, the treated sites were examined visually for the presence of bumps, papules or pustules. The gel caused follicular irritation in 3/30 and 10/30 subjects treated with the 2% and 4% strength respectively. No follicular reactions were observed in 20 subjects treated with the vehicle only.

Other tests for irritation

Murad et al. (1995) investigated the histopathological effects of glycolic acid at 2 days, 2 weeks, 2 months and 19 months after a single application of a 70% aqueous solution at its natural pH (0.6) to the arm of a single healthy subject. At 2 days, there was epidermolysis, necrosis of individual epidermal cells, and oedema and a perivascular infiltrate of lymphocytes and macrophages in the dermis. At 2 weeks, the epidermis was somewhat thickened and oedema persisted in the outer layer of the dermis. At 2 months, there were patches of thickened stratum corneum and increased thickness of collagen fibres in the dermis. At 19 months, all changes had reverted back to normal.

In a similar study, solutions containing 50% glycolic acid at pH 1.0 or 70% glycolic acid at pH 0.6, 1.8, 2.25 and 2.75 were applied to different areas of the face of 2 elderly subjects with sun-damaged skin and rinsed off 30 min later (Becker et al., 1996). After 48 h, biopsies were obtained and processed for microscopic examination. In case of the 70% solution, there was partial epidermal necrosis and epidermal crusting at pH 0.6, epidermal crusting at pH 1.8, and partial loss of stratum corneum at pH 2.25 and 2.75. The site treated with the 50% solution (pH 1.0) had lost its stratum corneum, but had no crusting or epidermal necrosis. The authors concluded that the irritant effect of a glycolic acid peel is both concentration- and pH-dependent.

11.2.3 Contact sensitisation tests

The repeat insult patch test is a standard method for testing the potential of a substance to induce allergic contact dermatitis (CIR, 1998; KRA, 1996). Various protocols are used, but in general subjects are treated with 24-h, 48-h or 72-h occluded and/or semi-occluded patches containing 0.1-0.2 mL of the test formulation 2-3 days per week for a total of 5-10 applications. After a rest period of 10-14 days, subjects are challenged by re-patching on both treated and untreated sites and examined for the presence of erythema, papules and blisters at 1 and 24-48 h after removal of the challenge patches. A reaction to the challenge that exceeds the reactions during the treatment phase or spreads beyond the patch site indicates sensitisation. The so-called maximisation test is a variation in which the sensitivity is increased by pre-treatment of the test sites with the skin irritant sodium lauryl sulphate.

Repeat insult patch testing has been performed on a total of 23 products containing from 0.5-50% glycolic acid at pH values ranging from 2.2-5.5, in groups comprising from 25-198 healthy volunteers per product (AMA Laboratories, 1993a-c, 1994; Consumer Product Testing Co., 1993a; CTFA, 1995d; Essex Testing Clinic, 1994a-i; Kanengiser et al., 1994a-b; Richerche e Technologie Cosmetologiche, 1996). All results were negative, except in the case of a 1.25% solution of a glycolic acid-cyclodextrin complex at pH 2.2, which induced strong irritation in most subjects and challenge reactions suggestive of sensitisation (Richerche e Technologie Cosmetologiche, 1996).

11.2.4 Tests for phototoxicity

Phototoxicity is defined as a non-immunological, light-induced dermatitis caused by a photoactive chemical. It is determined by applying the test product to 2 skin sites under occlusion for 24 h, irradiating one treated and an untreated control site

with UV light and comparing the degree of erythema and oedema of all 3 sites at 15 min, 24 h and 48 h post-irradiation (CIR, 1998; KRA, 1996).

Three commercial products containing 0.5-4% glycolic acid at pH 3.6-4.1 were tested in separate groups of 10 healthy volunteers (Consumer Product Testing Co., 1994b; CTFA, 1994e; Harrison Research Laboratories, 1994b). No evidence of phototoxicity was observed.

11.2.5 Tests for photosensitisation

A chemical is a photosensitiser if it reacts with light to produce one or more substances that induce allergic contact dermatitis. The standard test for photosensitisation is similar to the repeat insult patch test described above. However, the test sites are irradiated with UV light immediately after patch removal during the induction as well as the challenge phase and non-irradiated treated and irradiated untreated sites are included in the test as negative controls (CIR, 1998; KRA, 1996).

Five commercial products containing 0.5-6% glycolic acid at pH 3.6-4.2 were tested in separate groups of 25-27 healthy volunteers (Consumer Product Testing Co., 1994a; CTFA, 1994d; Harrison Research Laboratories, 1994a). No evidence of photosensitising potential was observed.

11.2.6 Comedogenicity tests

Substances applied to the skin may induce the formation of comedones (blackheads). The standard test for comedogenicity involves applying the test substance and a negative control under occlusive or semi-occlusive patches to the upper back of healthy volunteers (Mills & Kligman, 1982). The patches are changed 3 times per week for 4 weeks, providing 28 days of continuous exposure. At the end of the test period, a piece of stratum corneum with follicular extensions is lifted off from each site and examined for horny cylinders under a dissecting microscope. When so tested in 6 subjects, 5 commercial cosmetics (3 creams and 2 lotions) containing from 2-10% glycolic acid at pH 3.7-3.8 showed no potential to induce blackheads (CTFA, 1995c).

11.2.7 Use studies

A total of 22 studies provided information on the incidence of treatment-emergent adverse skin events during regular use of cosmetics with glycolic acid (CTFA, 1989, 1990a-c, 1991a-b, 1991d, 1992a-d, 1993, 1994b-c; Effendy et al., 1995; Hill Top, 1996; Kopera et al., 1996; Milmark Research, 1994; Morganti et al., 1996; Thibault et al., 1998; TKL Research, 1994a-b; Wang et al., 1997). These studies had a duration of 7 days to 6 months and monitored the use of various formulations and commercial products containing 0.5-50% glycolic acid at pH 1.2-5.5 by 770 healthy subjects, 59 subjects with photoaged skin, and 40 patients with acne. As shown in Table 11.1, adverse events were recorded in 24% of the subjects, with stinging accounting for 42% and signs of skin irritation for 55% of the total. None of the use studies provided information on systemic tolerability.

Table 11.1: Incidence of adverse skin events in 869 subjects using glycolic acid containing cosmetics for 7 days to 6 months

Adverse event	Number	Per cent
Stinging	87	10.0
Itching	37	4.3
Mild skin irritation (unspecified)	35	4.0
Erythema	20	2.3
Bumps	8	0.9
Flaking/scaling	7	0.8
Follicular erosions with oedema	6	0.7
Activation of local herpes simplex infection	3	0.3
Hyperpigmentation	3	0.3
Hypopigmentation	1	0.1
Skin necrosis	1	0.1
Total	*208*	*24.0*

11.2.8 Case reports and customer complaints

Isolated cases of hyperpigmentation in dark-skinned people have been reported in the trade press (Boschert, 1994).

Altomare et al. (1997) described 3 cases of recurrent, intensely burning oedematous dermatitis of the eyelids resulting from application to the face of two different creams containing 6% or 8% glycolic acid. Patch testing with the cream was done in one case and was negative. Two of the patients agreed to a challenge test which consisted in applying the cream to one eyelid after full recovery had occurred. In both cases, the challenge resulted in an intense inflammatory response. The authors concluded that the reaction was clearly irritant.

For the purposes of the present assessment, NICNAS asked all 36 applicants and notifiers importing or manufacturing glycolic acid containing cosmetics to provide information on any adverse events reported to them. Two large consumer goods companies selling creams and lotions containing 0.5-8% glycolic acid at pH 3.5-6.6 reported customer complaint rates of 140-455 per 1 million units sold. These complaints related to adverse events varying from slight stinging, over itchiness and redness, to rashes and presumed allergic reactions. Two importers stated that a tiny percentage of customers had reported stinging, reddened or dry skin from products containing 2.5-14% glycolic acid at pH 4.4. Nine importers and manufacturers stated that they had not received any adverse event reports relating to their products, whereas the remaining importers and manufacturers did not address the question. By comparison, the average rate of adverse skin events from topical cosmetics has been estimated at 10-200 per 1 million items sold (Meynadier et al., 1994).

11.2.9 Conclusions

A substantial number of experimental and commercial glycolic acid formulations have been tested for their potential to induce stinging, contact irritation, follicular irritation, contact sensitisation, phototoxicity, photosensitisation and comedone (blackhead) formation. The tests have employed methods that are generally

recognised as reliable and have been conducted in an adequate number of subjects.

The results of these tests indicate that cosmetic products containing glycolic acid do not induce contact sensitisation, phototoxicity or photosensitisation and are non-comedogenic. However, at concentrations ≥2% they induce stinging in a dose- and pH-related manner, skin irritation to a degree that appears to depend more on pH than glycolic acid content, and dose-related follicular irritation. The frequency and severity of these effects also depend on the choice of excipients, in ways which are not well understood.

The relevance of the test results is borne out by a high incidence of stinging (10%) and signs of skin irritation (13%) in a number of use studies involving 869 subjects. These effects were also frequent causes of spontaneous consumer complaints.

11.3 Special skin investigations

A number of *in vivo* and *in vitro* studies have investigated various biological skin effects of glycolic acid in humans, including effects that have been interpreted as indicative of a potential risk that glycolic acid may increase skin sensitivity to sunlight exposure.

11.3.1 Intact skin

Skin thickness was measured with micrometer callipers in 17 subjects with photoaged skin treated with a lotion containing 25% citric, glycolic or lactic acid adjusted to pH 3.5 and a placebo lotion applied to either forearm twice daily for 4-8 months (Ditre et al., 1996). On the AHA-treated side, 2-layer skin thickness increased by 24% from 11.5 to 14.3 mm, whereas it decreased from 12.2 to 11.9 mm on the vehicle control side. The difference was statistically significant and easily discerned by comparative pinching of the forearm skin. There were no differences between the thickening induced by citric, glycolic or lactic acid.

Twice-daily application of 2 creams containing 5.7% glycolic acid (pH not specified) or one cream with 10% glycolic acid at pH 5.5 for 6-8 weeks produced significant increases in skin firmness in healthy volunteers, whereas once-daily application of a 6% cream (pH not specified) for 4 weeks did not improve skin elasticity in a group of women with photodamaged skin (Morganti et al., 1996; Piérard et al., 1996; Smith, 1996).

11.3.2 The stratum corneum

The outermost, horny layer of the skin consists of several tiers of flat cells that are filled with keratin and have no nuclei or metabolic activity. These cells are continuously sloughed off or worn away and replaced by cells from the viable epidermis beneath them. In histological preparations the stratum corneum appears to be divided into an innermost layer of compacted cells (stratum compactum) and an outermost layer of loosely connected cells with empty spaces between them (stratum disjunctum).

Thickness

Van Scott and Yu (1974) observed that ointments or solutions containing 5-10% glycolic acid or other AHAs induced a remarkable thinning of the stratum corneum in patients with a variety of skin diseases in which the stratum disjunctum is pathologically thickened.

Stratum corneum thickness was determined microscopically in biopsies from healthy subjects treated with commercial cosmetic products containing glycolic acid (CTFA, 1994a,c). Twice daily applications of an 8% cream, pH 3.9 to 10 subjects for 4 weeks or a 4% formulation, pH 3.9 to 8 subjects for 6 months were not associated with significant stratum corneum alterations when compared with vehicle or untreated control sites.

DiNardo et al. (1996) treated 20 subjects with moderately dry skin with a formulation containing 8% glycolic acid at pH 3.25, 3.8 or 4.4; 3.25%, 6.5%, 9.75% or 13% glycolic acid at pH 3.8; or a vehicle control. The thickness of the stratum corneum was measured by microscopic examination of superficial skin biopsies. The changes in stratum corneum thickness after 3 weeks of twice daily application of the test formulations are showed in Table 11.2; no data were given on their statistical significance.

Table 11.2: Stratum corneum thickness, viable epidermis thickness, collagen deposition and glycosaminoglycan content in 20 subjects with moderately severe dryness of the skin after 3 weeks twice-daily treatment with glycolic acid (GA) or vehicle control (DiNardo et al., 1996)

Test formulation		% change compared with vehicle control site			
%GA	pH	Stratum corneum thickness	Viable epidermis thickness	Collagen deposition	Glycosamino-glycan content
3.25	3.8	-44	+50	+29	+267
6.5	3.8	-55	+56	+21	+167
8.0	3.25	-22	+18	+54	+350
8.0	3.8	-32	+21	+128	+33
8.0	4.4	-25	+36	+160	+300
9.75	3.8	-22	+42	+55	+25
13.0	3.8	+23	-25	+250	+167

In a double-blind study in 41 subjects with photoaged skin, a 50% glycolic acid or placebo gel was applied to either side of the face, dorsal forearms and hands for 5 min once weekly for 4 weeks (Newman et al., 1996). Skin biopsies were taken before treatment and one week after the last application and used for microscopic measurement of skin thickness. Compared to baseline, the thickness of the stratum corneum was decreased by 53% in skin treated with glycolic acid and unchanged at the vehicle control sites. The decrease in stratum corneum thickness mainly affected the outermost layer of loosely connected cells (stratum disjunctum). No statistical analysis was reported.

Fartasch et al. (1997) looked at the morphology of skin biopsies from 4 healthy subjects treated twice daily for 4 weeks with a lotion containing 4% glycolic acid at pH 3.8 or the vehicle formulation. Using light microscopy, the horny layer of glycolic acid treated skin appeared more compact than that of vehicle treated

skin. However, when examined by electron microscopy the number of layers in the stratum corneum was similar in both groups and the only discernible difference was an acceleration of the normal degradation of desmosomal plugs (which hold the cells together) in the stratum disjunctum of subjects treated with glycolic acid.

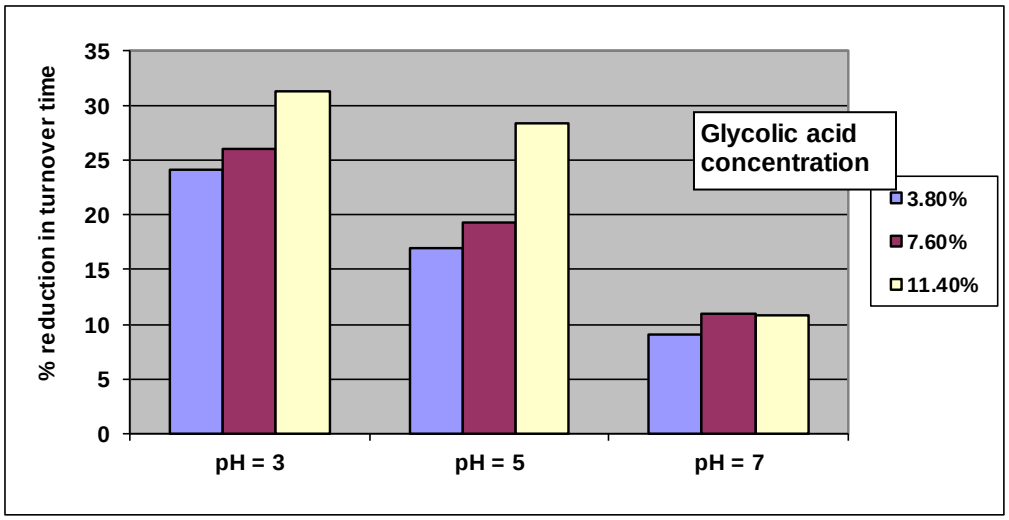
Turnover time

Effendy et al. (1995) measured stratum corneum turnover time in 6 healthy subjects using the dansyl chloride labelling technique described in section 10.9.1. The test substance was a 12% aqueous solution of glycolic acid at its natural pH (approximately 1.6) applied under occlusion for 60 min 5 days per week until the disappearance of the fluorescence. At untreated, vehicle control and glycolic acid sites, the mean turnover time was 18.3, 18.0 and 12.8 days respectively. The reduction in turnover time induced by glycolic acid was statistically significant.

Smith (1996) used the same technique to determine turnover rate in groups of at least 8 healthy subjects treated twice daily with 2 mg/cm^2 of 9 test products that employed the same vehicle, but differed in glycolic acid content and pH. The reduction in turnover time compared with an untreated control site is shown in Figure 11.3.

In a separate study, a test product containing 4% glycolic acid at pH 3, 5 or 7 decreased turnover time by 34%, 23% and 10% respectively (Smith, 1994). When a test product with 3% glycolic acid (pH not specified) was applied for 20 weeks, the decrease in turnover rate fell from 29% at the start of the treatment to 17% at 10 weeks and 10% at 20 weeks. The author concluded that the effect on turnover time diminished over time and with increasing pH of the formulation. Statistical details were not reported.

Figure 11.3: Average reduction of stratum corneum turnover time in groups of at least 8 subjects treated with a glycolic acid lotion at various concentrations and pH values (data from Smith (1996))



Hydration

The resistance of the stratum corneum to the flow of an alternating electrical current is inversely proportional to its water content. Measurement of skin capacitance is commonly used to assess the ability of cosmetic products to

hydrate or moisturise the skin. The available studies on the effect of glycolic acid on skin capacitance are summarised in Table 11.3. The data indicate that glycolic acid has a modest effect on stratum corneum hydration.

Table 11.3: The effect of glycolic acid (GA) on stratum corneum hydration as measured by electrical capacitance testing

Skin type (number of subjects)	Test product	Treatment protocol	Effect on hydration	Reference
Moderately dry (10 per group)	Lotion with 3.25-13% GA at pH 3.8-4.4	Twice daily application for 3 weeks	Increased 1.5-fold (13% GA, pH 3.8) to 3-fold (8% GA, pH 4.4) (no statistical analysis)	DiNardo et al. (1996)
Normal (6)	12% GA in water, pH 1.6	Applied under occlusion for 60 min 5 days per week for 2 weeks	Modest increase until 4th application, followed by a slight but significant decrease	Effendy et al. (1995)
Normal (3)	Lotion with 4% glycolic acid, pH 3.8	Twice daily application for 3 weeks	No change	Fartasch et al. (1997)
Normal (6)	Cream with 5.7% GA, pH not specified	Twice daily application for 6 weeks	Modest, but significant increase	Smith (1966)

11.3.3 The viable epidermis

The viable epidermis consists of several layers of nucleated, metabolically active cells which from the stratum corneum inwards include the stratum granulosum, the stratum spinosum and the stratum germinativum or basal cell layer. The latter contains a single tier of columnar cells that, on division, are pushed up into the stratum spinosum, start accumulating keratin and eventually reach the outer part of the stratum corneum in approximately 26-28 days. Including the stratum corneum, the epidermis is about 0.1 mm thick, except on the palms and soles where it is several times thicker.

Thickness

The thickness of the viable epidermis was determined microscopically in biopsies from healthy subjects treated with commercial cosmetic products containing glycolic acid (CTFA, 1994a, 1994c). Twice daily application of an 8% cream, at pH 3.9 to 10 subjects for 4 weeks or of a 4% cream at pH 3.9 to 14 subjects for 6 months was not associated with significant epidermal alterations when compared with vehicle treated or untreated control sites. When a portion of the biopsies from the 6-month study was examined by electron microscopy, no abnormalities were observed (CTFA, 1995g).

The thickness of the viable epidermis was measured by microscopic examination of biopsies from 20 subjects with moderately dry skin treated with an experimental formulation containing 8% glycolic acid at pH 3.25, 3.8 or 4.4; 3.25%, 6.5%, 9.75% or 13% glycolic acid at pH 3.8; or a vehicle control (DiNardo et al., 1996). After 3 weeks of twice daily application of the test

formulations, the viable epidermis was, on average, about 30% thicker at the treated than at the control sites (Table 11.2); statistical details were not reported.

In a double-blind study in 41 subjects with photoaged skin, a 50% glycolic acid or placebo gel was applied for 5 min once weekly for 4 weeks (Newman et al., 1996). In biopsies taken before treatment and one week after the last application, microscopic measurements showed a 19% increase in epidermal thickness compared to baseline. No statistical analysis was reported.

In 8 subjects with photoaged skin who were treated with a lotion containing 25% citric, glycolic or lactic acid adjusted to pH 3.5 and a placebo lotion twice daily for 4-8 months, the mean epidermal thickness was 62% greater in AHA-treated than in control specimens (Ditre et al., 1996). Statistically, this difference was highly significant.

None of the above studies identified any other structural effects on the epidermis.

Cell proliferation

Epidermal cell proliferation was measured in superficial skin biopsies from 6 healthy subjects treated twice daily for 24 weeks with a 4% glycolic acid emulsion, pH 3.9 and a conventional moisturiser, pH 6.6 (CTFA, 1995f). Following incubation with ^{3}H-labelled thymidine for 2 h, DNA-synthesising cells were visualised by autoradiography. The mean labelling index, that is, the percentage of DNA-synthesising cells, was 5.3 at the glycolic acid treated sites, 6.2 at the moisturiser treated sites, and 4.1 in biopsies from untreated skin areas. These indices were not statistically different. In an abstract, Bartolone et al. (1994) described an *in vitro* experiment in which glycolic and lactic acid significantly stimulated the proliferation of cultured human epidermal keratinocytes as compared to control cells. However, detailed study data were not available for assessment.

11.3.4 Skin barrier function

The skin barrier is a physiological concept that includes all the elements that enable the skin to protect the body from dehydration and restrict foreign chemicals from entering the systemic circulation. The barrier has been likened to a ‘brick wall’, with the keratin-filled, mature corneocytes being the bricks and the thin intercellular film of lipids, free fatty acids and cholesterol the mortar that fills the crevices between them (Guy, 1995). It has been calculated that the diffusion path of water across the barrier is about 0.9 mm long, whereas the stratum corneum itself is only 10-20 μm thick in most places. It is therefore conceivable that water and other small non-electrolytes do not cross the cells of the epidermis, but follow a tortuous route through the intercellular film of relatively polar lipids.

Skin barrier function is usually assessed by quantitative trans-epidermal water loss (TEWL) assays. Several studies have examined the effect of glycolic acid treatment on TEWL and are summarised in Table 11.4.

Two studies looked at the potential of repeated applications of glycolic acid formulations to modulate the increase in TEWL induced by sodium lauryl sulphate, which is known to disrupt skin barrier function.

Table 11.4: The effect of glycolic acid (GA) on skin barrier function as measured by trans-epidermal water loss (TEWL)

Skin type (number of subjects)	Test product	Treatment protocol	Effect on TEWL	Reference
Normal (11)	Cream with 8% GA, pH 4.4	Twice daily application of 2 mg/cm^2 cream for 4 weeks	No significant changes after 1, 2, 3 or 4 weeks of application	Berardesca et al. (1997)
Moderately dry (10 per group)	Lotion with 3.25-13% GA at pH 3.8-4.4	Twice daily application for 3 weeks	Slight increase (no statistical analysis)	DiNardo et al. (1996)
Normal (6)	12% GA in water, pH 1.6	Applied under occlusion for 60 min 5 days per week for 2 weeks	Significant increase which had not reverted to normal at 7 days post-treatment	Effendy et al. (1995)
Normal (3)	Lotion with 4% glycolic acid, pH 3.8	Twice daily application for 3 weeks	No significant change	Fartasch et al. (1997)
Normal (19)	Formulation containing 4% GA, pH 3.9	Twice daily application of 2 mg/cm^2 cream for 24 weeks	Slight but significant increase after 6, 12,18 and 24 weeks of application	KGL Skin Study Center (1995b)

In one study, 8 healthy subjects were treated twice daily for 4 weeks with a 4% glycolic acid formulation at pH 3.7-4.0 (CTFA, 1995a). In the other study, 2 mg/cm^2 of a cream with 8% glycolic acid, pH 4.4 was applied twice daily for 4 weeks (Berardesca, 1997). Vehicle treated and/or untreated control sites were used. At the end of the treatment period, TEWL was measured before and after application to the treated and control skin sites of an occluded patch containing sodium lauryl sulphate. In both studies, prior treatment with glycolic acid significantly reduced the barrier damage induced by sodium lauryl sulphate.

The impact of glycolic acid on the ability of the skin to keep out foreign substances was addressed in an investigation of the influence of a 10% glycolic acid lotion (pH 3.5) on the percutaneous penetration of model penetrants through human skin (Hill Top Reearch, 1996). Twenty healthy subjects were pre-treated with the test product or a vehicle control once daily 6 days a week for 15 weeks. ^{14}C-labelled model penetrants (hydrocortisone and glycerol) dissolved in acetone were then applied to separate sites on the treated skin area. One and 4 h later, sites were tape-stripped for a total of 21 times to remove the stratum corneum and the tape strips analysed for radioactivity. There were no significant differences in the amount of ^{14}C-hydrocortisone or ^{14}C-glycerol recovered from treated, vehicle control or untreated control sites, indicating that glycolic acid did not enhance absorption of the test substances.

11.3.5 The dermis

The dermis is a dense fibrous network of collagen and elastin, which serves as a supporting unit and reservoir of nutrients for the epidermis.

Thickness

Compared with vehicle control specimens, the mean thickness of the outer layer of the dermis was almost doubled in biopsies from 8 subjects with photoaged skin who were treated twice daily with a lotion containing 25% citric, glycolic or lactic acid adjusted to pH 3.5 for 4-8 months (Ditre et al., 1996).

In vitro fibroblast proliferation

Kim et al. (1998) studied the effect of glycolic acid on cultured fibroblasts obtained from circumcised neonatal foreskin. After incubation for 24 h in a medium containing glycolic acid at 0.001, 0.01 and 0.1 μM (0.076, 0.76 and 7.6 μg/L respectively), cell growth was measured using a commercially available assay kit. Glycolic acid induced a statistically significant, concentration-dependent, 1.2- to 1.4-fold increase in the number of viable cells. A similar proliferative response to glycolic acid in cultured human fibroblast was reported in abstract form by Bartolone et al. (1994).

Collagen and glycosaminoglycan synthesis *in vitro* and *in vivo*

Glycolic acid has been shown to stimulate the incorporation of ^{3}H-labelled hydroxyproline into type I collagen and to augment the synthesis of procollagen type I C-peptide in human skin fibroblasts cultured *in vitro* (Bartolone et al., 1994; Kim et al., 1998; Moy et al., 1996a).

In an *in vivo* study, DiNardo et al. (1996) estimated the dermal content of collagen and glycosaminoglycans in selectively stained histological slides prepared from biopsies from 20 subjects with moderately dry skin, who had been treated twice daily for 3 weeks with a formulation containing 8% glycolic acid at pH 3.25, 3.8 or 4.4; 3.25%, 6.5%, 9.75% or 13% glycolic acid at pH 3.8; or a vehicle control. As shown in Table 11.2, there was a slight to marked increase in both collagen and glycosaminoglycan content; statistical details were not reported. In another *in vivo* study, the dermal content of collagen and glycosaminoglycans appeared increased in biopsies from 8 subjects with photoaged skin who were treated twice daily with a lotion containing 25% citric, glycolic or lactic acid adjusted to pH 3.5 for 4-8 months (Ditre et al., 1996). By image analysis, however, the mean collagen fibre density at AHA-treated sites (53%) was not statistically different from that at control sites (43%).

FXIIIa(+) dendrocytes

Dendrocytes are connective tissue cells which populate the outer layer of the dermis in a perivascular distribution, are closely associated with mast cells and express Factor XIIIa, a coagulation enzyme that facilitates fibrin cross-linking and contributes to wound healing. They show enhanced FXIIIa expression in response to mast cell degranulation and their number is increased in a variety of skin diseases, including radiation dermatitis (Moretto et al., 1998; Sueki et al., 1993).

Immunoperoxidase and toluidine blue staining and electron microscopy were used to evaluate FXIIIa expression and mast cell degranulation in skin biopsies from 8 subjects with photoaged skin treated with a pH 3.5 lotion containing 25% citric, glycolic or lactic acid twice daily for 4-8 months (Griffin et al., 1996). Compared to vehicle control sites, AHA-treated skin appeared to have both an

increased number of FXIIIa(+) cells and an increase in the size of these cells. By image analysis, FXIIIa expression was increased 50-600% over controls in 6 of the 8 subjects. The increase was statistically significant in 4 of the subjects and was seen with all 3 AHAs studied. There was also a statistically significant increase in mast cell degranulation. By electron microscopy, the dendrocytes in AHA-treated skin appeared markedly enlarged with dilatation of rough endoplasmic reticulum, particularly when they were positioned close to degranulated mast cells.

11.3.6 Sensitivity to UV light

The available studies on the effect of post- or pre-exposure treatment with glycolic acid on the skin response to UV radiation are summarised in Table 11.5.

Table 11.5: The effect of glycolic acid on skin response to UV irradiation*

No. of subjects	Test product	Treatment protocol	Effect	Reference
Post-irradiation treatment				
5	Cream with 12% GA, pH 4.2	Applied 4 times daily beginning 4 h after exposure to 3 MEDs (vehicle control)	Markedly reduced erythema at 48 h; hyperpigmentation observed at 72 h	Perricone & DiNardo (1996)
5	Two lotions with 8% GA, pH 3.25	Applied once daily beginning 24 h after exposure to 3 MEDs (untreated control)	7-16% reduction in irritation	Perricone & DiNardo (1996)
Pre-irradiation treatment				
20	Lotion with approximately 1.5% GA, pH 3.7-4.1	Test product applied 15-30 min before irradiation	SPF = 8.82	Consumer Product Testing Co. (1993c)
19	Cream with 4% GA, pH not specified	Test product applied twice daily for 12 weeks prior to irradiation	SPF = 0.87	KGL Skin Study Center (1995a)
5	Two lotions with 8% GA, pH 3.25	Test products applied once daily for 3 weeks prior to irradiation	SPF = 2.4	Perricone & DiNardo (1996)
5	Two lotions with 8% GA, pH 3.25/50% GA peel, pH 2.75	Test products applied once daily for 3 weeks; 6-min peel 15 min prior to irradiation	SPF = 1.7	Perricone & DiNardo (1996)

* GA = glycolic acid
MED = minimal erythemal dose
SPF = sunlight protection factor
UV = ultraviolet

When administered after UV irradiation, 3 products containing 8-12% glycolic acid were reported to reduce erythema and irritation from UV irradiation when applied to the skin at intervals commencing 4-24 h post-exposure, although 6-hourly application of the 12% product was associated with hyperpigmentation.

With pre-exposure treatment, the effect was assessed in standard sunscreen efficacy tests and expressed as the mean sun protection factor (SPF), that is, the minimal erythemal dose (MED) for the treated site divided by the MED for the

untreated control site[1]. Vehicle controls were not used. Most test products were found to offer some degree of sun protection. However, in one study conducted by KGL Skin Study Center (1995a), twice-daily treatment with a 4% glycolic acid cream for 12 weeks induced a statistically significant reduction in the amount of UV radiation required to induce sunburn, yielding a mean SPF of 0.87. There was considerable inter-individual variation in the effect, with UV sensitivity being increased in 9 subjects (by 48-50% in 3 of them), unchanged in 9 subjects and decreased in 1 of the 19 panellists.

The study protocol included tests for skin hydration as measured by electrical capacitance and semi-quantitative analysis of skin scaling using the D-Squames® method[2]. Skin sites treated with the 4% cream had a higher capacitance (that is, stratum corneum hydration) and less scaling than control sites (KGL Skin Study Center, 1995a-b). Other studies showed that seasonal variations in sunburn sensitivity coincide with variations in skin dryness/roughness and that treatment with moisturisers or emollients or smoothing of the skin surface by scrubbing or shaving increase UV light sensitivity by 5-12% (KGL Skin Study Center, 1995c; TKL Research, 1995a-b). As such, the laboratory testing the cream concluded that the increase in sensitivity in the smoother, glycolic acid treated areas was a physiological phenomenon caused by reduced light scattering from the skin surface and the consequent increase in light absorbency.

This interpretation was contested by the research organisation whom FDA contracted to make an assessment of the published and unpublished literature on the effects of AHAs on the skin (KRA, 1996). They reanalysed the study data and concluded that there was hardly any correlation between an individual's sensitivity to UV light and skin capacitance and none at all between light sensitivity and the score for scaling. They also pointed out that 3/19 tested subjects had a MED of about 0.5 after glycolic acid treatment, meaning close to a doubling of the sensitivity to sunburn, and that individual MED reductions of that magnitude were not observed at skin sites smoothed by moisturisers, emollients or mechanical means.

Subsequent studies investigated the production of sunburn cells in subjects treated with glycolic acid before exposure to UV light. Sunburn cells occur in mammalian epidermis after exposure to UV radiation and are easily recognised by their pyknotic (small and dark-staining) nuclei and eosinophilic cytoplasma (Young, 1987). Sunburn cell production was examined in 3 groups of 15-16 healthy subjects who had been treated once daily for 4 days or 12 weeks with a 10% glycolic acid gel, pH 3.5-4.0, which was applied at a dose of 2 mg/cm^2 and rubbed into the skin (KGL, Inc., 1996a-b). Control sites were treated with a placebo gel, a glycerol-based moisturiser, a mineral oil emollient, rubbed with a moistened mechanical exfoliating sponge for 15 sec, or left untreated. Fifteen min after the last application, each site was irradiated with UV light equivalent to 1 individually determined MED. Within 16-24 h of irradiation, a biopsy was taken from each site and the number of sunburn cells determined by microscopic examination. The results of these studies are summarised in Table 11.6.

[1] One MED is defined as the minimal amount of UV radiation required to cause distinct redness of the skin.

[2] The D-Squames® kit comprises a transparent adhesive disk that is applied directly onto the body area to be tested, removed and analysed after it has been pressed onto a black control card, which collects and visualises the scales adhering to its surface.

Table 11.6: Geometric mean number of sunburn cells per high power field in histological sections of human epidermis exposed to 1 MED of UV light following treatment with a 10% glycolic acid gel (KGL, Inc., 1996a-b)

Duration of treatment	Type of treatment					
	Glycolic acid	Vehicle	Moisturiser	Emollient	Sponge	No treatment
4 days	0.27	-	0.16	-	0.24	0.18
12 weeks	0.77*	-	0.38	-	0.44	0.37
12 weeks	0.85**	0.31	-	0.26	-	0.37

* Statistically significant compared to skin treated with moisturiser and to untreated skin
** Statistically significant compared to any other group

Whereas treatment for 4 days had no effect, treatment for 12 weeks caused a small increase in sunburn cell production which was significantly different from untreated control sites as well as sites treated with a moisturiser, an emollient, or a vehicle control. Sunburn cells are not cancerous, but are generally recognised as an objective, easily quantified marker of acute skin damage elicited by UV irradiation. As such, the sunburn cell studies invalidate the hypothesis that increased sensitivity to UV irradiation following long-term treatment with topical glycolic acid is secondary to smoothing of the surface of the skin.

In a similar study, there was no increase in the number of sunburn cells in 4 healthy subjects treated once daily for 4 days with 2 creams containing 1.5% octyl methoxycinnamate (a sunscreen) and either 4% or 8% glycolic acid (DeLeo, 1996).

11.3.7 Discussion

The special skin investigations in humans reviewed above demonstrate that glycolic acid has a number of effects on the structure and function of human skin at concentrations and pH levels that are commonly encountered in cosmetic products on sale in Australia.

Epidermis

Topically applied glycolic acid was consistently found to increase stratum corneum turnover in a dose- and pH-related manner and to decrease the thickness of the outermost layer of loosely connected cells (stratum disjunctum) where the latter is unusually prominent, such as in dry or photoaged skin. It also increased the thickness of the viable epidermis in dry or photoaged skin, although the only study of its potential to stimulate epidermal cell proliferation concluded that the impact on DNA-synthesis in healthy epidermal cells was slight and non-significant. In tests for TEWL or absorption of model penetrants, formulations containing ≤10 % glycolic acid had at most a modest impact on skin barrier function tests, whereas exposure to a solution with 12% glycolic acid at pH 1.6 was associated with a long-lasting increase in skin permeability to water.

Overall, these effects of glycolic acid on the structure and function of the epidermis appear to represent a combination of physiological repair mechanisms in response to superficial damage to the stratum corneum and to insults to the living layers of the skin.

Dermis

Concentrations of <1 μg/L glycolic acid induced s small, but dose-related increase in skin fibroblast proliferation and collagen synthesis *in vitro*. However, the significance of this finding may be tenuous as few studies provide convincing *in vivo* evidence of increased collagen deposition and thickening of the dermis and only at concentrations in the 15-70% range. Although there was no histological evidence of skin inflammation in humans using commercially available cosmetics (other than an increase in FXIIIa(+) dendrocytes), the dermal effects in animals were preceded by corrosive or irritant reactions and associated with a slight inflammatory infiltrate (see section 10.9.3). It is therefore conceivable that any increase in skin thickness or firmness caused by glycolic acid is in response to a mild primary skin irritation.

Sensitivity to UV radiation

When 3 commercial creams and lotions containing 8-12% glycolic acid were applied to experimentally sunburned skin, they were found to reduce erythema compared to vehicle or untreated controls. These findings were claimed to be the result of anti-inflammatory, antioxidant and photoprotective effects of glycolic acid (Perricone & DiNardo, 1996). However, the weight of evidence indicates that glycolic acid may cause inflammatory reactions in the skin and is unlikely to act as an antioxidant or photoprotective agent as it is not metabolised in human skin (FDA, 1996) and does not contain chromophores that absorb light in the visible or UV spectrum (KRA, 1996).

There is ample evidence that UV irradiation of human skin results in a significant release of tumour necrosis factor α (TNF-α) and that sunburn cell production can be blocked by neutralising antibodies to TNF-α and by cromolyn sodium, an asthma drug impeding mast cell degranulation (Walsh, 1995). TNF-α also appears to mediate some of the immunosuppresive effects of UV irradiation, which are believed to facilitate the progression of DNA-damaged cells to increasingly malignant cancer cells. There are no studies on the effect of glycolic acid on TNF-α release, but a significant increase in mast cell degranulation and FXIIIa expression in dermal dendrocytes (which is enhanced by mast cell degranulation and TNF-α) was reported in skin exposed repeatedly to AHAs in relatively high concentrations. It is therefore conceivable that glycolic acid and UV irradiation can have an additive effect on the release of TNF-α from mast cells in the dermis and thereby on sunburn cell production in the epidermis.

Whether there are any adverse long-term effects from repeated combined exposure to glycolic acid and UV light will be investigated in a FDA-initiated lifetime study in hairless mice, which is scheduled to commence in 1999 and will take 3 years to complete.

Conclusions

In conclusion, topical treatment with glycolic acid may lead to smoothing of the stratum corneum and a slight increase in the thickness and firmness of the skin. These effects appear to involve subtle mechanisms similar to those caused by mild abrasion and wounding and can usually be achieved at exposure levels that are not associated with skin corrosion or irritation or indeed with any of the classical signs of inflammation: erythema, oedema and cellular infiltration.

Use of cosmetics with glycolic acid may increase the sensitivity of the skin to sunburn, possibly because glycolic acid and UV light have an additive effect on the release of TNF-α from mast cells in the dermis. At present, however, there is no evidence that glycolic acid facilitates any of the mechanisms that contribute to the development of sunlight-induced cancers of the skin.

12. Hazard Assessment and Classification

This section integrates data on kinetics and metabolism, animal toxicity and human effects in order to characterise the potential adverse human health effects of glycolic acid resulting from its use in the cosmetics industry. Any health hazards that were identified have been classified in accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (the Approved Criteria) (NOHSC, 1999a). The Approved Criteria are cited in the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c) and provide the mandatory criteria for determining whether a workplace chemical is hazardous or not.

Where adequate human data were unavailable, information from experimental studies (animal and *in vitro* bioassays) formed the basis for assessment. In extrapolating results from experimental studies to humans, consideration has been given to relevant issues such as quality of data, weight of evidence, metabolic and mechanistic profiles, inter- and intra-species variability and relevance of exposure levels.

12.1 Toxicokinetics and metabolism

In vitro investigations of human skin have shown that percutaneous absorption of glycolic acid is a passive diffusion process whose extent is proportional to time, concentration of undissociated acid, and degree of occlusion of the site of application. It is also influenced by formulation type and composition. The available data indicate that the permeability coefficient for undissociated glycolic acid in aqueous solutions is approximately 3×10^{-4} cm/h. For oil-in-water emulsions containing 5% glycolic acid at pH 3, maximum penetration through the skin averaged 12%, with a 95% confidence interval of 2-22%. No information was available about absorption in humans following inhalation or ingestion of glycolic acid. However, animal data show that absorption of the chemical from the intestinal tract is virtually complete and a comparison of its oral and inhalation toxicity in rats indicates that it is likely to be readily absorbed through the lungs as well.

The distribution volume of glycolic acid is small (0.56 L/kg) and corresponds to the size of the body water compartment. The chemical is taken up by liver cells by a transport mechanism and metabolised to glyoxylic acid by glycolic acid oxidase, which is a peroxisomal, hydrogen peroxide generating enzyme. Glyoxylic acid may be oxidised further to oxalic acid, transaminated to glycine, or decarboxylated to formic acid and carbon dioxide, although the latter route is of little significance in primates. The oxidation of glycolic acid to glyoxylic acid is rate-limiting and easily saturated, and at higher dose levels glycolic acid is predominantly excreted unchanged in the urine.

Healthy subjects have plasma concentrations of glycolic acid in the 0.1-0.6 mg/L range and excrete 1-100 mg/day in the urine. This is primarily of dietary origin. Based on the tables published by Harris & Richardson (1980), the estimated

average daily intake from dietary sources for a 60 kg adult is about 68 mg glycolic acid (1.1 mg/kg/day), based on a mean intake of 500 g fresh fruit and vegetables and 4 cups of beverages (tea, coffee, fruit juice) per day (ANZFA, 1999). The half-life of plasma glycolic acid has been determined at 7-10.5 h in a limited number of patients with ethylene glycol poisoning.

12.2 Health hazards

12.2.1 Acute lethal effects

In animal studies, glycolic acid was found to cause lethality by ingestion, inhalation or injection in all species tested. Deaths occurred up to 12 days following exposure, with kidney lesions being the most common finding at necropsy. In GLP studies in the rat conducted according to OECD's Test Guidelines or similar protocols, the oral LD_{50} was 1357 mg/kg and the LC_{50} from nasal inhalation of aerosolised glycolic acid was 2520 mg/m^3 (2.5 mg/L) in male and >3640 mg/m^3 (>3.6 mg/L) in female rats. No dermal toxicity studies were available. In mice and rats, lethal dose levels were consistently lower in males than in females, apparently because the metabolite oxalic acid, which is prone to precipitate as calcium oxalate in the kidney and urinary tract of rodents, is formed at a faster rate in male as compared to female animals.

Cases of human intoxication have not been reported. However, there is a considerable body of data on the effects of acute poisoning from ingestion of ethylene glycol, which is of low toxicity in itself, but is slowly metabolised to glycolic acid. The estimated lethal dose of ethylene glycol in humans is approximately 1600 mg/kg, with death occurring from metabolic acidosis, cardiopulmonary collapse and/or renal failure within one to several days of exposure (Cavender & Sowinski, 1994).

There is no evidence of non-lethal irreversible effects from single exposures to glycolic acid in animals, or in humans from ethylene glycol poisoning.

Classification. Glycolic acid meets the Approved Criteria for classification as harmful by inhalation and if swallowed (R20/22).

12.2.2 Corrosion/irritation

Skin

In several GLP studies for skin corrosion/irritation potential in rabbits conducted according to OECD Guideline No. 404, crystalline glycolic acid and a 70% solution at pH <0.5 caused full thickness destruction of skin tissue after a 1-h exposure, whereas solutions of 70% neutralised glycolic acid or ≤57% unneutralised glycolic acid caused visible irritation after a 4-h exposure.

The histopathological effects of a single, non-occluded application of skin peel solutions were investigated in 3 human subjects, 2 of whom were exposed for 30 min only. Solutions containing 70% glycolic acid at pH 0.6 caused crusting and partial necrosis of the epidermis and acute dermal inflammation, consistent with a strong irritant reaction.

A large number of experimental formulations and commercial cosmetic products have been tested for skin irritation in humans according to various cumulative

irritation test protocols. Out of a total of 77 formulations containing 2-20% glycolic acid at pH 2.0-4.4, 5% were classified as severely irritant and 16% as moderately irritant. By comparison, signs of skin irritation such as redness, swelling or itching were reported by 13% of 869 subjects taking part in use tests of a number of cosmetic products covering a wide range of concentrations and formulation pH values. This was about 55% of all recorded adverse skin events.

Tests for phototoxicity with a small number of commercial products containing 0.5-4% glycolic acid at pH 3.6-4.1 were negative.

Follicular irritation chest tests with a single product containing 2% or 4% glycolic acid at pH 3.9 showed a dose-dependent positive response.

Classification. Glycolic acid meets the Approved Criteria for classification as corrosive (R34).

Eyes

In rabbit studies consistent with OECD Guideline No. 405, a solution of 64% glycolic acid at unknown pH caused destruction of the eye, whereas a solution of 57% glycolic acid at pH 1.8 caused irreversible lesions of the cornea.

Classification. Glycolic acid meets the Approved Criteria for classification as a severe eye irritant (R41).

Respiratory system

In a study conducted according to OECD Guideline No. 403 and to GLP standards, male and female rats were exposed to nose-only inhalation of an aerosolised solution of 70% glycolic acid for 4 h. Nasal discharge and soreness with ulceration of the mucosal membranes of the larynx and nose occurred at all dose levels (420-3640 mg/m^3). Clinical signs included gasping, noisy breathing and ocular discharge which may have been secondary to irritation of the nasal cavity as rats are obligatory nose-breathers and swelling of the nasal turbinates may block the drainage of the tear ducts. Noisy breathing and nasal and ocular discharge were also observed in male rats exposed to nasal inhalation of an aerosolised solution of glycolic acid at 510 mg/m^3 and above for 2 weeks. These effects were not observed in animals exposed to 160 mg/m^3 glycolic acid. Moreover, noisy respiration accompanied by mouth breathing, nose bleeding, ocular discharge and/or a mucoid exudate in the nasal turbinates were observed in one acute lethality and 3 10- to 15-day developmental toxicity studies in rats. Irregular respiration and lung noise were also recorded in a 3-month toxicity test in rats. These were all studies in which aqueous solutions of unneutralised glycolic acid were administered by stomach tube. As such, the above clinical signs may have been due to nasal reflux or aspiration of small amounts of glycolic acid as a complication of oral gavage dosing.

Classification. Glycolic acid meets the Approved Criteria for classification as causing serious irritation to the respiratory system (R37).

12.2.3 Sensitisation and photosensitisation

One skin sensitisation study in guinea pigs conducted according to OECD Guideline No. 406 and to GLP standards was negative, as were repeat insult patch tests of numerous cosmetic products covering a wide range of concentrations and pH values in groups comprising 25-198 healthy human subjects per product. When a small number of commercial cosmetic products containing 0.5-6% glycolic at pH 3.6-4.2 were tested by repeat insult patching followed by UV irradiation, no evidence of photosensitising potential was observed.

There were no findings indicating that glycolic acid may be a respiratory sensitiser.

Classification. Glycolic acid does not meet the Approved Criteria for classification as a sensitiser.

12.2.4 Effects after repeated or prolonged exposure

According to the Approved Criteria, risk phrase R48 (Danger of serious damage to health by prolonged exposure) is assigned when serious damage (clear functional disturbance or morphological changes which have toxicological significance) is likely to be caused by repeated or prolonged exposure. Workplace chemicals are classified at least as harmful when these effects are observed at the following dose ranges:

- Oral, rat ≤50 mg/kg/day; and
- Inhalation, rat ≤0.25 mg/L, 6h/day.

These guide values apply directly when severe lesions have been observed in a 90-day test. The guide values are at least 3 times higher in a 28-day test, that is, at least ≤150 mg/kg/day by mouth or ≤0.75 mg/L, 6h/day by inhalation.

The NOAEL for oral exposure in male and female rats was 150 mg/kg/day in a 90-day toxicity test.

The repeated-dose inhalation study provided for assessment was a 14-day test in male rats exposed to aerosols containing 160, 510 or 1400 mg/m^3 glycolic acid for 6 h per day, 5 days per week. In this study, clear treatment-related effects (significant weight loss, dyspnoea, elevated serum liver enzymes and hepatocellular degeneration) leading to the sacrifice of 7/10 rats *in extremis* were seen at 1400 mg/m^3 (1.4 mg/L). At 510 mg/m^3 (0.51 mg/L), serum AST and ALT levels were increased and microscopic examination of the liver showed a mild hepatocellular degeneration. At the end of a 14-day recovery period, the liver enzyme levels had reverted to normal in the 1400 mg/m^3 group and in all but 2/10 animals in the 510 mg/m^3 group. Decreased urinary output was reported in the 510 mg/m^3 group, but no microscopic changes were seen in the kidneys. No treatment-related changes were seen at 160 mg/m^3 (0.16 mg/L), except for a very mild, diffuse hepatocellular degeneration in 1/10 animals by the end of the 2-week recovery period. These effects could be due to the acute toxicity of glycolic acid, as deaths occurred up to 12 days post-exposure in the single-dose inhalation study reviewed in section 10.1.3. However, it cannot be excluded that chronic effects would have developed at 160 mg/m^3 (0.16 mg/L) if exposure had occurred for a longer period such as 28 or 90 days. As such, it is not possible to determine the potential of glycolic acid to cause serious damage by prolonged inhalation exposure from this 14-day study.

No repeated dose toxicity studies by dermal exposure were available for assessment.

Classification. Glycolic acid does not meet the Approved Criteria for classification as causing danger of serious damage to health by prolonged exposure if swallowed. Based on the limited inhalation data available for assessment, glycolic acid is not classifiable with regard to serious damage to health by prolonged exposure through inhalation.

12.2.5 Reproductive effects

There were no human case reports or studies indicating any link between exposure to glycolic acid and birth defects or impaired fertility in humans.

Developmental toxicity

The findings in the available *in vivo* developmental toxicity studies are summarised in Table 12.1.

The classification system prescribed by the Approved Criteria applies a broad definition of developmental toxicity and does not distinguish between malformations and variations, allocate relative weights to particular findings or set cut-off levels for continuous variables such as the incidence of alterations or percentage reduction in foetal body weights.

A workplace chemical is included in Category 1 if there is sufficient evidence to establish a causal relationship between human exposure to the substance and subsequent developmental toxic effects in the progeny. It is included in Category 2 if there is sufficient evidence to provide a strong presumption that human exposure to the substance may result in developmental toxicity, generally on the basis of: (1) clear results in appropriate animal studies where effects have been observed in the absence of signs of marked maternal toxicity, or at around the same dose levels as other toxic effects but which are not a secondary non-specific consequence of the other toxic effects; (2) other relevant information.

Classification into Category 3 is based on similar criteria as for Category 2 but may be used where the experimental design has deficiencies which make the conclusions less convincing, or where the possibility that the effects may have been due to non-specific influences such as generalised toxicity cannot be excluded.

In general, classification in Category 3 or no category would be assigned on an *ad hoc* basis where the only effects recorded are small changes in the incidence of spontaneous defects, small changes in the proportions of common variants such as are observed in skeletal examinations, or small differences in postnatal developmental assessments.

Glycolic acid has not been linked with birth defects in humans. As shown in Table 12.1, there was statistically significant developmental toxicity as defined in the Approved Criteria in five dose groups administered ≥332 mg/kg/day glycolic acid by mouth or 833 mg/kg/day sodium glycolate by subcutaneous injection. There were signs of marked maternal toxicity at oral dose levels ≥600 mg/kg/day, whereas signs of maternal toxicity were mild in the 332 mg/kg/day glycolic acid group in the DuPont pilot study and in the 833 mg/kg/day sodium glycolate group

in the Dow study. In dams given 332 mg/kg/day glycolic acid by oral gavage, they included a decrease in weight gain limited to the last two days of gestation, wet fur, which is usually due to treatment-induced diarrhoea, and lung noise, presumably as a result of aspiration of small quantities of glycolic acid. In dams injected subcutaneously with 833 mg/kg/day sodium glycolate, the only effects recorded were small changes in the absolute and relative weight of the liver, which is the main site of glycolate metabolism. In the DuPont main study, there was developmental toxicity as well as marked maternal toxicity at 600 mg/kg/day, a marginal increase in foetal abnormalities and marginal maternal toxicity at 300 mg/kg/day, and no effects on either foetuses or dams at 150 mg/kg/day and below.

The DuPont study was a pilot study with only 5 pregnant animals per group and the Dow study did not follow OECD guidelines as there was only one dose level. Furthermore, the mechanistic studies reviewed in section 10.5.1 indicate that whereas the glycolate ion is a developmental toxicant in its own right, oral administration of unbuffered glycolic acid leads to generalised metabolic acidosis which is associated with a substantial increase in the incidence and severity of developmental effects.

As shown in Table 12.1, the effects recorded in the 332 mg/kg/day dose group in the DuPont pilot study included reduced foetal body weight and a substantial increase in skeletal variations (77 vs. 53%). In the Dow study, there was reduced foetal body weight and a substantial increase in skeletal variations of up to 93 vs. 32% in the sodium glycolate group. There was also an increase in total malformations in this exposure group. However, the increase was small (3.8 vs. 0.3%) and due to tail malformations which may also occur spontaneously.

The biological significance of these findings is supported by the fact that ethylene glycol, which is extensively metabolised to glycolic acid, induced foetal growth retardation and abnormalities of the axial skeleton and cranio-facial region in several developmental toxicity studies in rats and mice (Carney, 1994). One such study indicated that reduced body weights and abnormalities such as delayed ossification and fused ribs in rat pups of dams exposed to a large oral dose of ethylene glycol were reversible by day 63 after birth (Marr et al., 1992).

The molecular basis for the effects of glycolate and metabolic acidosis on foetal growth and skeletal development is unknown, although it is acknowledged that skeletal development is very susceptible to chemical agents that inhibit oxidative respiration (Faustman et al., 1997). Several other chelating agents are developmentally toxic and have pronounced effects on mineral metabolism and bone mineralisation in animal embryos, apparently because they induce zinc and/or copper deficiencies that inhibit the activity of a number of metallo-enzymes (Domingo, 1998).

In summary, both the DuPont pilot study and the Dow study (1) provide clear evidence of developmental toxicity in the form of reduced foetal body weight and a substantial increase in the incidence of skeletal variations at dose levels not associated with marked maternal toxicity; (2) have formal deficiencies in their experimental design; and (3) determined effects which may in part be due to non-specific influences. These studies conducted by two independent laboratories using different chemical forms of the substance (free acid and sodium salt) and

different routes of administration (oral and subcutaneous), clearly demonstrate that glycolic acid is a foetotoxic developmental toxicant.

Table 12.1: Foetal and maternal findings in 3 developmental toxicity studies in the rat*

Dose group	Foetal findings	Maternal findings
DuPont pilot study (DuPont, 1995a; Munley et al., 1999), 5 pregnant rats/group		
697 mg/kg/day	Increased resorptions (1.5 vs. 0.4%) Reduced foetal weight (18%) Increased incidence of total malformations (39 vs. 5%) Increased incidence of skeletal variations (64 vs. 53%)	Reduced weight gain GD7-22 (38%) Reduced body weight GD22 (12%) Reduced feed consumption GD9-22 (17%) Lung noise (88%), stained and wet fur (75%), salivation (50%), abnormal gait (25%)
332 mg/kg/day	Reduced foetal weight (9%) Increased incidence of skeletal variations (77 vs. 53%)	Reduced weight gain GD21-22 (38%) Wet fur (50%), lung noise (25%)
157 mg/kg/day	None	None
77 mg/kg/day	None	None
DuPont main study (DuPont, 1996; Munley et al., 1999), 5 pregnant rats/group		
600 mg/kg/day	Reduced foetal weight (13%) Increased incidence of total malformations (10.6 vs. 0.8%) Increased incidence of retarded ossification (67.9 vs. 31.5%)	Reduced weight gain GD7-22 (20%) Reduced body weight GD22 (12%) Reduced feed consumption GD21-22 Lung noise (32%), abnormal gait (20%), irregular respiration (8%), lethargy (8%)
300 mg/kg/day	Marginally significant incidence of skeletal malformations (fused ribs and vertebrae in 2/339 foetuses from 2/23 litters), p = 0.0555	Marginally increased incidence of lung noise (8%), p = 0.0553
150 mg/kg/day	None	None
75 mg/kg/day	None	None
Dow study (Carney et al., 1997, 1999), 25 pregnant rats/group		
650 mg/kg/day GA	Reduced foetal weight (17%) Increased resorptions (5.7 vs. 2.5 vs. a historical range of 3.5-14.1%) Increased total malformations (23.5 vs. 0.3%) Increased skeletal malformations (10.6 vs. 0.8) Increased skeletal variations (24,6,90, 72,39,13,10,13,23,46,41 vs. 0,0,32,2,0, 0,2,0,0,16,1%)	Reduced body weight gain GD9-21 (14%) Reduced body weight on GD16, GD21 (6%) Increased relative kidney (8%) and liver (13%) weights Mortality (16%), abnormal respiration (8%)
833 mg/kg/day NaG by subcutaneous injection	Reduced foetal weight (8%) Increased resorptions (4.3 vs. 2.5 vs. a historical range of 3.5-14.1%) Increased total malformations (3.8 vs. 0.3%) Increased skeletal variations (24,93,40, 8,9,5 vs. 9,32,2,0,2,1%)	Increased absolute (9%) and relative (11%) liver weight

* All dose indications refer to 100% glycolic acid (GA) or sodium glycolate (NaG). All results given were statistically significant unless otherwise stated. All structural abnormalities (malformations and variations) are reported in accordance with the terminology used in the study reports. GD = gestation day.

However, according to article 4.108 of the Approved Criteria, even when clear effects have been demonstrated in animal studies the relevance for humans may be doubtful because of the doses administered, for example, where effects have

been demonstrated only at high doses, or where marked toxicokinetic differences exist, or the route of administration is inappropriate.

With glycolic acid, statistically significant developmental toxicity occurred at doses of 332 mg/kg/day glycolic acid by mouth and 833 mg/kg/day sodium glycolate by subcutaneous injection. As shown in Appendix 2, section A2.3, these doses are assessed to be high as they correspond to an internal dose that is estimated to be unattainable in humans exposed to glycolic acid by skin contact and/or inhalation in the occupational environment.

Classification. Based on the above, glycolic acid is not classified for developmental toxicity.

Effects on fertility

No impairment of fertility was observed in a well-conducted study involving the oral administration of up to 600 mg/kg/day of glycolic acid to male and female rats for 18-22 weeks.

Classification. Glycolic acid does not meet the Approved Criteria for classification as toxic to reproduction.

Lactation effects

Neonatal growth during lactation was not retarded in a well-conducted rat study in which the dams were dosed orally with up to 600 mg/kg/day of glycolic acid for 3 months prior to mating and during pregnancy and lactation.

Classification. Glycolic acid does not meet the Approved Criteria for classification as having effects on lactation.

12.2.6 Genetic toxicity

Glycolic acid has been tested in a number of assays for genetic toxicity in accordance with OECD's Test Guidelines and to GLP standards. The tests available for assessment included *in vitro* assays for reverse mutation in bacteria, forward mutation in mouse lymphoma cells and chromosomal aberration in Chinese hamster ovary cells. An *in vivo* somatic cell mutagenicity test (mouse bone marrow micronucleus test) was also available. All tests were negative, except the *in vitro* assay for gene mutation in mouse lymphoma cells which was positive at high concentrations of glycolic acid (2500-5000 mg/L) in the presence of metabolic activation.

Glycolic acid is not structurally related to any known germ cell mutagens.

Classification. Glycolic acid does not meet the Approved Criteria for classification as mutagenic.

12.2.7 Carcinogenicity

No carcinogenicity studies were available for assessment and it is not possible to classify glycolic acid for carcinogenic effects. Ethylene glycol did not induce tumours in carcinogenicity studies in rats and mice and is not suspected of having carcinogenic effects in humans (Cavender & Sowinski, 1994).

12.2.8 Summary of hazard classification

The identified human health hazards and their classification according to the Approved Criteria are summarised in Table 12.2.

Table 12.2: Summary of hazards and lowest or no observed adverse effect levels of glycolic acid, with assigned risk phrases as per the Approved Criteria (NOHSC, 1999a)

Hazard	Effect level*	Species	Classification from review
Acute lethal effects			
• ingestion	LD_{50} = 1350 mg/kg	Rat	R20/22: Harmful by inhalation and if swallowed
• inhalation	LC_{50} = 2500 mg/m^3	Rat	
Corrosion			
• skin	LOAEL = 70%	Rabbit	R34: Causes burns
• eyes	LOAEL = 57%	Rabbit	R41: Risk of serious damage to eyes
Irritation			
• respiratory system	LOAEL = 420 mg/m^3	Rat	R37: Irritating to respiratory system
Sensitisation			
• skin	Negative	Guinea pig	None
• respiratory system	No data		Not classifiable
Systemic toxicity			
• ingestion	LOAEL = 300 mg/kg/day	Rat	None
• inhalation	LOAEL = 510 mg/m^3		Not classifiable
• dermal	No data		Not classifiable
Developmental toxicity	NOAEL = 150 mg/kg/day	Rat	None
Fertility effects	NOAEL = 600 mg/kg/day	Rat	None
Lactation effects	NOAEL = 600 mg/kg/day	Rat	None
Genetic toxicity	Negative	Various	None
Carcinogenicity	No data		Not classifiable

* LC_{50} = median lethal concentration
LD_{50} = median lethal dose
LOAEL = lowest observed adverse effect level
NOAEL = no observed adverse effect level

13. Current Controls

This section discusses currently employed measures to reduce the likelihood of adverse human health effects from occupational and consumer exposure to glycolic acid. The information reviewed includes national and international standards and guidelines, material safety data sheets (MSDS), labels, and consumer information materials. Where appropriate, measures for reducing exposure to glycolic acid are dealt with separately for formulation facilities and beauty salons.

Relevant information was provided by importers and users of cosmetic grade raw materials, manufacturers and importers of glycolic acid containing cosmetics in finished form, a small sample of beauty therapists and beauty therapy schools, and national and international industry associations.

They key issues discussed in this section include: workplace control measures; emergency procedures; hazard communication, including MSDS, labels for workplace and consumer products, education and training of workers, and consumer information materials; occupational and public health regulatory controls; and voluntary standards and guidelines.

13.1 Workplace control measures

Based on this assessment, glycolic acid is a hazardous substance in accordance with the NOHSC Approved Criteria (NOHSC, 1999a). According to the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c), exposure to hazardous substances should be prevented or, where this is not practicable, adequately controlled, so as minimise risks to health and safety.

In general, the control of worker exposure to any hazardous substance should be achieved through a hierarchy of control strategies comprising elimination, substitution, isolation, engineering controls, safe work practices, and personal protective equipment. Control measures are not mutually exclusive and effective control usually requires a combination of these measures. In relation to glycolic acid and the cosmetic industry, particular attention must to be paid to control measures that minimise skin contact with the chemical.

13.1.1 Elimination

Elimination implies the removal of a chemical from a process, such as the use of a non-chemical process in skin beautification. Such methods exist, but are generally more expensive and less convenient than the use of chemicals.

13.1.2 Substitution

Substitution includes substituting a less hazardous substance, the same substance in a less hazardous form or the same substance in a less hazardous process.

A comparative evaluation of the health effects of chemicals that may be substituted for glycolic acid in cosmetic products is beyond the scope of this

assessment. However, below is a summary of relevant literature sources. As a general principle, caution should be exercised when substituting an unknown hazard for a known hazard, particularly when replacing one material with another having similar chemical properties.

Lactic acid, which is the closest homologue of glycolic acid, is an ingredient in many cosmetic products, particularly moisturising creams and lotions. There is substantial evidence from human *in vivo* studies that glycolic acid and lactic acid have essentially similar skin effects (Berardesca et al., 1997; CIR, 1998; Ditre et al., 1996; Griffin et al., 1996; Johnson et al., 1997; KRA, 1996; Smith, 1994, 1996; Van Scott & Yu, 1974). The toxicology of lactic acid has been reviewed by the British Industrial Biological Research Association (BIBRA, 1990), CIR (1998) and in a literature survey commissioned by FDA (KRA, 1996).

A limited number of investigations have compared the human skin effects of glycolic acid with other AHAs such as citric acid, 2-hexanoic acid, 2-hydrobutyric acid, malic acid and tartaric acid (Berardesca et al., 1997; Ditre et al., 1996; Griffin et al., 1996; Smith, 1996; Van Scott & Yu, 1974).

Derivatives of glycolic acid such as citric acid esters and glycolic acid polymers are being promoted as safe alternatives to glycolic acid. However, there is no published evidence to support such claims.

In some beauty salons, glycolic acid is applied in viscous gel or cream formulations rather than in aqueous solutions as a simple and practicable way of reducing the risk of dispersion.

13.1.3 Isolation

Importers generally store glycolic acid raw materials in tightly closed containers in a separate corrosive materials store, in accordance with Australian Standard (AS) 3780-1994 (see section 13.5.1). As shown in Table 13.1, some small and all large cosmetics manufacturers employ a partially enclosed formulation process, with one or more unit operations such as neutralisation, dilution, mixing or transport taking place in closed vessels or pipework. In all but the smallest facilities, the filling and packaging processes are automated. These measures will to a large extent isolate workers from the chemical.

There is limited scope for isolation of beauty salon workers from potential exposure to glycolic acid as the application of the chemical to the skin of the client requires manual handling.

13.1.4 Engineering controls

In formulation plants, exhaust ventilation may be installed in weighing and mixing rooms and occasionally in filling and/or packaging areas (Table 13.1).

No exhaust ventilation is employed in beauty salons, apart from standard air conditioning.

13.1.5 Safe work practices

In formulation, filling and packaging facilities, no work practices were identified that can be characterised as unique to glycolic acid. Although there is no requirement to manufacture cosmetics in accordance with Good Manufacturing Practices (GMP), some facilities also manufacture therapeutic goods and operate to GMP standards (Table 13.1). These include strict observation of standard operating procedures for the handling of hazardous substances and training of staff in safe work practices.

Beauty salon workers are generally trained to handle all products they use exactly as prescribed in the manufacturer's instruction (see section 13.3.3).

Table 13.1: Control measures in 5 small and 6 large Australian formulation manufacturing facilities for glycolic acid containing cosmetics

	Maximum batch size	
Control measure	**≤200 kg (n = 5)**	**500-1100 kg (n = 6)**
Isolation		
• corrosive raw materials store	0	1
• partially enclosed process	1	6
• automated filling/packaging	3	6
Engineering controls		
• exhaust ventilation	2	4
Safe work practices		
• GMP observed	1	3
Personal protective equipment		
• eye protection	2	4
• face protection	2	3
• rubber gloves	4	6
• protective clothing	0	3
• respiratory protection	1	3

13.1.6 Personal protective equipment

Where other control measures are not practicable or adequate to control exposure, personal protective equipment (PPE) should be used. Appropriate PPE recommended in available MSDS for glycolic acid raw materials includes eye and face protection, rubber gloves, protective clothing, and respiratory protection if there is a possibility of airborne exposure from mists. In practice, whereas rubber gloves are widely used, only half of the facilities surveyed employ eye and face protection and only a quarter require their workers to wear protective clothing (Table 13.1).

A guide for the hairdressing and beauty industry published by the Queensland Workplace Health and Safety Authority (Anon, 1994) recommends the wearing of cotton-lined protective gloves to prevent contact with irritating chemicals and of safety glasses where there is a slight chance of a chemical entering the eye. Information provided by a small sample of beauty therapists indicates that only a minority of salon workers wear gloves and that safety glasses are hardly used at all.

13.2 Emergency procedures

For any hazardous chemical an emergency response plan is an essential component of occupational health and safety risk management. In the event of a substantial leak, spill, release or fire, a written procedure is necessary for workers and emergency services. Although such plans were not submitted for assessment, the following emergency procedures have been described in available MSDS:

- neutralise spills with lime or soda ash;
- collect into suitable container and dispose of, or incinerate, in accordance with applicable regulations;
- clean spill area with plenty of water;
- use carbon dioxide, dry chemical powder, foam or water spray for firefighting; and
- provide safety showers and eye washes in areas where glycolic acid is used.

With regard to storage of corrosive chemicals, AS 3780-1994 provides guidance on the preparation of emergency plans. With regard to transport, appropriate emergency procedures for corrosive substances are contained in AS 1678.8A1-1987, which is intended to be used in conjunction with the Australian Dangerous Goods (ADG) Code (FORS, 1998).

13.3 Hazard communication

13.3.1 Assessment of MSDS

MSDS are the primary source of information for workers involved in the handling of chemicals. Under the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c) and the corresponding State and Territory legislation, suppliers of hazardous chemicals for use at work are obliged to provide a current MSDS to their customers.

A total of 22 MSDS were provided for assessment, including 6 MSDS for synthetic, cosmetic grade glycolic acid (70-99%), 7 MSDS for AHA extracts containing 2.5-17% glycolic acid and 9 MSDS for finished products for salon end use containing 4-40% glycolic acid.

The MSDS were assessed against the NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994b). The most common deficiencies were:

- lack of date and page numbers;
- no Australian emergency telephone number;
- no information on classification according to the ADG Code;
- insufficient or no supporting toxicological data;
- lack of advice to doctor;
- no reference to engineering controls; and
- inadequate recommendations for PPE, particularly eye and face protection and protective clothing.

13.3.2 Assessment of labels

Raw materials and products for workplace use

Under the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c) and the corresponding State and Territory legislation, suppliers or employers shall ensure that all containers of hazardous substances used at work are appropriately labelled in accordance with the NOHSC *Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994a).

Five labels for synthetic, cosmetic grade raw materials provided for assessment conformed with all requirements of the NOHSC Code of Practice and the ADG Code. Three labels for AHA blends containing 5-10%, 10% and 12-17% glycolic acid respectively provided details of the overseas manufacturer and one of them also contained safety phrases relating to the use of PPE. They did not comply with any of the other requirements of the NOHSC Code of Practice.

Seven labels for salon end use products were available for assessment. None of these complied with the NOHSC Code of Practice, although two contained a safety phrase and a first aid procedure relating to eye irritation.

Finished products for consumer end use

Where products containing glycolic acid are intended for consumer end use, they need only comply with the ingredient labelling requirements in the *Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations*. According to these regulations, cosmetic products must be labelled with a list indicating their ingredients in descending order by volume or mass[1]. The names of the ingredients must be either their English names or their International Nomenclature Cosmetic Ingredient names and the list must be prominently shown and clearly legible. There is no requirement to declare the concentration of any ingredient or the pH of the formulation.

A total of 66 labels for consumer end use products were provided for assessment. Ten of these did not comply with the *Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations.* Four of the non-compliant products had no ingredient list at all, whereas one product listed glycolic acid but no other ingredients. Three products containing plant extracts listed these ingredients under the Latin name of their source, for example, *Saccharum officinarum* in lieu of sugar cane extract. Two labels were not clearly legible because the print was extremely small or covered by a sticker with the name and address of the Australian distributor. Nine products complied formally with the ingredient labelling requirements, but used ingredient names such as sugar cane extract, mixed fruit acids or mixed fruit AHA extracts, which the average consumer may not associate with glycolic acid.

13.3.3 Education and training of workers

Four formulation facilities that operate according to GMP stated that they train their workers in the handling of hazardous chemicals and safe work practices.

Vocational training of beauty therapists is offered by a number of Technical and Further Education (TAFE) institutes and private beauty schools. TAFE courses

[1] Ingredients in concentrations of <1% and colour additives may be listed separately in any order.

contain a module on occupational health and safety, including general information and standard safety measures relating to hazardous chemicals. These courses teach students to handle all products exactly as prescribed in the manufacturer's instruction and generally do not address the use of specific chemicals such as glycolic acid. Course material for facial treatment classes in one TAFE institute contained information about adverse effects of AHAs in clients, but did not mention the potential hazards to beauticians (Moreton, 1999).

The Queensland Workplace Health and Safety Authority has published a fact sheet on hazardous substances in the hairdressing and beauty industry, which is also available on the Internet (Anon, 1996). The fact sheet provides general information about MSDS, labels and control measures and contains a list of hazardous substances that are common in the hairdressing and beauty industry.

13.3.4 Consumer information materials

Some consumer products provide product information in excess of the ingredient labelling requirements of the *Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations*. This information may appear on the label of the primary container, on the outer packaging or in a leaflet supplied with the product.

Table 13.2 summarises the extent of such additional information supplied with 39 of 66 products that were available for assessment.

13.4 Occupational and public health regulatory controls

13.4.1 Exposure standards and health surveillance

There are no formal requirements for health surveillance programs in workplaces using glycolic acid and an exposure standard has not been established in Australia or overseas.

13.4.2 Australian Code for the Transport of Dangerous Goods by Road and Rail (ADG Code)

Glycolic acid is not listed in the ADG Code (FORS, 1998). However, when tested by the Corrositex® method, crystalline glycolic acid and solutions containing ≥30% glycolic acid at their natural pH meet the criteria for classification as corrosive substances (Class 8) and for assignment to Packing Group II (DuPont, 1993; DuPont, 1997a). Such goods would therefore come under UN Number 3260 (corrosive solid, acidic, organic, not otherwise specified) or UN Number 3265 (corrosive liquid, acidic, organic, not otherwise specified) and must comply with the corresponding requirements of the ADG Code with regard to packaging, storage, labelling etc.

13.4.3 Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP)

Glycolic acid is not listed in the current SUSDP (Australian Health Ministers' Advisory Council, 1999).

Table 13.2: Type of voluntary consumer information supplied with 39 cosmetic products containing glycolic acid

Type of information	Products supplied with this information	
	Number	%
Identification		
• name of active ingredient(s)	26	67
• cosmetic form	21	54
• glycolic acid content by weight or volume	5	13
• pH	0	0
What the product is used for	36	92
How the product works	12	31
Advice before using the product		
• contraindications*	21	54
• precautions for use	0	0
• special warnings†	5	13
How to use the product properly		
• dosage	18	46
• method of administration	37	95
• frequency of administration	33	85
• duration of use	1	3
Unwanted effects		
• description of undesired effects§	32	82
• action to be taken if experienced	32	82
Storage conditions	0	0
Where to go for further information	19	49
Name and address of the Australian product sponsor	24	62
Date of information	0	0

* Use on sensitive or irritated skin
† Effects on sun sensitivity
§ Eye and/or skin irritation and/or stinging

13.5 Voluntary standards and guidelines

13.5.1 Australian Standards

The following Australian Standards (AS) and Australian and New Zealand Standards (AS/NZS) contain information that is relevant to the handling of glycolic acid in the cosmetic industry, given the corrosive nature of the chemical:

- AS/NZS 1337:1992 – Eye protectors for industrial application;
- AS 1678.8A1-1987 – Emergency procedure guide – transport – group text card 8A1 – corrosive; and
- AS/NZS 2161.2:1998 – Occupational protective gloves – general requirements.

13.5.2 Industry guidelines

Occupational exposure standards

One large raw material manufacturer has established a control level of 10 mg/m^3 (8- and 12-h TWA) glycolic acid in workroom air (DuPont, 1999b). This level was based on the results of a subacute inhalation study in rats in which the only effect in the lowest dose group (160 mg/m^3) was a very mild, diffuse hepatocellular degeneration in 1/10 animals by the end of the recovery period (DuPont, 1983). As such, this concentration was considered to approach a NOAEL for exposure through inhalation (Kennedy & Burgess, 1997).

Salon products

The Esthetics Manufacturers and Distributors Alliance of the American Beauty Association recommends that the concentration of glycolic acid products for salon end use not exceed 30%, with a pH of at least 3.0 (EMDA, 1996).

The safety of glycolic acid in cosmetic products was reviewed by the CIR Expert Panel under the US Cosmetic, Toiletry and Fragrance Association (CIR, 1998). Based on the information included in the CIR report, the Expert Panel concluded that glycolic acid was safe for use by professional beauty therapists at concentrations ≤30%, at pH values ≥3.0, in products designed for brief, infrequent, rinse-off use, when application was accompanied by directions for daily use of sun protection. This conclusion was intended to address concerns about adverse health effects on clients such as potential irritation, enhancement of the penetration of other ingredients and increase in sensitivity to sunlight. The Expert Panel did not consider potential adverse health effects on beauty salon workers.

Consumer products

With regard to cosmetic products for consumer end use, the CIR Expert Panel concluded that glycolic acid was safe at concentrations ≤10%, at final pH values ≥3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection (CIR, 1998). This conclusion was intended to address concerns about adverse health effects such as potential irritation, enhancement of the penetration of other ingredients and increase in sensitivity to sunlight.

The European Cosmetic Toiletry and Perfumery Association has suggested an industry code of practice that limits the concentration of AHAs including but not limited to glycolic acid in retail non-rinse skin care cosmetics to a maximum of 12% and the pH to a minimum of 3.0 (COLIPA, 1996).

In 1996, the Australian Society of Cosmetic Chemists (ASCC) issued a position paper on AHAs, β-hydroxy acids and α-keto acids (ASCC, 1996). The paper did not set concentration or pH limits, but recommended that formulators carry out the appropriate development, clinical and dermatological tests to determine efficacy and potential irritancy so as to be able to bring to the consumer AHA-based products which are effective and safe to use. This position paper is currently under review. According to a spokesperson for the ASCC Technical Committee, the revised paper will agree with the CIR findings and suggest limits for the concentration of glycolic acid (and lactic acid) and pH in consumer products for skin renewal. These limits are likely to be a concentration >2% but ≤10% and a pH >3.5 (ASCC, 1999). The aim of the 2% limit is to keep the

widespread use of lactic acid and, to a lesser extent, glycolic acid as a pH adjustment agent exempt from regulations.

Neither the Cosmetic, Toiletry and Fragrance Association nor any other Australian beauty industry association have established guidelines for the formulation or use of glycolic acid containing products.

14. Discussion and Conclusions

14.1 Health effects

The acute lethality of glycolic acid by oral or inhalation exposure, its potential to cause skin, eye and respiratory system corrosion or irritation, and its subchronic, developmental and reproductive toxicity have been investigated in well designed and well conducted animal studies. However, there were no acute or repeated-dose animal studies of the toxic effects from dermal exposure, other than single-dose tests for skin corrosion/irritation.

The available animal studies indicate that glycolic acid is harmful by single-dose ingestion or inhalation. Depending on concentration and pH, it may be either corrosive or irritating to the skin, eyes and respiratory system. Furthermore, it is toxic to the kidneys by prolonged or repeated oral administration. When glycolic acid is given by mouth on a daily basis, it induces malformations at high, maternally toxic doses. A marginal increase in foetal abnormalities was seen at a dose of 300 mg/kg/day, which was also associated with marginal maternal toxicity, with no effects on foetal development at lower doses. There is little information on the systemic health effects of glycolic acid in humans. In acute ethylene glycol poisoning, the severity of clinical and biochemical abnormalities are proportional to the plasma concentration of the metabolite glycolic acid and plasma levels in excess of 760 mg/L are associated with kidney injury. There are no case reports in the published literature of systemic or developmental toxicity resulting from exposure to glycolic acid itself.

A large number of experimental and commercial cosmetic formulations containing glycolic acid have been tested in humans, mainly in studies conducted by cosmetic manufacturers to ensure the acceptability of their products. Overall, these tests have shown a high incidence of adverse events from regular, short- or long-term use of glycolic acid skin care products, with irritation and stinging recorded in 13% and 10% of subjects respectively.

Skin irritation is related to glycolic acid concentration, pH, the nature of excipients and time of residence on the skin. Products containing 20% glycolic acid or less, at pH 3.5 or above, are not expected to cause skin irritation, although they may cause a mild to moderate transient stinging sensation in certain individuals. Products formulated at 20-40% glycolic acid and pH ≥3.5 may cause slight irritation. Products formulated at ≥40% glycolic acid at pH 3.5, or 10% at pH 3.0 may cause moderate skin irritation. At pH 2.5 and below, products containing 10% or more glycolic acid may be severe skin irritants. Salon products formulated at concentrations of 40-60% where the pH is <3.5 may be moderate to severe skin irritants; at these concentrations, irritation is inversely correlated to pH. Concentrations of 50% glycolic acid cause sloughing of the epidermis, while 70% glycolic acid is corrosive.

Although stinging is a relatively frequent adverse effect, it is short-lived, not associated with visible skin lesions and not predictive of more severe reactions to the chemical.

Products formulated at 10-20% glycolic acid, pH 3.8-4.0 would be expected to cause mild to moderate eye irritation. If the concentration is greater than 10% and the pH lower than 3.8, it is expected that eye irritation would be moderate to severe.

One study showed that long-term use of a skin cream with 4% glycolic acid increased sensitivity to sunburn by up to 50% in some subjects. Glycolic acid has the dual effects of increasing skin thickness by hydration, while removing the topmost layer of the epidermis. Thus, immediately following use of cosmetic products containing glycolic acid, increased hydration of the dermis may afford protection against sunburn. However, it is reasonable to assume that increased sensitivity to sunburn may occur if hydration is not maintained and the stratum corneum has been thinned by exfoliation, or if skin irritation develops. Mechanistically, this is likely to represent an additive effect of glycolic acid and UV light on the release of mediators of inflammation.

A lifetime study in hairless mice investigating the long-term effects from repeated combined exposure to topically applied glycolic acid and UV irradiation will begin in 1999 and be completed by 2002. At present there is no evidence from animal or human studies that glycolic acid facilitates any of the mechanisms that contribute to the development of sun-induced skin cancers.

14.2 Current use in Australia

Information collected from applicants at the beginning of 1999 indicates that the consumption of glycolic acid for cosmetic uses in Australia is at least 5.7 t/y, of which about 2/3 is imported as an ingredient in products manufactured overseas and the remainder in raw material form.

The chemical is an ingredient in at least 180 cosmetic products, of which 1/7 is for end use in beauty salons and 6/7 is sold to the public for use at home. Salon products contain from 4-60% glycolic acid and consumer products between 0.01% and 20% of the chemical. All salon products and more than 90% of consumer products are used to beautify the skin, with the balance accounted for by shampoos, conditioners and other hair products used at home. Cosmetic grade raw materials include crystalline glycolic acid, aqueous solutions containing 70% glycolic acid and a number of AHA blends containing 2.5-17% glycolic acid mixed with other AHAs such as lactic, citric, malic and tartaric acids.

There are at least 8 importers of glycolic acid in cosmetic raw materials, 17 importers of finished cosmetic products containing glycolic acid, and 19 businesses that manufacture such products locally. Many of the latter contract out the formulation. Although some contract formulators manufacture for several distributors, even the largest facilities do not usually produce more than one batch per month. Some of the businesses that import, formulate or distribute cosmetics with glycolic acid are local subsidiaries of, or agents for, large multinational companies with considerable expertise in the testing of cosmetic products for safety and acceptability. The majority, however, are small businesses, which do not have access to such expertise and, in most cases, do not belong to the national industry association: The Cosmetic, Toiletry and Fragrance Association of Australia.

It is estimated that skin treatments with glycolic acid formulations are available in the majority of Australia's 2500-3000 full-service beauty salons. These salons also sell glycolic acid skin care products to their customers for home use, as do most of Australia's 15,000 pharmacies, supermarkets and department stores. Hair care products with glycolic acid are predominantly distributed through hair salons, which number about 12,000 nation-wide, although a few are available from pharmacies and supermarkets.

14.3 Occupational exposure

In Australia, glycolic acid containing cosmetics are formulated at less than 20 facilities, with a maximum of 5 workers per facility who handle the chemical. As such, the total number of formulation workers exposed to glycolic acid is low. Furthermore, exposure occurs at intervals of several days to several months.

There are 2500-3000 full-service beauty salons in Australia. The percentage of salons that use glycolic acid and the average number of workers per salon are unknown, but as a rough estimate it can be assumed that the number of

Workers in the cosmetic industry are unlikely to be exposed to glycolic acid by beauticians who use glycolic acid, in some cases on a daily basis, is at least 1000-2000. ingestion. Skin contact may occur as a result of accidental splashes or spills. Exposure through inhalation is likely to be low to negligible as the volatility of glycolic acid is very limited and respirable aerosols formed under vigorous mixing conditions would contain minimal concentrations of the chemical. As with other corrosive substances, accidental burns to the skin and eyes from glycolic acid raw materials are potentially serious and may lead to disfiguration and time off work.

In reasonable worst-case scenarios, the potential external exposure is conservatively estimated at 6.3 mg/kg/day in workers in formulation facilities and at 1.7 mg/kg/day in beauty salon staff. The NOAEL based on a 3-month oral rat toxicity test and on maternal and developmental toxicity in pregnant rats given oral bolus doses of glycolic acid is 150 mg/kg/day.

As such, it is concluded that the known uses of glycolic acid (and products containing glycolic acid) in the cosmetic industry in Australia are unlikely to pose significant risks to the health of workers if exposure is appropriately controlled and that a full occupational risk assessment by NICNAS is not required. Nonetheless, as glycolic acid is a hazardous chemical, employers of formulation and beauty salon workers (and self-employed beauticians) should conduct a risk assessment of their individual workplace and, where necessary, give due consideration to the control measures discussed in section 13.

14.4 Public exposure

The public will be exposed from skin contact with a variety of cosmetic products such as face creams, body lotions and gels, scrubs, shampoos, conditioners and skin peeling solutions. Inhalation exposure may also occur, but vaporisation from cosmetic formulations would be very low, and public exposure via this route is expected to be negligible.

In reasonable worst-case scenarios, the maximum skin exposure is calculated as 10 mg/kg in clients undergoing treatment in beauty salons and 28 mg/kg/day in consumers using glycolic acid cosmetics at home, based on the following estimates of exposure:

- In beauty salons, a single treatment of the arms, legs and backs of the hands and feet (an area of approximately 7800 cm^2) with two applications of a 40% gel in an amount of 1 mg/cm^2 of the product per application, massaged into the skin, and then rinsed off; and
- For use at home, twice daily application of 0.8 g of a 10% face cream and of 7.5 g of a 10% body lotion massaged into the skin and left on without being rinsed off.

In both cases, it is assumed that the exposed person has a body weight of 60 kg.

The NOAEL based on a 3-month oral rat toxicity test and on maternal and developmental toxicity in pregnant rats given oral bolus doses of glycolic acid is 150 mg/kg/day. As such, the calculated margin of exposure (the NOAEL divided by the estimated human exposure) for the above scenarios would be in the range of 5.4-15, based on external exposure.

Based on the calculations detailed in Appendix 2, section A2.2, the estimated maximum systemic absorption in reasonable worst-case scenarios are 4.7 mg/kg on the day of a salon treatment and 3.4 mg/kg/day for home-use. Exposure margins calculated from these estimates for systemic uptake range from 32-44.

Absorption through the skin is slower than absorption from the intestine and therefore would be expected to lead to lower peak blood levels. Although experimental data are not available, it is possible to estimate the blood levels of glycolic acid from percutaneous absorption of the chemical in humans and compare them to the estimated blood levels from ingestion of doses that represent a reliable NOAEL in animals *in vivo*. This can be achieved by means of a simple, one-compartment kinetic model based on the available human and animal data relating to the absorption, elimination and distribution of the chemical (for details, see Appendix 2, section A2.2). The modelling indicates that in the skin exposure scenarios outlined above, blood levels would peak at 2.6 mg/L and 2.5 mg/L respectively[1]. By comparison, peak blood levels in animals are estimated at 130 mg/L for oral administration of 150 mg/kg/day, which is the NOAEL obtained in a well-conducted 3-month oral rat toxicity test as well as the NOAEL based on maternal and developmental toxicity in pregnant rats given oral bolus doses of glycolic acid on day 7-21 of gestation. Based on the estimated peak blood levels of glycolic acid, the calculated margin of exposure is 50 for beauty salon and 52 for at-home applications.

As a rule, for chemicals that are widely used by the general population a margin of exposure <100 is an indication that problems may arise. However, when considering the significance for risk of the exposure margins referred to above, the following particulars should be taken into account:

- The highest internal exposure and estimated peak blood level are in consumers undergoing treatment in beauty salons which is taken at intervals

[1] In normal adult subjects, blood levels of glycolic acid (originating predominantly from dietary intake) range from 0.1-0.6 mg/L (see Section 9.2).

of one to several weeks. A NOAEL for single exposures in rats is not available but is likely to be higher than 150 mg/kg. As such, the true margins of exposure are likely to be higher than the estimates provided above.

- The target organs for toxicity of glycolic acid in the rat are the kidney and, to a lesser extent, the liver. Studies of a number of cases of human intoxication with ethylene glycol indicate that kidney damage in humans is absent or slight at plasma concentrations of glycolic acid below 760 mg/mL and significant liver effects have not been recorded.
- The developmental effects in rats are aggravated by the metabolic acidosis induced by oral bolus doses of glycolic acid solutions at their natural pH. By contrast, all cosmetic products with glycolic acid for salon or consumer use are pH-adjusted and only a part of the content of glycolic acid is present as undissociated acid. Moreover, absorption of glycolic acid through the skin is slower than from the gastro-intestinal tract and therefore less likely to exhaust the physiological mechanisms that maintain the acid-base balance of the body.

As such, it is concluded that the possibility of systemic and/or developmental toxicity in humans is remote and that normal professional and domestic use of cosmetic products containing glycolic acid is unlikely to present a significant risk to public health. Nonetheless, given the potential of glycolic acid to cause skin and eye irritation at high concentrations and low pH values, this report should be referred to the National Drugs and Poisons Schedule Committee (NDPSC) for their consideration. In addition, manufacturers, importers and suppliers of consumer products should inform consumers that the use of skin exfoliant cosmetic products may result in an enhanced sensitivity to sunburn, and that use of sunscreen protection is advised.

14.5 Current regulations and controls

14.5.1 Occupational measures

A survey of workplace control measures showed that none of 11 Australian formulation facilities employ the full spectrum of measures available to control exposure to glycolic acid, such as keeping corrosive raw materials in a separate store, using partially enclosed processes and automated filling and packaging, installing exhaust ventilation where aerosols may be formed, and providing workers with appropriate PPE. Control measures are most deficient in the smallest facilities and least deficient in facilities operating to GMP.

In beauty salons, control measures are limited to the occasional substitution of solutions with gels or creams to minimise dispersion and of gloves to reduce hand exposure to the chemical.

An assessment of MSDS and labels for workplace chemicals containing glycolic acid found a number of deficiencies, particularly with respect to MSDS and labels for AHA blends and beauty salon products. No MSDS was available for 16/25 products (64%) intended exclusively for in-salon use and of 7 labels available for examination none was found to comply with the requirements for workplace chemicals.

14.5.2 Labelling of products for consumer end use

Unless one of their ingredients is listed on the SUSDP, cosmetic products for consumer end use have to comply only with the ingredient labelling requirements in the *Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations*. These regulations are enforced by the Australian Competition and Consumer Commission through surveys conducted at regular intervals (DIST, 1998). Nonetheless, 10/66 (15%) of the labels that were available for assessment did not meet the ingredient labelling requirements and 18/66 products examined (27%) were labelled in a way that did not explicitly disclose the presence of glycolic acid in the formulation.

Almost 60% of the products examined were labelled or supplied with voluntary information over and above the prescribed ingredient labelling. In general, these consumer information materials were found to provide adequate instructions about the method and frequency of administration, common undesired effects, and actions to be taken should such effects occur. None of 39 labels or leaflets examined provided information on the pH of the product, 34 (87%) did not state the concentration of the active ingredient, and only 5 (13%) contained a warning about the possible risk of increased sensitivity to sunburn.

14.6 Data gaps

Glycolic acid has substantial biological and physiological effects, some of which have not been investigated in detail. The most important data gaps identified during this assessment of glycolic acid in cosmetic products relate to studies of:

- the systemic toxicity of glycolic acid when applied in repeated doses to the skin of laboratory animals, with toxicokinetic measurements as required to extrapolate the findings to humans;
- a developmental toxicity study of glycolic acid in a second species by dermal administration which would confirm or otherwise the occupational exposure estimates for the dermal route utilised in the hazard classification in section 12.2.5;
- chronic toxicity and carcinogenicity, with toxicokinetic measurements as required to extrapolate the findings to humans; and
- the rate and extent of systemic absorption of glycolic acid through human skin *in vivo*, including peak and steady state blood concentrations in humans exposed to standardised at-home and salon treatments, which would confirm or otherwise the skin absorption parameters estimated from human *in vitro* data and utilised in the public exposure assessment in section 14.4.

It is noted that a lifetime study in hairless mice to investigate the effects of repeated combined skin exposure to glycolic acid and UV irradiation is scheduled to commence in 1999.

14.7 Conclusions

In conclusion, this preliminary assessment has identified the following health and safety issues relating to the use of glycolic acid for cosmetic purposes:

- Moderate to severe skin and eye irritation may result from the use of cosmetics containing glycolic acid at high concentrations and low formulation pH values.
- Glycolic acid may thin the stratum corneum by exfoliation and if skin hydration is not maintained or skin irritation develops, increased sensitivity to sunburn could occur.
- Glycolic acid is a hazardous workplace chemical.
- Many MSDS and workplace labels are incomplete and several options available to reduce worker exposure are not pursued.
- Notwithstanding the statutory requirement for ingredient labelling of cosmetics, a quarter of the labels examined failed to inform the consumer that the product contained glycolic acid.
- Many products are supplied without any accompanying consumer information and when written health and safety advice is provided, it is often incomplete.

15. Recommendations

NICNAS does not recommend a full (risk) assessment of glycolic acid in cosmetic products at this time. Nevertheless, given the findings discussed in the previous section, the following recommendations are made:

15.1 NOHSC occupational hazard classification

In accordance with the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999a) and based on an assessment of health hazards, the recommended classification for any use of glycolic acid in the workplace is as follows:

R20/22 **Harmful by inhalation and if swallowed**

R34 **Causes burns**

R41 **Risk of serious damage to eyes**

R36/38 **Irritating to eyes and skin**

R37 **Irritating to respiratory system**

It is recommended that glycolic acid be included in the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999b).

The overall classification of a mixture, product or preparation for use at work depends on the concentration of the hazardous chemicals it contains. It is usually based on cut-off concentration levels which are tabulated in the NOHSC *Approved Criteria for Classifying Hazardous Substances* (NOHSC, 1999a). However, where a mixture has been tested and classified as a whole, the classification can be based on the test results rather than on the reference cut-off concentration levels.

In case of glycolic acid, it should be taken into account that the available skin and eye corrosivity and irritation studies indicate that the chemical is not corrosive at concentrations <30% and is only slightly irritant at concentrations <10%. As such, it is recommended to establish concentration cut-off levels for corrosive and irritant effects of glycolic acid that are similar to those applied to other moderately strong organic acids listed in the NOHSC *List of Designated Hazardous Substances* (NOHSC, 1999b), such as acetic and propionic acids[1].

As such, the recommended reference cut-off levels for each of the classified hazards of glycolic acid are as follows: ≥10% and <25% for R36/38; ≥20% for R37; and ≥25% for R20/22, R34 and R41.

As an acid placed on the market in mixtures at various concentrations which require different labelling, glycolic acid should be listed with labelling note B. This note requires the supplier to state on the label of workplace chemicals the percentage concentration of the hazardous chemical in the mixture (for example,

[1] For acetic and propionic acids the cut-off points for R36/38 are ≥10% and <25%, whereas the cut-off point for R34 (which implies R41) is ≥25%.

70% glycolic acid). As there is no precedent in the NOHSC *Designated List of Designated Hazardous Substances* (NOHSC, 1999b) for taking the pH of a mixture into account in the classification of hazardous workplace substances, the percentage concentration would mean the sum of the concentration of undissociated glycolic acid and of glycolate ion, expressed as glycolic acid.

Mixtures, products or preparations containing other hazardous substances should be classified by taking into account the health effects of all ingredients, or, if they have been tested as such, according to the actual test results.

15.2 Further studies

Glycolic acid is not classifiable with regard to serious damage to health by prolonged exposure in contact with skin or through inhalation because of no or limited data respectively. It is recommended that testing be carried out investigating the systemic toxicity of glycolic acid following repeated dose administration by the dermal and inhalation administration route.

15.3 Hazard communication

As glycolic acid is a hazardous substance, employers and suppliers are required to provide information, such as MSDS and labels, about the hazards of the chemical. Details of these obligations, consistent with employers' general duty of care, are provided in the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c).

15.3.1 MSDS

The NOHSC *National Code of Practice for the Preparation of Material Safety Data Sheets* (NOHSC, 1994b) provides guidance for the preparation of MSDS.

It is recommended that suppliers amend their MSDS to take account of the classification and cut-off levels recommended in section 15.1 and, where necessary, rectify the deficiencies identified in this assessment. Particular attention needs to be paid to the following:

- inclusion of a statement of hazardous nature;
- appropriate risk and safety phrases;
- inclusion of an Australian emergency contact number;
- inclusion of appropriate advice to doctor;
- inclusion of appropriate engineering controls such as exhaust ventilation if there is a possibility of aerosol formation; and
- inclusion of appropriate recommendations for PPE, including, in addition to rubber gloves, the use of eye and face protection, protective clothing, and respiratory protection if there is a possibility of exposure to aerosols (mists).

15.3.2 Workplace labels

It is recommended that suppliers of glycolic acid raw materials or products for use at work update their labels to take account of the classification and cut-off levels recommended in section 15.1 and, where necessary, rectify the deficiencies identified in this assessment. The labelling requirements are outlined below:

NOHSC requirements

The NOHSC *National Code of Practice for the Labelling of Workplace Substances* (NOHSC, 1994a) provides guidance for the labelling of workplace hazardous substances. Requirements for glycolic acid are as follows:

Signal word (hazard category)

In accordance with NOHSC requirements, a 'signal word' should be used in the labelling of hazardous substances. For glycolic acid the signal words 'HARMFUL' or 'HAZARDOUS' are appropriate for workplace chemicals.

Ingredient disclosure

The presence of glycolic acid in a mixture or preparation must be disclosed on the label (together with its concentration) when present in a mixture at or above 25% w/w.

Risk phrases

The risk phrases recommended for mixtures, products and presentations containing various concentrations of glycolic acid are as follows:

Concentration (w/w):	***Risk phrase:***	
≥10% but <25%	R36/38	Irritating to eyes and skin
≥20%	R37	Irritating to respiratory system
≥25%	R34	Causes burns
	R41	Risk of serious damage to eyes[1]

Safety phrases

The recommended safety phrases for raw materials for industrial use are:

S7 Keep container tightly closed; and

S36/37/39 Wear suitable protective clothing, gloves and eye/face protection.

The following safety phrases are recommended for products that are likely to be used in places to which members of the general public have access, such as beauty salons:

S2 Keep out of reach of children;

S7 Keep container tightly closed;

S25 Avoid contact with eyes; and

S37 Wear suitable gloves.

First aid statements

[1] When an ingredient or mixture is classified as corrosive and assigned R34, the risk of severe damage to the eye is considered implicit and R41 may be omitted from the label.

The following first aid statements are recommended for raw materials for industrial use as well as for products that are likely to be used in places to which members of the general public have access, such as beauty salons:

S26 In case of contact with eyes, rinse immediately with plenty of water and contact a doctor or Poisons Information Centre; and

S45 In case of accident or if you feel unwell, contact a doctor or Poisons Information Centre immediately (show the label where possible).

Decanting

Where glycolic acid (or a mixture, product or preparation containing ≥10% w/w of the chemical) is decanted into non-original containers and not consumed immediately, such containers must be labelled with the name of the product and the appropriate risk and safety phrases.

Other hazardous ingredients

Glycolic acid products containing other hazardous ingredients should be classified and labelled accordingly.

Dangerous goods requirements

The following information should also appear on the label for glycolic acid in mixtures, products or preparations containing ≥30% of the chemical in order to comply with the requirements of the ADG Code (FORS, 1998):

- **UN Number 3260** (if in solid form in containers with a capacity ≥500 g)
- **UN Number 3265** (if in liquid form in containers with a capacity ≥500 mL)
- **Dangerous Goods Class – Class 8.**

15.3.3 Education and training of workers

Guidelines for the induction and training of workers potentially exposed to hazardous substances are provided in the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c).

Workers potentially exposed to glycolic acid need to be trained in safe handling, storage, transportation and disposal of the chemical. Training should provide information on the health and safety hazards of glycolic acid and should address appropriate control and safety measures required to minimise occupational exposure. It is recommended that beauty therapy teachers and employers of beauty salon workers refer to the following publication: Guide for the hairdressing and beauty industry. Brisbane, QLD, Division of Workplace Health and Safety, Department of Employment, Vocational Education, Training and Industrial Relations (Anon, 1994).

MSDS for glycolic acid and/or glycolic acid containing products should be made freely available to all workers with potential exposure.

15.4 Occupational control measures

Under the NOHSC *National Model Regulations for the Control of Workplace Hazardous Substances* (NOHSC, 1994c), an employer shall ensure that an assessment is made of the risks to health at any workplace using a hazardous chemical. Where the assessment indicates that it is necessary, the employer shall ensure that exposure is either prevented or, where that is not practicable, adequately controlled so as to minimise risks to health. With regard to glycolic acid, particular attention should be paid to worker exposure via skin contact and the inhalation of aerosols (mists). A number of relevant control measures such as isolation, ventilation and the use of PPE are described in section 13.

15.5 Public health recommendations

Given the potential of glycolic acid to cause skin and eye irritation when used in cosmetic products at high concentrations and low pH values, this report should be referred to the National Drugs and Poisons Schedule Committee (NDPSC) for their consideration.

It is also recommended that importers and manufacturers of cosmetic products comply with the ingredient labelling requirements in the *Trade Practices (Consumer Product Information Standards) (Cosmetics) Regulations* and clearly indicate whether such products contain glycolic acid. Furthermore, importers and manufacturers that supply a consumer information document with their products should amend the information to rectify the deficiencies identified in this assessment. In particular, consumers should be advised that the use of skin exfoliant cosmetic products may result in an enhanced sensitivity to sunburn and that use of sunscreen protection is advised, and to immediately discontinue use of the product if skin irritation or increased sensitivity to sunburn occurs.

15.6 Uses outside the scope of the assessment

The scope of this assessment was limited to glycolic acid in cosmetic products. However, many of the recommendations set out above are applicable to other industrial or domestic uses of the chemical. As such, this report will be forwarded to agencies and government bodies responsible for the use of chemicals in other industries, in non-cosmetic products for domestic use, or by or as directed by members of the medical profession.

16. Secondary Notification

Under Section 65 of the *Industrial Chemicals (Notification and Assessment) Act 1989*, secondary notification of glycolic acid may be required where an introducer of the chemical becomes aware of any circumstances that may warrant a reassessment of its hazards and risks. Specific circumstances include:

- the function or use of glycolic acid has increased, or is likely to change, significantly;
- the amount of glycolic acid introduced into Australia has increased, or is likely to increase, significantly;
- manufacture of glycolic acid has begun in Australia; and
- additional information has become available to the introducer as to the adverse health effects of glycolic acid, such as the results of any of the studies identified in sections 14.6 and 15.2.

The Director (Chemicals Notification and Assessment) must be notified within 28 days of the manufacturer/importer becoming aware of any of the above or other circumstances prescribed under section 65 of the Act.

Appendix 1

Cosmetic Products Containing Glycolic Acid

This appendix provides a list of cosmetic products containing glycolic acid that were marketed in Australia in 1998/99. The list includes the trade name of each product and, where available, the concentration of glycolic acid in the product (in % w/w) and the pH of the formulation. Where the notified pH covered a range of values, the pH listed is the mean of that range.

The list was compiled during the first half of 1999 from information supplied by applicants and notifiers. It is not intended to be a comprehensive listing. Formulations may have changed since the preparation of the list and some products may no longer be commercially available.

Trade name	% glycolic acid	pH
ADN Revitalising Skin Renewal Complex	1.20	6.30
AHA Biofruit Liposome	0.23	4.10
AHA Booster Complex	2.50	4.40
Anew All-In-One Intensive Complex Cream	2.00	3.90
Anew All-In-One Perfecting Complex Cream	1.00	3.80
Anew All-In-One Perfecting Complex Lotion	1.00	3.80
Anew Intensive Line Minimiser	8.00	3.80
Anew Peel Off Mask	6.00	4.50
Antioxidant Performance Night Cream	0.48	4.25
Antioxidant Triple Performance AHA Fruit Peel	1.45	4.25
Aqua Glycolic Astringent	6.50	3.80
Aqua Glycolic Body Cleanser	8.00	4.40
Aqua Glycolic Body Scrub	8.00	4.40
Aqua Glycolic Face Cream	5.60	4.40
Aqua Glycolic Facial Cleanser	6.50	4.40
Aqua Glycolic Hand & Body Lotion	8.00	4.40
Aqua Glycolic Shampoo	8.00	4.40
Arbre Fruit Extracts Booster Serum	6.30	
Arbre Fruit Extracts Cleanser and Tonic	0.20	
Arbre Fruit Extracts Hand & Body Lotion	9.50	
Arbre Fruit Extracts Masque	30.00	
Beta Alistine Skin Science AHA Treatment Serum	9.00	
Better Body Works Facial Cream	5.00	5.50
BiON Glycolic Acid Exfoliator 30%	30.00	2.30
BiON Glycolic Acid Exfoliator 40%	40.00	2.30
BiON Glycolic Acid Exfoliator 60%	60.00	2.00
BiON Glycolic Cleanser	4.00	3.70
BiON Glycolic Gel	15.00	3.20
BiON Glycolic Salicylic Gel	10.00	3.20
Body Works Shower Gel	0.01	5.20
Bodysilk Exfoliating Gel	20.00	3.40
Buffered Alphahydroxy Peel	40.00	3.00
C'est Ravir AHA Revitalising Body Lotion	10.00	4.00
C'est Ravir Glyco-Excell	30.00	3.50

Trade name	% glycolic acid	pH
C'est Ravir Glyco-Gel	15.00	3.50
C'est Ravir Glycolic Body Scrub	8.00	3.80
C'est Ravir Glycolic Cleanser	8.50	3.80
C'est Ravir Glycolic Complex Serum	6.00	3.50
C'est Ravir Glycolic Eye & Lip Crème	1.00	4.00
C'est Ravir Glycolic Facial Lotion	8.50	4.00
C'est Ravir Glycolic Pro-Gel	10.00	3.50
C'est Ravir Glycolic Transformation	5.00	3.50
C'est Ravir Renu Skin Defense	6.00	3.80
C'est Ravir Soft Grain Scrub	1.00	3.70
Colored & Permed Conditioner	0.01	5.30
Colored & Permed Shampoo	0.03	5.95
David Jones Natural Extracts Skin Repair Cream	1.00	4.20
Demineralising Shampoo	0.03	5.45
Dermasilk Exfoliating Clay Mask	15.00	3.30
Dermasilk Eyecare Complex		3.60
Dermasilk Resurfacing Cleanser	10.00	3.50
Dermasilk Resurfacing Cream 5%	5.00	3.60
Dermasilk Resurfacing Cream 10%	10.00	3.40
Dermasilk Resurfacing Cream 15%	15.00	3.20
Dermasilk Resurfacing Cream 20%	20.00	3.00
Dermasilk Resurfacing Gel 10%	10.00	3.30
Dermasilk Resurfacing Gel 15%	15.00	3.20
Dermasilk Resurfacing Gel 20%	20.00	3.10
Dermasilk Resurfacing Lotion 10%	10.00	3.30
Dermasilk Resurfacing Lotion 15%	15.00	3.20
Dermasilk Resurfacing Lotion 20%	20.00	3.10
Dermasilk Toning Mist	10.00	3.50
Dermline Selftanning Lotion	5.00	3.70
Elucent Skin Refining Day Cream	4.00	4.00
Elucent Skin Refining Face & Body Lotion	4.00	4.00
Elucent Skin Refining Gentle Cleanser	4.00	4.00
Elucent Skin Refining Night Cream	4.00	4.00
Energy Lift Body Wash	0.01	5.20
Equalise Shampoo	0.01	5.25
Fleur de Mer Fruit Acid Active Hand & Body Cream	1.45	4.00
Fleur de Mer Fruit Acid Active Moisturising Cream	1.00	4.00
Fleur de Mer Fruit Acid Active Solution	14.50	4.50
Frith's Pharmacy's Glycollic Acid 5%	5.00	
Frith's Pharmacy's Glycollic Acid 10%	10.00	
Glycolic Polymer Crème 5%	5.00	3.50
Glycolic Polymer Crème 10%	10.00	3.00
Glycolic Polymer Eye Crème	4.00	3.50
Glycolic Polymer Solution 5%	5.00	3.00
Glycolic Polymer Solution 10%	10.00	2.50
Glycolic Polymer Solution 20%	20.00	1.50
Glymed Plus Active Exfoliator	15.00	3.20
Glymed Plus AHA Accelerator	9.60	3.70
Glymed Plus AHA Exfoliating Masque	5.10	3.70
Glymed Plus Alpha Therapeutic Foot Cream	5.00	3.80

Trade name	% glycolic acid	pH
Glymed Plus Alpha Therapeutic Hand & Body Lotion	9.20	3.80
Glymed Plus Eye & Lip Renewal Complex	3.20	4.50
Glymed Plus Facial Hydrator	8.70	3.70
Glymed Plus Gentle Facial Wash	8.60	3.70
Glymed Plus Prep Solution	7.00	3.20
Glymed Plus Serious Skin Action Gel	9.40	3.80
Glymed Plus Therapeutic Body Scrub	9.50	3.80
Glymed Plus Treatment Cream	9.80	3.70
Hair Energising Complex	0.01	4.95
Hand & Nail Treatment Crème	5.00	5.00
Intensive Hair Treatment	0.01	4.25
Juvena Skin Balancer Gel	0.10	4.50
MD Body Scrub	8.90	3.80
MD Facial Cleanser	7.10	3.80
MD Facial Cream	8.30	3.80
MD Facial Lotion	7.10	3.80
MD Glycare 10	8.30	3.80
MD Glycare 5	4.20	3.80
MD Glycare Cleansing Gel	7.10	3.80
MD Glycare Perfection Gel	3.20	3.25
MD Glycare Shampoo & Body Gel	7.10	3.80
MD Glycolic Facial Gel	25.80	3.25
MD Hand & Body Cream	8.30	3.80
MD Hand Treatment Gel	25.80	3.25
MD Nail & Cuticle Complex	6.00	3.80
MD Pedicream	10.70	3.80
MD Sensitive Skin Cleanser	6.70	4.40
MD Sensitive Skin Cream	7.80	4.40
MD Sensitive Skin Lotion	6.70	4.40
MD Skin Bleaching Gel	5.60	4.40
MD Skin Cleansing & Prepping Scrub	9.70	3.25
MD Skin Cleansing & Prepping Solution	4.50	3.25
MD Smoothing Complex	6.50	3.25
MD Vit-A-plus	2.80	4.40
Medi-Care Shampoo	0.03	5.25
Natio Wrinkle Defence Cream	1.00	4.40
Natura Bissé Glyco Eye	10.00	4.50
Natura Bissé Glyco-Peeling	25.00	4.50
Natura Bissé Glyco-Peeling Plus	50.00	4.50
Natural Care Skin Balancing Lotion	0.10	4.10
Natural Care Skin Renewal Lotion	0.10	4.10
Neostrata AHA Skin Smoothing Cream	8.00	3.50
Neostrata AHA Skin Smoothing Lotion	10.00	3.80
Neostrata AHA Solution for Oily/Acne Prone Skin	8.00	4.00
Neutrogena Healthy Skin Eye Cream	0.50	6.60
Neutrogena Healthy Skin Face Lotion	8.00	3.50
Neutrogena Healthy Skin Face Lotion Delicate Skin	4.00	4.10
Peaceful Moment Body Wash	0.01	5.20
Pevonia After Shaving Cream	5.00	4.50
Pevonia After Shaving Gel	5.00	4.50

Trade name	% glycolic acid	pH
Pevonia Body Moisturizer	5.00	4.00
Pevonia Clarifyl Care Cream	5.00	3.50
Pevonia Clarifyl Purifying Mask	5.00	4.00
Pevonia Clarifyl Spot Treatment	9.80	3.60
Pevonia Desincrustation Gel	9.80	3.60
Pevonia Eye Cream	2.00	4.50
Pevonia Foot Dry Oil	5.00	3.50
Pevonia Multi Active Foot Cream	10.00	3.50
Pevonia Multi Active Hand Cream	8.00	4.50
Pevonia O_2-Oxygenating Treatment	9.70	3.60
Pevonia Radiance Glycocides Cream	8.00	4.50
Pevonia Radiance Lightening Fluid	5.00	4.00
Pevonia Radiance Lightening Mask	5.00	4.00
Poly Glyco Body Lotion	10.00	3.50
Pond's Age Defying Complex Cream - Delicate	4.00	3.80
Pond's Age Defying Complex Cream - Normal	8.00	3.80
Pond's Age Defying Lotion	4.00	3.80
Principal Secret AHA Booster Complex	2.50	4.40
Refining Body Cleanser	4.00	4.10
Refining Facial Cleanser	6.00	4.00
Revelery Skin Logics AHA Cream	1.00	4.20
Revitalising Crème	7.00	5.80
Revitalising Lotion	10.00	5.80
Riche Crème Anti-Wrinkle	1.00	4.70
RVB Fluid Smoother		5.50
RVB Opalising Cream	0.06	4.50
RVB Opalising Intensive Drops	1.12	5.75
RVB Opalising Mask	1.12	5.75
RVB Restructuring Cream	1.12	4.50
RVB Restructuring Intensive Drops	1.12	4.75
RVB Restructuring Mask	1.12	5.75
RVB Soothing Cream	1.12	4.60
RVB Soothing Intensive Drops	1.12	5.40
RVB Vitalising Cream - Dry Skin	1.12	4.40
RVB Vitalising Cream - Oily Skin	0.06	5.75
Sanctum Firming Clay Mask	0.30	6.00
Sanctum Skin Rejuvenation Fruit-Acid Night Lotion	0.75	6.00
Shine & Volume Conditioner	0.01	5.30
Shine & Volume Shampoo	0.03	5.25
Skinbiance Daily Moisterising Cream with AHAs	0.70	4.25
Skinbiance Daily Moisturising Lotion with AHAs	0.70	4.25
Spa Dynamique Cellulite Smoothing Gel	1.00	5.00
Tropical Escape Body Wash	0.01	5.20
Wild Mate Naturally Rich Moisturising Lotion w/ AH	1.50	5.00
Works Moiturising Liquid Keratin Complex	0.01	3.00
Yves Saint Laurent Fruit Jeunesse	2.50	

Appendix 2

Exposure Calculations

A2.1 Occupational exposure

A2.1.1 Modelling of airborne levels

The EASE model was used to provide an independent estimate of glycolic acid air concentrations for all scenarios for which measured levels were available. The input to the model for each of these scenarios is summarised in Table A1.1. For liquids, the input also included the vapour pressure of glycolic acid over a 70% aqueous solution at 45°C given in Table 5.1.

Table A1.1: Input to EASE model used to estimate glycolic acid air levels in various occupational settings

Setting	Process temperature	Average glycolic acid concentration	Use pattern	Control pattern	LEV*
Synthesis	200°C	70%	Closed system	Full containment	No
Purification	50°C	70%	Closed system	Full containment	No
Road tanker loading	25°C	70%	Non-dispersive	Segregation	Out-doors
Drumming	25°C	70%	Non-dispersive	Segregation	No
Simulated blending	25°C	70%	Non-dispersive	Segregation	No
Formulation manufacture	40°C	40%	Closed system	Full containment with significant breaching	No
Formulation manufacture	25°C	5%	Non-dispersive	Segregation	No
Formulation manufacture	28°C	45%	Non-dispersive	Segregation	No
Beauty salon use	25°C	20%	Non-dispersive	Direct handling	No

* Local exhaust ventilation

The output was converted from ppm to mg/m^3 by multiplication with 3.1 (see section 5.1) and reduced proportionally to account for process mixtures containing <70% glycolic acid, as recommended in the EASE manual (EC, 1996). The final estimates are shown in Table 8.1.

Based on the measured and modelled data reproduced at section 8.2.1, a breathing zone concentration of 2 mg/m^3 was taken to be the maximum airborne exposure from mixtures containing ≥70% glycolic acid, whereas a breathing zone concentration of 1 mg/m^3 was taken to be the maximum airborne exposure from any mixture containing ≤45% glycolic acid.

A2.1.2 Dermal exposure

Dermal exposure was estimated for occupational exposure to a 70% raw material and a 40% final formulation. In case of the former, direct skin contact was assumed to be

incidental (one event per day, typically resulting from splashes or spills). In case of the final formulation, skin contact was assumed to be intermittent, that is, 2-10 events per day.

When these variables were entered into the EASE model, the predicted maximum dermal exposures amounted to 0.1 mg/cm^2/day of the raw material and 1 mg/cm^2/day of the final formulation. These values were then converted to mg/day glycolic acid by factoring in the concentration of glycolic acid (70% and 40% respectively) and the exposed skin area, which by convention was assumed to be predominantly the hands and forearms (2000 cm^2).

As such, the calculated dermal exposure was 140 mg/day from the raw material (70% glycolic acid) and 800 mg/day from the final formulation (40% glycolic acid). Dermal exposure from a final formulation containing 70% glycolic acid as used in skin clinics under medical supervision was calculated at 1400 mg/day.

A2.1.3 Combined inhalation and skin exposure

Combined exposure through inhalation and skin contact expressed as mg/kg/day was calculated as the sum of AL x T x R/BW and DE x T/8/BW, where AL is the airborne level, T the exposure time in hours, R the standard inhalation rate of 1.3 m^3/h for occupational exposure during light work activities (OECD, 1993), BW the standard bodyweight of 70 kg for men and 60 kg for women, and DE the dermal exposure in mg/day.

Formulation plant workers

In a reasonable worst-case scenario based on the manufacture of a 40% formulation from a raw material containing 70% glycolic acid, one worker would spend 2 h at pre-weighing and mixing followed by 4 h at the filling line. The resulting exposures are:

- inhalation: [(2 mg/m^3 x 2 h + 1 mg/m^3 x 4 h) x 1.3 m^3/h] / 70 kg = 0.1 mg/kg/day
- skin contact: [(140 mg/day x 2/8) + (800 mg/day x 4/8)] / 70 kg = 6.2 mg/kg/day
- total: 6.3 mg/kg/day.

Beauty salon workers

Workers in beauty salons may be exposed to inhalation of vapours originating from, and to intermittent skin contact with, products they work with. In a reasonable worst-case scenario, a beautician may perform 3 skin peels per day, each lasting 15-20 min, corresponding to a maximum of 1 h of direct handling of glycolic acid. Assuming that all peels are done with a 40% formulation, the resulting exposures are:

- inhalation: (1 mg/m^3 x 1 h x 1.3 m^3/h) / 60 kg = 0.02 mg/kg/day
- skin contact: [800 mg/day x 1/8] / 60 kg = 1.7 mg/kg/day
- total: 1.7 mg/kg/day.

Skin clinic workers

Nurses and other staff in skin clinics handle and apply formulations containing up to 70% glycolic acid. In a reasonable worst-case scenario, it is assumed that such staff, like beauty salon workers, may perform 3 applications per day, each lasting 15-20 min, corresponding to a maximum of 1 h of direct handling of glycolic acid. During this time they would be exposed to air levels of glycolic acid equal to a maximum of 2 mg/m^3 and have intermittent skin contact with the formulation corresponding to a maximum dermal

exposure to the hands and forearms (2000 cm^2) of 1 mg/cm^2/day of the formulation or 1400 mg/day of glycolic acid. This would result in the following total exposure:

- inhalation: (2 mg/m^3 x 1 h x 1.3 m^3/h) / 60 kg = 0.04 mg/kg/day
- skin contact: [1400 mg/day x 1/8] / 60 kg = 2.9 mg/kg/day
- total: 2.9 mg/kg/day.

A.2.2 Estimated internal exposure and blood levels of glycolic acid in consumers

Blood levels were calculated from a simple, one-compartment kinetic model based on the available human or animal data relating to the absorption, elimination and distribution of glycolic acid. The simulations were carried out using the Micromath Scientific Software. Programming involved modification of package routines to reflect the timing of dosing and the particular input for the various scenarios.

For at-home treatment with leave-on products, systemic uptake was estimated at 3.4 mg/kg/day by multiplying the external exposure (28 mg/kg/day, see section 8.3.1) by 0.12, which was the maximum *in vitro* penetration from a 5% glycolic acid cream applied to skin specimens from several human donors in an amount equal to 3 mg/cm^2 (Kraeling & Bronaugh, 1997). Furthermore, absorption through the skin was assumed to occur at a constant rate, that is, 3.4/24 = 0.14 mg/kg/h for twice daily application of a 10% face cream and body lotion.

The reasonable worst-case scenario for beauty salon treatment was defined as the application of a 40% glycolic acid formulation at pH 3.0 to the arms, legs and back of the hands and feet, massaged into the skin and then rinsed off. According to industry sources, the rinse off takes place after 15 min in the case of neck and hand treatments. For a treatment of the arms, legs and back of the hands and feet the maximum contact time was estimated at 20 min to allow for the additional time needed to manually rinse off a larger skin area. Because of the high concentration of glycolic acid and short exposure time, skin absorption was calculated from the experimentally determined permeability coefficient given in section 9.1.1, the concentration of free glycolic acid in a 40% solution at pH 3.0 estimated from the graph in Figure 5.2, the area of treated skin, and the exposure time, as follows: (3 x 10^{-4} cm/h x 0.9 x 400 mg/mL x 7800 cm^2 x 1/3 h)/60 kg = 4.7 mg/kg.

Other kinetic parameters included the distribution volume of glycolic acid determined at 0.56 L/kg by Jacobsen et al. (1988) and the elimination half-life, which was assumed to be the lower of the two values reported in the literature (see section 9.4), that is, 7 h. For absorption through the skin, the absorption half-life was assumed to be 10 h.

The calculation of a reference blood level in animals was based on a NOAEL of 150 mg/kg, which was the highest oral dose level that did not cause systemic toxicity in a 3-month rat study or maternal or developmental toxicity in pregnant rats exposed to glycolic acid on day 7-21 of gestation (DuPont, 1996, 1999a). Other kinetic parameters included a distribution volume of 0.66 L/kg and an elimination half-life of 3 h as determined by Carney et al. (1997, 1999) in pregnant rats[1]. Absorption was assumed to be complete, with an absorption half-life of 1 h.

The results of the toxicokinetic modelling are shown in the graphs below. The peak blood levels were as follows:

[1] The distribution volume was calculated from the dose (650 mg/kg or 8.55 mmol/kg), the area under the curve (55.9 mmol·h/L) and the elimination half-life.

(A) 2.5 mg/L in humans from twice daily application of a standard quantity of a face cream and a body lotion containing 10% glycolic acid;

(B) 2.6 mg/L in humans from weekly skin peels of the arms, legs and back of the hands and feet with a formulation containing 40% glycolic acid; and

(C) 130 mg/L in rats from a daily oral bolus dose of 150 mg/kg glycolic acid.

A2.3 Factors limiting occupational exposure

The following sections provide detailed considerations in relation to doses for classification of glycolic acid for developmental toxicity.

In assessing the potential harmful effects from inhalation or skin contact with glycolic acid in the workplace, consideration must be given to a number of factors that tend to limit the quantity of glycolic acid that is likely to enter the body. These include the physical properties of the chemical (see section 5.1), the permeability of human skin to glycolic acid (section 9.1.1), and the tendency for concentrated formulations and aerosols (mists) of glycolic acid to cause acute irritation of the skin and respiratory system respectively (section 12.2.2).

A.2.3.1 Potential for volatilisation

Glycolic acid can be characterised as a practically non-volatile substance, with zero vapour pressure in solid form at 25°C and a partial vapour pressure of approximately 2 Pa (0.0144 mm Hg) over a 70% solution at 45°C (Table 5.1). Even upon boiling of pure or dissolved glycolic acid, which causes the chemical to decompose, the vapour pressure does not exceed 1 kPa (7.5 mm Hg). As such, significant airborne exposure to glycolic acid can only occur with substantial mist formation, that is, the generation of aerosols of tiny, air-suspended droplets of an aqueous solution of the chemical. During formulation, the potential for aerosol formation is limited even in worst-case process scenarios such as vigorous stirring and mixing, with air levels of glycolic acid not exceeding 2 mg/m^3 a few cm above an open vessel (DuPont, 1999b). However, the aerosol was found to consist of particles in the 0.4-1 μm or respirable range.

It should be noted that the above findings do not necessarily apply to other uses of glycolic acid in other industries. An analysis of this subject is beyond the scope of this assessment. However, it is known that glycolic acid is an ingredient in water-based industrial cleaning products, which may be applied in spray form or to hard surfaces under pressure, thus resulting in mist formation. Therefore, the possibility of occupational exposure to significant air levels of glycolic acid, although unlikely in the cosmetic industry, cannot be excluded in a wider context.

A2.3.2 Absorption and local irritation from skin contact

Skin absorption from glycolic acid solutions containing >10% glycolic acid at their natural pH (<0.1) is a linear function of concentration, time and the exposed skin area. Its extent in mg/day can be estimated by multiplication of the concentration (mg/mL) with the permeability coefficient (3 x 10^{-4} cm/h), duration of exposure (8 h/day), and exposed skin area (by convention, the hands and forearms = 2000 cm^2). The likelihood of systemic toxic effects from occupational skin exposure to glycolic acid can then be determined from the lowest glycolic acid concentration (C_{min}) that would lead to an internal exposure equal to the NOAEL for developmental effects in experimental animals (150 mg/kg/day, see Table 12.2).

For a person weighing 70 kg the applicable equation is:

$$C_{min} \text{ mg/mL} \times 3 \times 10^{-4} \text{ cm/h} \times 2000 \text{ cm}^2 \times 8 \text{ h/day} = 150 \text{ mg/kg/day} \times 70 \text{ kg}$$

which solved for C_{min} gives a concentration of 2200 mg/mL (or 1500 mg/mL for a 12-h exposure). It corresponds to a concentration in excess of 100%[1]. It can therefore be concluded that developmental toxicity from occupational skin exposure to glycolic acid is unlikely to constitute a practical hazard.

This is supported by animal and *in vitro* observations indicating that formulations containing ≥30% glycolic acid are corrosive (section 10.2.1). Spills on the skin would therefore cause acute discomfort and most likely be rinsed off immediately.

A.2.3.3 Absorption and local irritation from aerosol inhalation

Internal exposure to glycolic acid from the inhalation of aerosols can be calculated in a similar manner. The bioavailability of inhaled glycolic acid is unknown, although the small particle size of aerosols from cosmetic grade raw materials means that it may be high. For the purposes of this evaluation it will be assumed to be 100%.

For a 70-kg worker with an inhalation rate of 1.3 m^3/h (OECD, 1993), the lowest airborne concentration (AC_{min}) of glycolic acid leading to an internal exposure equivalent to 150 mg/kg/day can be calculated from the following equation:

$$AC_{min} \text{ mg/m}^3 \times 1.3 \text{ m}^3\text{/h} \times 8 \text{ h/day} = 150 \text{ mg/kg/day} \times 70 \text{ kg}$$

which solved for AC_{min} gives an airborne concentration of 1000 mg/m^3 (or 670 mg/m^3 for a 12-h exposure)[2]. An aerosol concentration of 1000 mg/m^3 is physically feasible as air levels as high as 3640 mg/m^3 have been achieved experimentally by means of nebulisation (DuPont, 1998c). On the other hand, the available inhalation studies in experimental animals showed serious irritation of the respiratory tract at airborne exposures ≥420 mg/m^3 (DuPont, 1998c). It is therefore unlikely that a worker would tolerate more than very brief periods of inhalation of glycolic acid aerosols at the levels required to attain an internal dose that is equivalent to the NOAEL for developmental effects in experimental animals.

A.2.3.4 Absorption from combined skin contact and aerosol inhalation

Similar calculations can be applied to scenarios involving combined skin contact and inhalation of glycolic acid. An airborne exposure equal to the level associated with respiratory system irritation in animals (420 mg/m^3) would result in an internal dose of 420 mg/m^3 x 1.3 m^3/h x 8 h/day / 70 kg = 62 mg/kg/day, which means that the balance of 150 – 62 mg/kg/day = 88 mg/kg/day would have to come from skin contact. Substituting this dose for the NOAEL in the equation given in section A2.3.2 and solving for C'_{max} gives a concentration of 1280 mg/mL glycolic acid for an 8-h and of 860 mg/mL for a 12-h exposure (or 1170 mg/mL and 740 mg/mL respectively for a 60-kg worker). Even the lowest of these C'_{max} values corresponds to a solution containing about 60% glycolic acid. Therefore, combined airborne exposure and skin contact is unlikely to result in an internal dose equivalent to the NOAEL in animals based on developmental effects from repeated exposure.

[1] For a female worker weighing 60 kg, C_{min} is 1900 mg/mL (or 1250 mg/mL for a 12-h exposure). This corresponds to a solution containing >100% or, for a 12-h exposure, >80% glycolic acid.
[2] For a female worker weighing 60 kg, AC_{min} is 865 mg/m^3 (or 575 mg/m^3 for a 12-h exposure).

[Graphs]

Appendix 3

Studies Excluded from Assessment

This appendix provides a list of references to animal and human studies that were available for assessment but were not reviewed for the reasons set out in sections 10 and 11.

Acute toxicity

Delphaut J (1951) A study of hepato-renal diuresis. VIII. Pharmacodynamic studies. Médicin Tropical, **12**:641.

Delphaut J, Bernard P (1951) A study of hepato-renal diuresis. IV. Trials with glycolic acid. Médicin Tropical, **12**:634-638.

DuPont (1940) Report No. MR-86-1, HL-2-40. Newark, DE, Haskell Laboratory.

DuPont (1962) Hydroxyacetic acid 70% technical: Federal Hazardous Substances Labelling Act tests. Report No. MR-644-1, HL-44-62. Newark, DE, Haskell Laboratory.

DuPont (1964) Report No. MR-712-1, HL-33-64.

DuPont (1973) Report No. MR-1968-1, HL-418-73. Newark, DE, Haskell Laboratory.

DuPont (1981) Acetic acid, hydroxy-: Inhalation median lethal concentration (LC50) in rats. Report No. MR-3817-1, HL-862-81. Newark, DE, Haskell Laboratory.

Corrosivity and irritation

Carpenter CP, Smyth HF (1946) Chemical burns of the rabbit cornea. American Journal of Ophthalmology, **29**:1363-1372.

Dermatech (1993) Mixed fruit acid (MFA) dermal safety: 10 day primary irritancy study. Unpublished data submitted by CTFA (95-AHA-0108). Washington, DC, Cosmetic Ingredient Review.

DuPont (1940) Corneal cloudiness (eye fog) from material formed in the glycol process at Belle. Report No. MR-86-1, HL-2-40. Newark, DE, Haskell Laboratory.

DuPont (1962) Hydroxyacetic acid 70% technical: Federal Hazardous Substances Labelling Act tests. Report No. MR-644-1, HL-44-62. Newark, DE, Haskell Laboratory.

DuPont (1964) Hydroxyacetic acid (70%), phosphoric acid (85%): Eye irritation test. Report No. MR-712-2, HL-33-64. Newark, DE, Haskell Laboratory.

DuPont (1968) Preliminary test record. Dosing for variety of injury – demonstration. Report No. MR-0010-131. Newark, DE, Haskell Laboratory.

DuPont (1973) Hydroxyacetic acid 70%: Department of Transportation skin corrosion test on rabbit skin. Report No. MR-1968-1, HL-418-73. Newark, DE, Haskell Laboratory.

Skin sensitisation

Unilever (1994) Glycolic acid: Safety assessment for use in skin care products (draft). Unpublished data submitted by CTFA. Washington, DC, Cosmetic Ingredient Review.

Subacute-chronic toxicity

Conner RT (1943) Chronic toxicity study of sodium hydroxyacetate in rats. General Foods Corporation. Cited in CIR (1998).

Krop S, Gold H (1945) On the toxicity of hydroxyacetic acid after prolonged administration: Comparison with its sodium salt and citric and tartaric acids. Journal of the American Pharmaceutical Association, **34:**86-89.

Rose WC, Carter H (1943) Toxicity study of glycolic acid. General Foods Corporation. Cited in CIR (1998).

Sanchez IM, Bull RJ (1990) Early induction of reparative hyperplasia in the liver of B6C3F1 mice treated with dichloroacetate and trichloroacetate. Toxicology, **64:**33-46.

Silbergeld S, Carter HE (1959) Toxicity of glycolic acid in male and female rats. Archives of Biochemistry and Biophysics, **84**:183-187.

Genetic toxicity

DuPont (1981) Acetic acid, hydroxy-: Mutagenicity evaluation in Salmonella typhimurium. Report No. MR-3815-1, HL-608-81. Newark, DE, Haskell Laboratory.

Yamaguchi T, Nakagawa K (1983) Mutagenicity of and formation of oxygen radicals by trioses and glyoxal derivatives. Agricultural and Biological Chemistry, **47**:2461-2465.

Human studies

Ash K, Lord J, Zukowski M, McDaniel DH (1998) Comparison of topical therapy for striae alba (20% glycolic acid/0.05% tretinoin versus 20% glycolic acid/10% L-ascorbic acid). Dermatologic Surgery, **24**:849-856.

Bernstein EF, Uitto J (1995) Connective tissue alterations in photoaged skin and the effects of alpha hydroxy acids. Journal of Geriatric Dermatology, **3**:7A-18A.

Ellis DAF, Tan AKW, Ellis CS (1995) Superficial micropeels: Glycolic acid and alpha-hydroxy acid with kojic acid. Facial Plastic Surgery, **11**, 15-21.

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Leyden JJ, Lavker RM, Grove G, Kaidbey K (1995) Alpha hydroxy acids are more than moisturizers. Journal of Geriatric Dermatology, **3**:33A-37A.

Morganti P, Randazzo SD, Palombo P, Bruno C (1994) Topical gelatin-glycine and alpha hydroxy acids for photoaged skin. Journal of Applied Cosmetology, **12**:1-10.

Moy LS, Murad H, Moy RL (1993) Glycolic acid peels for the treatment of wrinkles and photoaging. Journal of Dermatologic Surgery and Oncology, **19**:243-246.

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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. Dermatologic Surgery, **22**:449-452.

Rubin MG (1994) The clinical use of alpha hydroxy acids. Australasian Journal of Dermatology, **35**:29-33.

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Van Scott EJ, Yu RJ (1984) Hyperkeratinization, corneocyte adhesion, and alpha hydroxy acids. Journal of the American Academy of Dermatology, **11**:867-879.

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AMA Laboratories (1993a) Fifty human subject repeat insult patch test skin irritation/sensitization evaluation. Dated 19 May 1993. Unpublished data submitted by CTFA (95-AHA-0002). Washington, DC, Cosmetic Ingredient Review.

AMA Laboratories (1993b) Fifty human subject repeat insult patch test skin irritation/sensitization evaluation. Dated 27 August 1993. Unpublished data submitted by CTFA (95-AHA-0005). Washington, DC, Cosmetic Ingredient Review.

AMA Laboratories (1993c) Fifty human subject repeat insult patch test skin irritation/sensitization evaluation. Dated 27 August 1993. Unpublished data submitted by CTFA (95-AHA-0003). Washington, DC, Cosmetic Ingredient Review.

AMA Laboratories (1994) Fifty human subject repeat insult patch test skin irritation/sensitization evaluation. Dated 22 July 1994. Unpublished data submitted by CTFA (95-AHA-0004). Washington, DC, Cosmetic Ingredient Review.

An-eX (1994) Human skin penetration of radiolabelled glycolic acid – in vitro assessment. Unpublished data submitted by CTFA (95-AHA-43). Washington, DC, Cosmetic Ingredient Review.

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