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Wilmington, DE 19898

DuPont SHE Excellence Center

AR201-13125

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July 17, 2001

Christine Todd Whitman
Administrator
U.S. EPA
P.O. Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

Dear Administrator Whitman:

E. I. du Pont de Nemours & Co., Inc. is pleased to submit the proposed test plan along with the robust summary for the chemical Glycolic acid, CAS# 79141. DuPont understands there will be a 120-day review period for the test plan and that all comments received by EPA will be forwarded to DuPont for consideration.

This submission includes one electronic copy in .pdf format.

Please feel free to contact me with any questions or concerns you might have concerning this submission at Edwin.L.Mongan-1@usa.dupont.com or 302-773-0910.

Sincerely

Edwin L. Mongan III
Manager, Environmental Stewardship

ELM
Enclosure

CC: Charles Auer – U.S. EPA

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10-July-2001

ROBUST SUMMARY FOR GLYCOLIC ACID

Summary

Glycolic acid is a colorless, odorless, crystalline solid, but is usually supplied as a 70% solution. In this form it is a clear, colorless liquid with a mild odor. As a 70% solution, it has a saturation point of 10°C, boiling point of 112°C, and is non-flammable.

The Henry's Law constant for glycolic acid is estimated to be 8.5×10^{-8} atm-m^3/mole, therefore glycolic acid will not volatilize rapidly from water surfaces. The estimated half-life from a river is 373.8 days and 2721 days from a model lake based on volatilization alone, with no accounting for biodegradation. If discharged into water, it is estimated that glycolic acid will partition predominately in the water compartment. Glycolic acid biodegrades quickly, with and without acclimation using a variety of microbial inoculum. Accordingly, glycolic acid is not expected to biopersist or bioaccumulate in the environment.

Glycolic acid exhibits low toxicity to aquatic organisms. Based on measured test concentrations, the following endpoint values have been reported: 96-hour LC_{50} with fathead minnows of 168 ppm and 48-hour EC_{50} with *Daphnia* of 14 1 mg/L. Glycolic acid caused stimulation of algal growth at pH 7.5 under illumination, but when used as a carbon source, did not support heterotrophic growth in the dark.

Glycolic acid (70% solution) is slightly toxic via the oral route, having an LD_{50} in rats of 193 8 mg/kg. It is moderately toxic via the inhalation route in male rats with a 4-hour LC_{50} of 3.6 mg/L. Glycolic acid is a skin and eye corrosive, but it is not a skin sensitizer in animals. However, numerous studies in humans with cosmetic products containing lower percentages of glycolic acid have shown some skin irritation potential, but no corrosivity. Repeated exposures to glycolic acid via inhalation produced liver, spleen, thymus changes, and gastrointestinal tract alterations. Repeated administration of glycolic acid to rats by oral intubation caused decreases in body weight, body weight gain, food consumption, and food efficiency. In addition, toxicologically significant changes in hematologic measurements, clinical chemistry, and urinalysis parameters, as well as kidney lesions were observed. Maternal and developmental toxicity of crystalline, 99.6% pure, glycolic acid in the rat was seen at 300 and 600 mg/kg/day. The maternal and developmental NOEL was 150 mg/kg/day, thus glycolic acid is not considered a unique developmental hazard to the conceptus. Glycolic acid did not affect reproductive performance in rats during a one-generation reproduction study following a 90-day feeding study. The compound was negative in the *in vitro* bacterial reverse mutation assay (*Salmonella* and *E. coli*). Glycolic acid produced a positive response in the *in vitro* mouse lymphoma assay only at excessively high concentrations under activated conditions, but was negative in the *in vivo* mouse micronucleus assay.

General Exposure Information

Glycolic acid is an a-hydroxy acid that occurs widely in **nature.** It is present in several edible fruits, vegetables, and beverages at concentrations ranging up to approximately 56 ppm. Most commercially used glycolic acid, however, is manufactured through various processes involving

chemical synthesis. The annual U.S. market of 25-30 million lbs. is primarily supplied through domestic production, with imports accounting for approximately 5% of sales.

Glycolic acid is primarily used in a broad range of industrial products, but it also finds application in a few consumer formulations. Applications include removal of mineral scale, acidity control (pH adjustment), water treatment, intermediate in chemical synthesis, and personal care products. Most applications start with glycolic acid as an approximate 70% aqueous solution, which is diluted significantly for the end-use.

Approximate applications as a percentage of sales volume are: household, institutional, and industrial cleaning = 35%; chemicals manufacture = 18%; pH control = 11%; electronics applications = 7%; textile applications = 5%; metal finishing = 4%; oil and gas treatment = 4%; water treatment = 2%; and miscellaneous = 14%. Miscellaneous applications include leather and paper manufacture, laundry aid component, additive in adhesives, and personal care products (primarily facial creams). Glycolic acid is an FDA-approved indirect food additive. The amount of glycolic acid used in these applications varies from about 0.2% to about 30% of the final product weight. The range is widest in the industrial, household, and institutional cleaning segment (0.2-20%).

Exposure through natural occurrence: Glycolic acid is naturally present in a variety of fruits, vegetables, meats, and beverages in concentrations ranging from approximately 0.5-5.6 mg/100 g (vegetables), approximately 5-50 mg/kg (fruits), l-5 mg/kg (beef and chicken), and approximately 0.5-30 mg/kg (various common non-alcoholic beverages). The dietary intake of glycolic acid from these sources is estimated to be about 1.0 mg/kg/day.

Exposure ***during manufacture:*** Glycolic acid is manufactured in closed systems where reactors and downstream equipment are hard-piped, to minimize both losses to the environment and potential exposure to workers. Routine air monitoring in DuPont facilities indicate workplace concentrations to average <0.4 mg/m^3, 8-hour time weighted average (TWA). Continuous exposure at this level for an entire 8-hour shift would correspond to a daily intake of <0.04 mg/kg/day. Glycolic acid is normally packaged and sold in drums or in bulk. Air monitoring of drumming and bulk loading operations show typical exposure levels to be <0.2 and <0.4 mg/m^3, respectively. This would correspond to an intake of <0.02 and <0.04 mg/kg/day for exposed workers, assuming continuous exposure at these levels for an entire 8-hour shift.

Exposure during use (product formulation): In the majority of glycolic acid applications, customers blend the chemical with other ingredients. Typical air monitoring data from household cleaner and personal care production operations, most of which involve partially enclosed manufacturing systems, show levels below 0.10 mg/m^3, 8-hour TWA. This corresponds to a daily intake of <0.01 mg/kg/day for exposed workers.

Exposure during use (household or institutional cleaner use): Bathroom soap scum cleaners containing glycolic acid are typically applied using a hand pump spray followed by wiping and rinsing. The typical estimated daily exposure to glycolic acid for workers handling these

products is about 0.06 mg/kg/day for household use and about 0.10 mg/kg/day for institutional use.

Based on the above, the dietary intake of glycolic acid from naturally occurring foods exceeds the intake that might result from exposure to the compound during manufacture and use in all industrial applications. DuPont's Acceptable Exposure Limit (AEL or safe exposure limit) for glycolic acid, which is based on an assessment of all available toxicity data on the compound, is 10 mg/m^3, 8- and 12-hour TWA.

Exposure during use *(personal* care *applications):* Glycolic acid formulations have been used by dermatologists for over 25 years for cosmetology and the treatment of a variety of shin disorders. In the last decade, glycolic acid has been included as a component in several over-the-counter personal care products, which include exfoliants, pH adjusters, and shin conditioning agents. Since the concentrations used, the condition and duration of use, and the pH range of these products span a broad spectrum, the estimation of overall or average exposure is infeasible. It is recognized, however, that the amount of glycolic acid systemically absorbed through the shin in 24 hours ranges from about 30% to 3% of the quantity applied for products ranging in pH from 3 to 7, respectively. While localized irritation at the site of application has been observed, no systemic toxicity has been noted as a result of these dermal applications. Several toxicity studies on a variety of these products by independent dermatologists and toxicologists have shown that glycolic acid is safe for personal care use when it is formulated and used within recommended pH limits and concentrations to minimize skin irritation,

TEST PLAN FOR GLYCOLIC ACID

Glycolic acid CAS No. 79-14-l	Data Available	Data Acceptable	Testing Required
	Y/N	Y/N	Y/N
PHYSICAL/CHEMICAL CHARACTERISTICS			
Melting Point	Y	Y	N
Boiling Point	Y	Y	N
Vapor Pressure	Y	Y	N
Partition Coeffieient	Y	Y	N
Water Solubility	Y	Y	N
ENVIRONMENTAL FATE			
Photodegradation	Y	Y	N
Stability in Water	Y	Y	N
Transport (Fugacity)	Y	Y	N
Biodegradation	Y	Y	N
ECOTOXICITY			
Acute Toxicity to Fish	Y	Y	N
Acute Toxicity to Invertebrates	Y	Y	N
Acute Toxicity to Aquatic Plants	Y	Y	N
MAMMALIAN TOXICITY			
Acute Toxicity	Y	Y	N
Repeated Dose Toxicity	Y	Y	N
Developmental Toxicity	Y	Y	N
Reproductive Toxicity	Y	Y	N
Genetic Toxicity Gene Mutations	Y	Y	N
Genetic Toxicity Chromosomal Aberrations	Y	Y	N

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The studies listed below were selected to represent the best available study design and execution for these HPV toxicity endpoints. Other data of equal or lesser quality are not summarized, but are listed as additional references in this document. Additionally, this summary does not contain references to glycolic acid used in treatment of dermatologic conditions.

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1.0 Substance Information

CAS Number:	79-14-1
Chemical Name:	Acetic acid, hydroxy-
Structural **Formula:**	$HO–CH_2–COOH$
Other Names:	Glycolic acid Hydroxyethanoic acid HAA Glycollic acid Glypure® alpha-Hydroxyacetic acid Gluco-hydroxy-acid 2-Hydroxyacetic acid
Exposure Limits:	3 ppm (10 mg/m^3), 8- and 12-hour TWA: DuPont Acceptable Exposure Limit (AEL)

2.0 Physical/Chemical Properties

2.1 Melting Point

Value:	78-79°C (solid)
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	unknown
Reference:	Sax, N. I. and R. J. Lewis, Sr. (eds.) (1987). Hawley's Condensed Chemical Dictionary, 11th ed., p. 620, Van Nostrand Reinhold Co., New York, NY.
Reliability:	Not assignable because limited study information was available.

Value:	10°C (Saturation point of a 70% solution)
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	Unknown
Reference:	Sax, N. I. and R. J. Lewis, Sr. (eds.) (1987). Hawley's Condensed Chemical Dictionary, 11th ed., p. 620, Van Nostrand Reinhold Co., New York, NY.

Reliability: Not assignable because limited study information was available.

Additional References for Melting Point:

Solid

Budavari, S. (ed.) (1996). The Merck Index, 12th ed., p. 766, Merck & Co., Inc., Whitehouse Station, NJ,

DuPont Co. (2000). Material Safety Data Sheet No. DUO05926 (March 8).

Hoechst AG (1994). Product Information, Glycolic Acid 57% in Aqueous Solutions, Department of Marketing – Chemicals (1 1/21/94) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Lewis, R. J., Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1882, John Wiley & Sons, Inc., New York.

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 697, Van Nostrand Reinhold Co., New York.

70% Solution

DuPont Co. (1985). Product Information Bulletin: Hydroxyacetic Acid 70% Solution. Technical Properties, Uses, Storage, and Handling.

DuPont Co. (1999). Material Safety Data Sheet No. DUO05927 (December 7).

57% Solution

Hoechst AG (1994). Product Information, Glycolic Acid 57% in Aqueous Solutions, Department of Marketing – Chemicals (1 1/2 1194) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Hoechst AG (1996). EC Safety Data Sheet, Glycolic Acid in 57% Aqueous Solution (6/19/96) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

2.2 Boiling Paint

Value:	No Data
Decomposition:	Decomposes at 100°C (solid)
Pressure:	No Data
Method:	No Data
GLP:	unknown

Reference:	Gerhartz, W. (exec. ed.) (1 P&present). Ullmann's Encyclonedia of Industrial Chemistry, 5th ed., Vol. Al, p. 509, VCH Publishers, Deerfield Beach, FL.
Reliability:	Not assignable because limited study information was available.

Value:	112°C (70% solution)
Decomposition:	No Data
Pressure:	760 mm Hg
Method:	No Data
GLP:	unknown
Reference:	DuPont Co. (1999). Material Safety Data Sheet No. DUO05927 (December 7).
Reliability:	Not assignable because limited study information was available.

Additional References for Boiling Point:

Solid

Lewis, R. J., Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1882, John Wiley & Sons, Inc., New York.

Verschueren, K. (1983). Handbook of Environmental Data on Organic Chemicals, 2nd ed., p. 697, Van Nostrand Reinhold Co., New York.

70% Solution

DuPont Co. (1985). product Information Bulletin: Hydroxyacetic Acid 70% Solution. Technical Properties, Uses, Storage, and Handling.

Hoechst AG (1994). Product Information, Glycolic Acid 57% in Aqueous Solutions, Department of Marketing – Chemicals (1 1/21/94) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Hoechst AG (1996). EC Safety Data Sheet, Glycolic Acid in 57% Aqueous Solution (6/19/96) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

2.3 Density

Value:	1.36 g/cm^3 (solid)
Temperature:	26°C
Method:	No Data
GLP:	unknown
Results:	No additional data.

Reference:	DuPont Co. (2000). Material Safety Data Sheet No. DUO05926 (March 8).
Reliability:	Not assignable because limited study information was available.

Value:	1.25 g/cm^3 (70% solution)
Temperature:	26°C
Method:	No Data
GLP:	unknown
Results:	No additional data.
Reference:	DuPont Co. (1999). Material Safety Data Sheet No. DUO05927 (December 7).
Reliability:	Not assignable because limited study information was available.

Additional References for Density:

Solid: None Found.

70% Solution

DuPont Co. (1985). Product Information Bulletin: Hydroxyacetic Acid 70% Solution. Technical Properties, Uses, Storage, and Handling.

57% Solution

Hoechst AG (1994). Product Information, Glycolic Acid 57% in Aqueous Solutions, Department of Marketing – Chemicals (1 1/2 1/94) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Hoechst AG (1996). EC Safety Data Sheet, Glycolic Acid in 57% Aqueous Solution (6/1 9/96) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

% Glycolic Acid Not Specified

Freier (ed.) (1976). Aqueous Solutions: Data for Inorganic and Organic Compounds 1, p. 277, Walter de Gruyter, Berlin, Germany, New York (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Gerhartz, W. (exec. ed.) (1985 to present). Ullmann's Encyclopedia of Industrial Chemistry, 5th ed., Vol. Al, p. VA13 509, VCH Publishers, Deerfield Beach, FL.

2.4 Vapor Pressure

Value:	0.017 mm Hg

Temperature:	25°C
Decomposition:	No Data
Method:	Extrapolated
GLP:	Not Applicable
Reference:	Daubert, T. E. and R. P. Danner (1985). Data Compilation Tables of Properties of Pure Compounds, p. 450, American Institute of Chemical Engineers (SRC Database). Daubert, T. E. and R. P. Danner (1991). Physical and Thermodynamic Properties of Pure Chemicals: Data Compilation. Supplement 1, Design Institute for Physical Property Data, American Institute of Chemical Engineers, Hemisphere Pub. Corp., New York, NY (SRC Database).
Reliability:	Not assignable because limited study information was available.

Value:	Nil (70% solution)
Temperature:	No Data
Method:	No Data
GLP:	unknown
Reference:	DuPont Co. (1999). Material Safety Data Sheet No. DUO05927 (December 7).
Reliability:	Not assignable because limited study information was available.

Additional References for Vapor Pressure:

Solid

Daubert, T. E. and R. P. Danner (1989). Thermodynamic Properties of Pure Chemicals Data Compilation, Taylor and Francis, Washington, DC (HSDB/5227).

DuPont Co. (2000). Material Safety Data Sheet No. DUO05926 (March 8).

70% Solution: None Found.

57% Solution

Hoechst AG (1994). Product Information, Glycolic Acid 57% in Aqueous Solutions, Department of Marketing – Chemicals (1 1/21/94) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Hoechst AG (1996). EC Safety Data Sheet, Glycolic Acid in 57% Aqueous Solution (6/19/96) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

2.5 Partition Coefficient (log Kow)

Value:	-1.11
Temperature:	19°C
Method:	Measured; estimated accuracy ±20%
GLP:	Unknown
Reference:	Collander (1951). Acta Chem. Scand., 5:774-780 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).
Reliability:	Not assignable because limited study information was available.

Additional References for Partition Coefficient (log Kow):

Anon. (1996). Epiwin Version 2.0 Syracuse Research Corporation, Environmental Science Center Merill Lane, Syracuse, NY 132 10 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Hansch , C. and A. Leo (1987). The Log P Database, Pomona College, Claremont, CA (HSDB/5527).

Hoechst AG (1996). Internal Calculation, Dept. SU Environment/Product Safety (8/27/96) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Leo, A. J. (1978). Report on the Calculation of Octanol/Water Log P Values for Structures in EPA Files (ISHOW/301724).

Lewis, R. J., Sr. (2000). Sax's Dangerous Properties of Industrial Materials, 10th ed., p. 1882, John Wiley & Sons, Inc., New York.

Verschueren, K. (1983). Handbook of Evironmental Data on Organic Chemicals, 2nd ed., p. 697, Van Nostrand Reinhold Co., New York.

2.6 Water Solubility

Value:,	Approximately 2440 g/kg H_2O (>99% glycolic acid)
Temperature:	25°C
pH/pKa:	Approximately 1.8 @ 570 g/L
Method:	According to Apelblat and Manzurola (1987). J. Chem. Thermodynamics 19:3 17. original information includes mole fraction 0.3695 (corresponds to about 0.586 mole glycolic acid/mol H_2O).
GLP:	unknown
Reference:	Hoechst AG (1996). EC Safety Data Sheet, Glycolic Acid

57% in Aqueous Solution (5/22/1996) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Reliability: Not assignable because limited study information was available.

Additional References for Water Solubility:

Solid

DuPont Co. (2000). Material Safety Data Sheet No. DUO05926 (March 8).

Budavari, S. (ed.) (1996). The Merck Index, 12th ed., p. 766, Merck & Co., Inc., Whitehouse Station, NJ.

Sax, N. I. and R. J. Lewis, Sr. (eds.) (1987). Hawley's Condensed Chemical Dictionary, 1 1th ed., p. 620, Van Nostrand Reinhold Co., New York, NY.

70% Solution

DuPont Co. (1999). Material Safety Data Sheet No. DUO05927 (December 7).

Freier (ed.) (1976). Aqueous Solutions: Data for Inorganic and Organic: Compounds 1, p. 277, Walter'de Gruyter, Berlin, Germany, New York (cited in IUCLID (1698). IUCLID Data Sheet "Glycolic acid" (October 6)).

Gerhartz (ed.) (1985). Ullmann's Encvclooedia of Industrial Chemistry, 5th ed., Vol. A13, pp. 507417, VCH Verlagsges.mbH, Weinheim. (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Hoechst AG (1993). EC Safety Data Sheet, Glycolic Acid 70% in Aqueous Solution (5/22/93) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid' (October 6)).

% Solution Not Specified

Van Ness (1978Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed., Vol. 13, pp. 80-103 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

2.7 Flash Point: Not Applicable.

2.8 Flammability

Results: Contact with active metals may produce flammable hydrogen gas (solid)

Method: No Data

GLP:	unknown
Reference:	DuPont Co. (2000). Material Safety Data Sheet No. DUO05926 (March 8).
Reliability:	Not assignable because limited study information was available.

Results:	Non-flammable (70% solution)
Method:	No Data
GLP:	unknown
Reference:	DuPont Co. (1999). Material Safety Data Sheet No. DUO05927 (December 7).
Reliability:	Not assignable because limited study information was available.

Additional References fur Flammability:

Solid: None Found.

70% Solution

DuPont Co. (1985). Product Information Bulletin: Hydroxyacetic Acid 70% Solution. Technical Properties, Uses, Storage, and Handling.

3.0 Environmental Fate

3.1 Photodegradation

Concentration:	100 mmol/L
Temperature:	25°C
Direct Photolysis:	Degradation was approximately 20% after 90 minutes. The oxygen consumption was 0.2 mL/hr. The reaction was somewhat accelerated catalytically by Fe(III)-ions (1.8 mL/hr). Additional presence of the sensitizer anthraquinone-2-sulfonate brought about a further slight acceleration of the oxygen consumption (3.4 mL/hr).
Indirect Photolysis:	Not Applicable
Breakdown Products:	Formaldehyde was found as a photoproduct.
Method:	Glycolic acid was photodegraded by photolysis in water using a mercury lamp as the light source, calculated light spectrum of 240-300 nm, and concentration of substance of 100 mmol/L @ 25°C. The test conditions included reaction volume of 20 mL and irradiation in redistilled water in a quartz vessel. The parameter was O_2 consumption (determined volumetrically) and analysis of the reaction mixture by capillary isotachophoresis.
GLP:	unknown

Reference: Klementova and Wagnerova (1990). Mar. Chem., 30:89-103 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Reliability: Medium because a suboptimal study design was used.

Additional References for Photodegradation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Hoechst AG (1996). Internal Calculation, Dept. SU Environment/Product Safety (8/27/96) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Kolesnikow et al. (1967). Biokhimia, 33:553-556 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

3.2 Stability in Water

Concentration: Not Applicable

Half-life: The WVOL program estimates the volatilization half-lives from a model river and lake using the methodology from Lyman et al., 1990, Estimation Handbook (adsorption to suspended solids and sediments is ignored). The user can input an experimental water solubility, vapor pressure, or Henry's Law constant, or EPI will automatically estimate a Henry's Law Constant from SRC's Henry program for this calculation. WsKow estimates the water solubility (WSol) of an organic compound using the compounds log octanol-water partition coefficient (Kow).

The Henry's Law constant for glycolic acid is estimated to be 8.54×10^{-8} atm-m^3/mole (Henry v3.10 Program, Bond SAR Method in SRC Epiwin v3.05) from its estimated vapor pressure, 0.017 mm Hg (Modified Grain Method) and water solubility, 2.44×10^6 mg/L (Hoechst AG, 1996). This Henry's Law constant indicates that glycolic acid will not volatilize rapidly from water surfaces. Based on this Henry's Law constant, the estimated volatilization half-life from a model river (1 m deep, flowing 1 m/sec, wind velocity of 3 m/sec) is approximately 373.8 days (Epiwin v3.05). The estimated volatilization half-life from a model lake (1 m deep, flowing 0.05 m/sec, wind velocity of 0.5 m/sec) is approximately 272 1 days (Epiwin v3.05).

% Hydrolyzed: Not Applicable

Method:	Modeled Data: Syracuse Research Corporation EPIWIN v3.05.
GLP:	No
Reference:	Lyman, W. J. et al. (1990). Handbook of Chemical Pronerty Estimation Methods, American Chemical Society. Hoechst AG (1996). EC Safety Data Sheet, Glycolic Acid 57% in Aqueous Solution (5/22/1 996) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)). The following journal article describes the estimation methodology: Meylan, W. M. et al. (1996). Environ. Toxicol. Chem., 15:100-106.
Reliability:	Estimated value based on accepted model.

Additional Reference for Stability in Water:

Data from this additional source support the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Hoechst AG (1996). Internal Calculation, Dept. SU Environment/Product Safety (8/27/96) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

3.3 Transport (Fugacity)

Media:	Air, Water, Soil, Sediments	
Distributions:	Air:	0.0018%
	Water:	99.8%
	Soil:	0.0115%
	Sediment:	0.149%
Adsorption Coefficient:	Not Applicable	
Desorption:	Not Applicable	
Volatility:	Not Applicable	
Method:	Calculated according to Mackay, Level III, Syracuse Research Corporation Epiwin Version 3.05. Emissions (1000 kg/hr) to water compartment using EPA Model Defaults. Data Used: Molecular Weight: 76.05 Henry's Law Constant: 8.54×10^{-8} atm-m^3/mole (Henry	

Database)
Vapor Pressure: 0.017 mm Hg (Daubert and Danner, 1985; 1991)
Log Kow : -1 .1 1 (Kowwin program)
Soil Koc : 0.0318 (Log Kow estimate)

GLP: Not Applicable

Reference: Daubert, T. E. and R. P. Danner (1985). Data Compilation Tables of Properties of Pure Compounds, p. 450, American Institute of Chemical Engineers (SRC Database).

Daubert, T. E. and R. P. Danner (1991). Physical and Thermodynamic Proaerties of Pure Chemicals: Data Compilation. Supplement 1, Design Institute for Physical Property Data, American Institute of Chemical Engineers, Hemisphere Pub. Corp., New York, NY (SRC Database).

Syracuse Research Corporation EPIWIN v3.05 contains a Level III fugacity model. The methodology and programming approach was developed by Dr. Donald Mackay and co-workers which is detailed in:

Mackay, D. (1991). Multimedia Environmental Models: The Fueacitv Annroach, pp. 67-l 83, Lewis Publishers, CRC Press.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1618-1626.

Mackay, D. et al. (1996). Environ. Toxicol. Chem., 15(9):1627-1637.

Reliability: Estimated value based on accepted model.

Additional Reference for Transport (Fugacity):

Data from this additional source supports the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Hoechst AG (1996). Internal Calculation, Dept. SU Environment/Product Safety (8/27/96) (cited in IUCLID (1998). IUCLID Data Sheet "'Glycolic acid" (October 6)).

3.4 Biodegradation

Value: 89.6% after 7 days

Breakdown Products: No Data

Method:	The Closed Bottle Test was performed to determine if glycolic acid was "readily biodegradable.'* The Time-O DO (Dissolved Oxygen) was measured and was considered the starting point. The Closed Bottle Test is a closed system, therefore, no additional dissolved oxygen was added to the system for the duration of the test. Biodegradation was measured as the loss of dissolved oxygen within the closed bottle. Glycolic acid was readily biodegradable, demonstrating 89.6% biodegradability after 7 days. The 28-day test was terminated after 7 days since glycolic acid demonstrated "ready biodegradability" within the first week. The control chemical, sodium acetate, exceeded 60% biodegradability within 14 days, therefore, the test is valid. The Theoretical Oxygen Demand of glycolic acid was calculated as 0.5 mg O_2 per mg of active substance.
GLP:	No
References:	DuPont Co. (1994). Unpublished Data, AEM Laboratory Report No. 142-94.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Biodegradation:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Babeu, L. and D. D. Vaishnav (1987). J. Ind. Microbiol., 2:107-1 15 (also cited in BIODEG/100610).

Billen et al. (1980). Estuarine Coastal. Mar. Sci., 11:279-294 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Heukelekian, H. and M. C. Rand (1955). J. Water Pollut. Contr. Assoc., 27:1040-1053 (also cited in BIODEG/100611).

Hoechst AC (1979). Unpublished Data (10/5/79) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Howard, P. H. et al. (1992). Environ. Toxicol. Chem., 11(5):593-603.

Ladd et al. (1982). Appl. Environ. Microbiol., 44:32 l-329 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

McKinney, R. E. et al. (1956). Sew, Indust. Wastes, 28:547-557.

Pitter and Chudoba (eds.) (1990). Biodegradability of Organic Substances in the Aquatic Environment, p. S. 275, CRC Press (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

3.5 Bioconcentration:

Value:	BCF = 3.162 (log BCF = 0.5). This estimated BCF suggests the potential for bioconcentration in aquatic organisms is low.
Method:	Bioconcentration factor (BCF) was calculated by BCFWIN Computer Program, Version 2.13, Syracuse Research Corporation. The estimated value was calculated using a log Kow of -1.11 and a regression-derived equation.
GLP:	Not Applicable
Reference:	The estimation methodology used by BCFWIN is described in the following document prepared for the U.S. Environmental Protection Agency (OPPT): "Improved Method for Estimating Bioconcentration Factor (BCF) from Octanol-Water Partition Coefficient," SRC TR-97-006 (2nd Update), July 22, 1997; prepared for Robert S. Boethhng, EPA-GPPT, Washington, DC, Contract No. 68-D5-0012; prepared by William M. Meylan, Philip H. Howard, Dallas Aronson, Heather Printup, and Sybil Gouchie, Syracuse Research Corp., Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212.
Reliability:	Estimated value based on accepted model.

Additional References for Bioconcentration: None Found.

4.0 Ecotoxicfty

4.1 Acute Toxicity to Fish

Type:	**96-hour LC_{50}**
Species:	*Pimephales promelas* (fathead minnow)
Value:	168 ppm (0.0164%; 95% confidence interval, 0.0154-0.0175%)
Method:	Glass aquaria (20 L) containing 15 L of test solution (19 cm depth) were employed. Ten fish were randomly added to each aquarium (1 aquarium per concentration). Fish were not fed for 48 hours prior to the test, or during the test. Loading was 0.081 g/L. Test solutions were held between 21.9 and 22.7°C (mean 22°C) with aeration and a

photoperiod of 16 hours light (350 Lux) versus 8 hours darkness. Dissolved oxygen and pH were measured in the water control and in all test concentrations before fish were added at the beginning of the test and daily thereafter. Total alkalinity, EDTA hardness, and conductivity of the water control were measured before fish were added at the beginning of the test.

Fathead minnows (aged 103-158 days, mean length 2.1 cm, and mean weight 0.12 g) were exposed to nominal test concentrations of glycolic acid of 0 (water control), 0.0064, 0.0081, 0.010, 0.013, 0.016, and 0.020% (v/v). Observations were made every 24 hours. No chemical analyses of the test solutions were performed. The LC_{50} was calculated based on nominal test concentrations using the moving, average-angle method.

GLP: Yes

Test Substance: Glycolic acid, nominal purity 7090%

Results: Total mortality was 0, 0, 0, 0, 0, 30, and 100% at 0, 0.0064, 0.0081, 0.010, 0.013, 0.016, and 0.020%, respectively. All deaths occurred within 24 hours. All surviving fish in controls and test solutions behaved normally throughout the test.

At the start of the test, the total alkalinity and EDTA hardness of the water control were 8 1 and 75 mg/L as $CaCO_3$, respectively. The conductivity, dissolved oxygen, and pH of the water control at the start of the test were 150 umhos/cm, 8.8%, and 8.1, respectively.

Reference: DuPont Co. (1989). Unpublished Data, Haskell Laboratory Report No. 75 l-89.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References far Acute Toxicity to Fish:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Appiegate, V. C. et al. (1957). Toxicity of 4346 Chemicals to Larval Lamprevs and Fishes, United States Department of the Interior, Washington, DC.

DuPont Co. (1963). Unpublished Data, Haskell Laboratory Report No. 159-63.

Data from these additional sources were not summarized because insufficient

study information was available.

Hoechst AG (1988). Unpublished Data, Report No. 88.05 18 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Mori, Z. (1975). Jan. Kokai., 751121,425 (9/23/75) (cited in IUCLID (1998). IUCLID Data Sheet "'Glycolic acid" (October 6)).

Data from this additional source was not summarized because the study design was not adequate.

Hidaka et al. (1992). Nippon Suisan Gakkaishi, 5 8: 1179- 1187 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

4.2 Acute Toxicity to Invertebrates

Type:	**48-hour EC_{50}**
Species:	*Daphnia magna*
Value:	141 mg/L (95% confidence interval, 100300 mg/L)
Method:	Nominal concentrations of 25, 50, 100, 200, 400, and 800 mg/L glycolic acid (not adjusted for purity) and a dilution water control were used in the study. Beakers containing 200 mL of the test solution (6.8 cm test solution depth) were used as test chambers. Four replicate test chambers were used per test concentration with 5 daphnids in each chamber (20 daphnids per concentration). The test chambers were covered with a glass plate during the test. Random numbers were used to assign test concentrations to the test chambers and position of test concentrations in the water bath. *Daphnia magna* neonates, < 24 hours old were used in the study. Observations of test organisms were made daily. The criterion for the effect (immobility) was the inability to swim at least 2 body lengths in any direction within 15 seconds after application of a gentle stimulus. Daphnids were not fed during the test. A recirculating water bath was used to maintain mean temperature in the test chambers during the 48-hour test at approximately 20.5°C with a range of 20.4-20.7°C. In addition, a continuously recording thermometer was used to check for temperature variation in the water bath. A photoperiod of 16 hours light (approximately 5 1 O-52 1 Lux) and 8 hours darkness was employed, which included 30 minutes of transitional light (7-8 Lux) preceding and

following the 16-hour light interval.

Dissolved oxygen concentration, pH, and temperature were measured in all replicates of the control and test substance concentrations. These measurements were taken before daphnids were added at test start, and at test end or at total immobility in a replicate chamber. Total alkalinity, EDTA hardness, and conductivity of the water controls and the highest test substance concentration were measured before daphnids were added at the beginning of the test. Test solutions were not aerated during the test.

The EC_{50} and 95% confidence intervals were calculated by the binomial method.

GLP: Yes

Test Substance: Glycolic acid (tested as a 70% solution in water), purity >98%

Results: The stock and test solutions were clear and colorless with no insoluble material present. Dilution water quality was acceptable based on OECD and ASTM criteria, with no quantifiable levels of pollutants and pesticides present in the most recent semi-annual dilution water analysis. Total alkalinity for the water control at test start was 54 mg/L $CaCO_3$. EDTA hardness, and conductivity of the dilution water control and 800 mg/L test solution at test start ranged from 120-123 mg/L $CaCO_3$ and 290-490 µmhos/cm, respectively. The increased conductivity of the 800 mg/L test concentration can be attributed to the physical properties of the test material. During the test, dissolved oxygen concentrations ranged from 8.8-8.9 mg/L. The pH ranged from 3.0-7.8. The pH decreased as the concentration of test material increased. The mean temperature was 20.5°C with a range of 20.4-20.7°C.

No immability was observed in the dilution water control. Immobility at the end of the study in the 25, 50, 100,200, 400, and 800 mg/L nominal test concentrations was 0, 0, 0, 100, 100, and 100%. There were no sublethal effects observed in the surviving daphnids.

Reference: DuPont Co. (2000). Unpublished Data, Haskell Laboratory Report No. DuPont-3658.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Acute Toxicity to Invertebrates: None Found.

4.3 Acute Toxicity to Aquatic Plants

Type:	**Growth Rate**
Species:	***Haematococcus pluvialis*** (algae)
Value:	No Data
Method:	***Haematococcus pluvialis was grown in*** ASPG medium. To minimize pH changes, 2.0 mM urea was substituted for $NaNO_3$ as the source of nitrogen without any reduction in the rate of growth. The alga was grown in Erlenmeyer flasks containing medium. Growth was estimated turbidimetrically. Glycolic acid was tested at 5 mM (pH 5.0 and 7.5) for autotrophic growth, and at 10 and 15 mM (pH 5.0 and 7.5) for photoheterotrophic growth (growth in light under essentially CO_2-free conditions). For autotrophic growth, flasks were plugged with cotton, and incubated at 2 1 °C under 3000 Lux of continuous illumination provided by cool-white fluorescent lamps for 4 and 8 days. Cultures for photoheterotrophic growth were inoculated directly into Erlenmeyer flasks fitted with screw caps, which were tightened and sealed for 10 days. Cotton plugged flasks for heterotrophic growth were wrapped and incubated at 21°C in the dark for 14 days. Succinate (5 .0 mM) was added to maintain the desired pH, and additional controls were established containing 10 mM succinate.
GLP:	unknown
Test Substance:	Glycolic acid, purity not specified
Results:	Glycolic acid caused stimulation of algal growth at pH 7.5 under illumination. When used as a carbon source for heterotrophic growth in the dark, glycolic acid did not support growth during 14 days incubation at pH 5.0 or 7.5. Glycolic acid (pH 5) was an effective substrate for photoheterotrophic growth.
Reference:	McLachlan, J. and J. S. Craigie (1965). Can. J. Bot., 43: 1449-1456.
Reliability:	Medium because a suboptimal study design was used, as the purity of the test substance was not specified.

Additional Reference for Acute Toxicity to Aquatic Plants:

Data from this additional source was not summarized because the study design was not adequate.

Wright (1970). Symp. Org. Matter Natur. Waters (Univ. Alaska, Sept. 1968), pp. 521-553 (cited in IUCLID (1998). IUCLID Data Sheet "'Glycolic acid" (October 6)).

5.0 Mammalian Toxicity

5.1 Acute Toxicity

Type:	**Oral LD_{50}**
Species/Strain:	Male and female rats/Crl:CD®(SD)IGS BR
Value:	1938 mg/kg (95% confidence interval, 1424-2363 mg/kg)
Method:	Five male and 5 female rats (aged 57-58 and 78-79-days old, respectively) were intragastrically intubated with single doses of 1000, 2000, or 3000 mg/kg of a 70% solution of glycolic acid. Individual dose volumes for the neat test substance were calculated using fasted body weights obtained prior to dosing, and were based on the test substance density of 1.25 g/mL. Additionally, the doses were adjusted for purity. Rats were fasted approximately 18 hours prior to dosing with food being returned to the animals approximately 3 hours after dosing. Rats were dosed at a volume of approximately 1.13, 2.27, and 3.40 mL per kg of body weight for the 1000, 2000, and 3000 mg/kg dosage groups, respectively. The test substance was stirred prior to and throughout the dosing procedure. Observations during the 1 S-day test period included mortality checks, body weight determinations, and observations for clinical signs of toxicity. All rats found dead or sacrificed by design were necropsied to detect grossly observable evidence of organ or tissue damage or dysfunction. The LD_{50} value for male and female rats was calculated using the method of Finney.
GLP:	Yes
Test Substance:	Glycolic acid (tested as a 70% solution in water), purity >98%
Results:	Mortality ratios for male rats were 0/5, 2/5, and 5/5 at 1000, 2000, and 3000 mg/kg, respectively. Mortality ratios for female rats were 0/5, 4/5, and 4/5 at 1000, 2000, and 3000 mg/kg, respectively. Deaths occurred up to 4 days after dosing. Test substance-related clinical signs most often observed included lethargy (all dose levels, males and females), lung noise (1000 mg/kg males and 2000 mg/kg males and females), ocular discharge (2000 mg/kg males and females), and prostrate posture (2000 and 3000 mg/kg, males and females). Other test substance-related clinical signs included hunched-over posture (1000 and 2000 mg/kg males), stained face or chin (2000 mg/kg males), clear oral discharge (2000 mg/kg males), bloating (2000 mg/kg

males), pallor (3000 mg/kg males), appeared not to be eating (3000 mg/kg males), and moribundity (3000 mgikg males). Weight loss of 3-28% of the fasted body weight occurred in male rats dosed at 1000 or 2000 mg/kg, and in female rats dosed at 2000 or 3000 mg/kg. Sporadic weight loss of 2-4% occurred in some female rats dosed at 1000 or 3000 mg/kg.

Test substance-related black stomach discoloration was observed in 5 male rats at the 3000 mg/kg dosage level, and 1 and 4 female rats at the 2000 and 3000 mg/kg dosage levels, respectively. A black, 1 mm thick layer on the otherwise normal gastric mucosa was easily removed by scraping. Most of the rats with this finding also had stomachs distended with black fluid. The nature of this black material was unknown. Brown lung discoloration, possibly due to a gavage accident, was observed in one female rat at the 2000 mg/kg dosage level. The gross observations for the other male and female rats were nonspecific and not indicative of target organ toxicity.

Reference: DuPont Co. (1998). Unpublished Data, Haskell Laboratory Report No. DuPont-1614.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Acute Oral Toxicity:

Data from these additional sources support the study results summari'zed above. The studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Aldrich (1989). Sigma-Aldrich Material Safety Data Sheets on CD-Rom, Aldrich Chem. Co., Gillingham-Darset, England, originally cited in Chemis (1993). Glycolic acid: Chemis total information, Federal Office of the Environment (search of 12/17/93) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Althaus, J. (1978). Effective concentrations of health-damaging substances – Study from the Hygiene Institute, Gelsenkirchen; Addition of 1978; originally cited in INFUCHS (1994). INFUCHS Information System (DABAWAS) (Search of 9/1/94) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid' (October 6)).

Amdur, M. 0. et al. (eds.) (1991). Casarett and Doull's Toxicology, 4th ed., p. 704.

Bove, K. E. (1966). Am. J. Clin. Path., 45:46-50 (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

DuPont Co., Unpublished Data:

(1962a). Haskell Laboratory Report No. 44-62.
(1962b). Haskell Laboratory Report No. 56-62.
(1963). Unpublished Data, Haskell Laboratory Report No. 20-63.

Eastman Kodak Co. (n.d.). Unpublished Data (cited in Patty, F. A. (1963). Industrial Hygiene and Toxicology, 2nd revised ed., Interscience Publishers, Inc., New York).

Hoechst AG (1996). EC Safety Data Sheet, Glycolic Acid 57% in Aqueous Solution (6/19/96) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Smyth, H. F. et al. (1941). J. Ind. Hyg. Toxicol., 23(6):259-268.

Data from these additional sources were not summarized because insufficient study information was available.

Delphaut, J. (195 1). Medicin Tropical, 12:641 (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

Delphaut, J. (195 1). Medicin Tropical, 12:634-638 (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

Type:	**Inhalation LC_{50}**
Species/Strain:	Male and female rats/Crl:CD®(SD)IGS BR
Exposure Time:	4 hours
Value:	> 5.2 mg/L (female rats) 3.6 mg/L (male rats)
Method:	One group of 5 male and 5 female rats and 3 groups of 10 male rats each (aged approximately 8 weeks and weighing 237-295 and 198-202 g, respectively) were exposed nose-only to aerosols of glycolic acid (70% solution) for a single 4-hour exposure. These rats were designated for LC_{50} determination.

Male rats were exposed to chamber concentrations of either 0.60, 2.1, 3.8, or 5.2 mg/L glycolic acid. Female rats were exposed to 5.2 mg/L glycolic acid only. Chamber atmospheres were generated by aerosolization of glycolic acid in air using a nebulizer. The test substance was metered into the nebulizer. Filtered houseline air, introduced at the nebulizer, atomized the test substance and carried the aerosol into the exposure chamber. Chamber concentrations of glycolic acid were controlled by varying the test substance feed rate to the atmosphere generator. The control atmosphere was generated by passing high pressure air through a nebulizer and into the exposure chamber. The atmospheric concentration of glycolic acid was determined by gravimetric analysis at approximately 30- or 45-minute intervals during each exposure. Two samples to determine particle size distribution were taken during each exposure. Chamber airflow, temperature, relative humidity, and oxygen concentration were recorded.

Because of the dense atmosphere resulting from the high aerosol concentration of the test substance, observations for clinical signs could not be conducted during the exposures. During a 14- or 15-day recovery period, these rats were weighed and observed for clinical signs of toxicity. All surviving rats underwent gross pathological examination at the end of the recovery period. In addition, the nose, larynx, pharynx, and lungs were examined microscopically.

Four groups of 5 male rats each were exposed along with the groups designated for LC_{50} determination. These rats were designated as satellite animals, and were neither weighed nor observed for clinical signs of toxicity. All surviving satellite animals were sacrificed approximately 24 hours after exposure for microscopic examination of the nose, larynx, pharynx, and lungs. No gross evaluations were conducted on the rats designated as satellite animals.

One group of 10 male rats (designated as controls) was exposed to air only. These animals were neither weighed nor observed for clinical signs of toxicity. Five control rats were sacrificed approximately 24 hours after exposure for microscopic examination of the nose, larynx, pharynx, and lungs. The remaining 5 rats were allowed to recover for 14 days, then received the same treatment as the control rats from the initial sacrifice. No gross evaluations were conducted on control rats.

GLP:	Yes
Test Substance:	Glycolic acid (tested as a 70% solution in water), purity >98%
Results:	Characterization of the chamber atmosphere during each exposure showed the mean total aerosol concentration to be 0.60, 2.1, 3.8, and 5.2 mg/L glycolic acid. The test atmospheres were considered respirable in rats with a mass median aerodynamic diameter (MMAD) of the aerosol generated during the exposures of 2.3-3.1 pm; 8.0-18% of the particles were less than 1 µm, 50-62% of the particles were less than 3 µm, and 93-99% of the particles were less than 10 µm. During exposure chamber airflow, temperature, relative humidity, and oxygen concentration were 35 L/min, 20-26°C, 53-69%, and 21%, respectively. Mortality ratios in male rats were O/10,2/10,6/10, and 3/5 at 0.60, 2.1, 3.8, and 5.2 mg/L. The mortality ratio for female rats was 0/5 at 5.2 mg/L (the only concentration tested). Mortality occurred during exposure or within 12 days of exposure. No mortality was observed in male rats designated as satellite animals or in control rats, Rats from the 0.60 and 2.1 mg/L exposure groups experienced slight to severe body-weight losses the day following exposure (0.3-14% and 2.4-14%, respectively). Rats that survived the 3.8 mg/L exposure experienced moderate to severe body-weight losses the day following exposure (6.5-16%). Rats exposed to 5.2 mg/L glycolic acid experienced slight to severe body-weight losses the day after exposure (12-15% and O.l-5.1% in male and female rats, respectively). All rats in the 0.60, 2.1, and 3.8 mg/L groups and one rat in the 5.2 mg/L group experienced an overall weight gain during the recovery period, although some transient weight losses did occur. Clinical signs of toxicity included lung noise (all exposure levels), gasping (all exposure levels), hunched posture (all exposure levels), ocular and nasal discharge (all exposure levels), stained and/or wet fur and/or perinea (all exposure levels), vocalization (2.1 mg/L), lethargy (2.1 and 3.8 mg/L), sores of the eyes, nose, and/or chin (2.1 and 3.8 mg/L), and alopecia (3.8 mg/L). No test substance-related target organ gross changes were observed in exposed male or female rats designated for LC_{50} determination. Test substance-related microscopic changes,

attributable to tissue irritation, were observed in nose, larynges, and lungs of male rats and nose and larynges of female rats. Minimal to mild nasal lesions, seen in all treated groups, consisted of degeneration/regeneration of respiratory and/or olfactory epithelium.

Mild to severe laryngeal ulceration was present in all treated male groups, and mild effects were present in the female group. Hyperplasia of squamous epithelium, and more rarely, respiratory epithelium of the laryngeal mucosa was noted as a compensatory response to injury in some rats. In addition, hyperplasia of squamous epithelium of the dorsal pharynx was present in some sections in which hyperplasia of squamous epithelium of the larynx was noted.

Minimal to mild subacute/chronic inflammation was present in lungs of rats exposed to 2.1, 3.8, and 5.2 mg/L glycolic acid. In no animal did the change involve all lung lobes. There were no other test substance-related microscopic findings.

Reference: DuPont Co. (1998). Unpublished Data, Haskell Laboratory Report No. DuPont-1516.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Acute Inhalatlon Toxicity:

Data from this additional source supports the study results summarized above. The study was not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (198 1). Unpublished Data, Haskell Laboratory Report No. 862-8 1.

Data from this additional source were not summarized because insufficient study information was available.

Eastman Kodak Co. (n.d.). Unpublished Data (cited in Patty, F. A. (1963). Industrial Hygiene and Toxicology, 2nd revised ed., Interscience Publishers, Inc., New York).

Type: **Dermal Toxicity:** No Data.

Type: **Dermal Irritation**
Species/Strain: Male rabbit/Albino
Exposure Time: 24 hours
Method: A 0.5 mL sample of undiluted material was applied to intact

	and abraded skin under a double l-inch square of gauze. The treatment area was wrapped for 24 hours. Observations were made at 24, 48, and 72 hours.
GLP:	No
Test Substance:	Glycolic acid (70% technical), purity not specified
Results:	Glycolic acid was classified as a very strong primary skin irritant bordering on corrosive when applied to the skin of one rabbit. It caused strong erythema and mild edema on the intact skin, and strong erythema and necrosis along the lines of abrasion on the abraded skin at 24 hours. All erythema was cleared by 72 hours, however, the necrosis along the line of abrasion remained.
Reference:	DuPont Co. (1962). Unpublished Data, Haskell Laboratory Report No. 44-62.
Reliability:	High because a scientifically defensible or guideline method was used.

Type:	**Dermal Irritation**
Species/Strain:	Human
Exposure Time:	30 minutes
Method:	Solutions containing 50% glycolic acid at pH 1 .O 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 minutes later. After 48 hours, biopsies were obtained and processed for microscopic examination.
GLP:	unknown
Test Substance:	Glycolic acid (50 or 70% solution), purity not specified
Results:	In the 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 comeum at pH 2.25 and 2.75. The site treated with the 50% solution (pH 1.0) had lost its stratum comeum, but had no crusting or epidermal necrosis.
Reference:	Becker, F. F. et al. (1996). Dermatologic Surgery 22:463-465 (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).
Reliability:	Low becausean inappropriate method or study design was used.

Additional References for Dermal Irritation:

Data from these additional sources support the study results summarized above. The studies were not chosen for detailed summarization because the data were not

substantially additive to the database.

Hoechst (1984). Unpublished Data, Report No. 84.0024 (cited in IUCLID (1998). ITJCLID Data Sheet "Glycolic acid" (October 6)).

Moy, L. S. et al. (1996). Dermatologic Surgery, 22:429-432 (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

Murad, H. et al. (1995). Cosmetic Dermtology, 1:3:285-307 (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

Data from these additional sources were not summarized because the primary focus of the study was skin corrosion.

Barrat, M. D. (1996). Toxicology *In Vitro*, 10:85-94.

DuPont Co., Unpublished Data:

(1973). Haskell Laboratory Report No. 418-73.
(1993a). Haskell Laboratory Report No. 430-93.
(1993b). Haskell Laboratory Report No. 425-93.
(1997a). Haskell Laboratory Report No. 1997-01084.
(1997b). Haskell Laboratory Report No. 1997-O 1086.
(1998). Haskell Laboratory Report No. 1998-01659.
(1999). Haskell Laboratory Report No. DuPont-3696.

Hoechst AG (1996). EC Safety Data Sheet, Glycolic Acid in 57% Aqueous Solution (6/19/1996) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Data from the foilowing study was not summarized because there was insufficient study information available.

Dermatech (1993). Unpublished Data, submitted by CTFA (95-AHA-0108), Washington, DC, Cosmetic Ingredient Review (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

Data from these additional sources were not summarized because the test substance was a mixture or otherwise inappropriate.

Alfieri, D. R. (1996). Cosmet. Dermatol., 9:42-52 (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

DiNardo, J. C. (1995). Unpublished Data, submitted by CTFA, Washington, DC, Cosmetic Ingredient Review (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

DiNardo, J. C. (1996). AHAs and Skin Rejuvenation. A Supplement to Cosmetic Dermatology (May), pp. 12-13 (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

DuPont Co. (1994). Unpublished Data, Haskell Laboratory Report No. 56-94.

Hilltop Research, Unpublished Data, submitted by CTFA, Washington, DC, Cosmetic Ingredient Review (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia):

(1994a). CTFA 95-AHA-0094.
(1994b). CTFA 95-AHA-0095.
(1995). CTFA 95-AHA-0093.
(1996). HTR Reference No. 96-1077-70.

Kostarelos, K. et al. (1999). Cosmet. Toiletries, 114:43-50 (TOXLINE/1999/162867).

Natura Bisse (1996). Unpublished Data, submitted by CTFA, Washington, DC, Cosmetic Ingredient Review (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

CTFA, Unpublished Data, Washington, DC, Cosmetic Ingredient Review (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia):

(1989). CTFA 95-AHA-0027.
(1990a). CTFA 95-AHA-0023.
(1990b). CTFA 95-AHA-0022.
(1990c). CTFA 95-AHA-0028.
(1991 a). CTFA 95-AHA-0029.
(1991b). CTFA 95-AHA-0066.

(1991c). CTFA 95-AHA-0030.
(199%). CTFA 95-AHA-0068.
(1992b). CTFA 95-AHA-0065.
(1992c). CTFA 95-AHA-0024.
(1992d). CTFA 95-AHA-0025.
(1993). CTFA 95-AHA-003 1.
(1994a). CTFA 95-AHA-0026.
(1994b). CTFA 95-AHA-0062.
(1995). CTFA 95-AHA-47.

Effendy, I. et al. (1995). Acta Dermato-Venereologica, 75:455-458 (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

Kopera, D. et al. (1996). Acta Dermato-Venereologica, 76:461-463 (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

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Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

Type: **Dermal Sensitization (Modified Buehler Method)**

Species/Strain: Guinea pigs/ Hartley

Method: The left flank of 20 guinea pigs (weighing 341-5 16 g on the day prior to the first induction application or on the day of the rangefinding application) were closely clipped on the day prior to test substance administration (Day -1). The clipping was repeated weekly during the induction phase of the study. The right flank of each animal exposed to the test substance in the induction phase was closely clipped on the day prior to the challenge application. Similar areas were clipped on the left flank (caudal) and right flank of each animal (exposed to vehicle in the induction phase) on the day prior to challenge applications.

Induction applications were performed using a 26% w/v solution of glycolic acid in normal saline solution, and the challenge applications were performed using a 20% w/v solution of glycolic acid in normal saline solution. A 0.5 mL aliquot of a 26% w/v solution of glycolic acid in normal saline solution was applied to the test site, and covered with a piece of occlusive dental dam. Plastic wrap was then wrapped snugly around the trunk of the animal and overwrapped with elastic bandage. Approximately 6 hours after application, the entire wrapping was removed, and the test sites were wiped with normal saline solution and then deionized water.

A separate group of 10 animals (vehicle and test substance irritation control group) were clipped and treated with 0.5 mL normal saline solution in the same manner as the test animals.

The test sites were scored for irritation at approximately 24 and 48 hours following application. This procedure was performed at 7-day intervals for 3 consecutive weeks.

Following the 3rd application of test substance to the test sites, the animals were rested for approximately 15 days. On Day 29, the animals were clipped as described above. The challenge application was performed on the right flank using a 0.5 mL aliquot of a 20% w/v solution of glycolic acid in normal saline solution. Similarly, animals in the vehicle and test substance irritation control group were treated with

normal saline solution on the left flank and a 0.5 mL aliquot of a 20% w/v solution of glycolic acid in normal saline solution on the right flank. The application of test substance and vehicle were as described above. Approximately 6 hours after application of the test substance and/or vehicle, the entire wrapping was removed, and the test site(s) wiped with normal saline solution and then deionized water. Approximately 24 and 48 hours after the challenge application, the test sites were examined for dermal irritation or signs of elicited sensitization.

A positive control was not run concurrently with the test substance. However, a dermal sensitization test using a positive control (a-hexylcinnamaldehyde, technical grade 85%) was periodically performed to validate the system.

Clinical observations and body weights were recorded.

GLP: Yes

Test Substance: Glycolic acid (tested as a 70% solution in water), purity >98%

Results: Observations of no to faint redness were noted for guinea pigs exposed to glycolic acid 24 and 48 hours after the 1st induction application. No to faint redness at 24 hours, and no redness at 48 hours were observed following the 2nd induction application. Scratches at the test site were observed in 8 guinea pigs at 24 hours. Five of these guinea pigs exhibited focal ulcerations and 2 exhibited focal necrosis at 48 hours. Six other animals exhibited exfoliation at 48 hours. No to moderate redness was observed at 24 and 48 hours following the 3rd induction. Two incidences of scratches at the test site and 1 incidence of exfoliation were observed at 24 and 48 hours.

After the challenge application, no redness was observed at the test substance sites at 24- and 48-hours. At 48 hours there were 4 incidences of scratches at the test site. The incidence of sensitization was 0/20 (0%).

Dermal irritation was not observed after the induction applications to the vehicle control animals. Challenge application at the vehicle sites also failed to induce dermal irritation. No redness was observed at the test substance irritation control sites 24 and 48 hours after the challenge application.

All vehicle and test substance animals appeared to be normal

throughout the study. One guinea pig exhibited a weight loss from day 14 to day 21. All guinea pigs exhibited an overall gain in body weight during the study. There were no statistically significant differences in individual body weight percentage gains of the test substance group when compared to the vehicle and test substance irritation control group.

Signs of irritation were observed in the animals treated with 2.0% α-hexylcinnamaldehyde in ethanol (HCA; positive control material). The incidence of sensitization after the challenge application of HCA was SO% (10/20), and the severity was 0.63 at 24 hours and 0.68 at 48 hours.

It was concluded that repeated administration of glycolic acid did not produce a delayed contact sensitization response to guinea pigs, and is not considered a dermal sensitizer under the study conditions utilized.

Reference: DuPont Co. (1998). Unpublished Data, Haskell Laboratory Report No. DuPont- 1152.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Dermal Sensitization:

Data from these additional sources support the study results summarized above. The studies were not chosen for detailed summarization because the data were not substantially additive to the database.

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Data from this additional source was not summarized because the result was inconsistent with the majority of the other findings.

Richerche e Technologie Cosmetologiche (1996). Unpublished Data, **submitted to CIR,** Study No. RTC/001/V, Washington, DC, Cosmetic Ingredient Review (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

Type:	**Eye Irritation**
Species&train:	Rabbits/Albino
Method:	One-tenth milliliter of the undiluted liquid was placed into the right conjunctival sac of each of 2 albino rabbit eyes. After 20 seconds, 1 treated eye was washed with tap water for 1 minute. The treated eye of the other rabbit was not washed. Observations of the cornea, iris, and conjunctiva were made with a hand-slit lamp at 1 and 4 hours, and at 1, 2, 3, 7, and 14 days. Fluor-I-strip® stain and a biomicroscope were used at examinations after the day of treatment.
GLP:	No
Test Substance:	Glycolic acid, purity 64%
Results:	Glycolic acid (0.1 mL, undiluted) was corrosive to rabbit eyes. Ocular effects in both the washed and unwashed eye were severe and irreversible. By 14 days, observation was terminated because 1 treated, unwashed eye, which had become very small, had no reaction to light. The other eye, which had been washed following treatment, reacted to light, although the cornea appeared as if it would rupture.
Reference:	DuPont Co. (1977). Unpublished Data, Haskell Report No. 446-77.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for Eye Irritation:

Data from these additional sources support the study results summarized above. The studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (1964). Unpublished Data, Haskell Laboratory Report No. 33-64.

Carpenter, C. P. and H. F. Smyth, Jr. (1946). Am. J. Ophthamol., 29(11):1363-1372.

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McLaughlin, R. S. (1946). Am. J. Ouhthamol., 29(11):1363-1372.

Data from this addition&l source was not summarized because insufficient information was available.

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(1994g). CTFA Number 95-AHA-0079, TM Study No. 94-277.
(1994h). CTFA Number 95-AHA-0084, TM Study No. 94-278A.
(1994i). CTFA Number 95-AHA-007 1, TM Study No. 94-377.

Data from this additional source was not summarized because the study design was not adequate.

DuPont Co. (1940). Unpublished Data, Haskell Laboratory Report No. 2-40.

5.2 Repeated Dose Toxicity

Study No. 1

Type:	**90-Day Gavage**
Species/Strain:	Rats/Crl:CD®(SD)IGS BR
Sex/Number:	Male and female/ 40 per sex per dose group
Exposure Period:	90 days
Frequency of Treatment:	Daily
Exposure Levels:	0, 150, 300, 600 mg/kg
Method:	Rats (approximately 48 days old) were administered glycolic acid in water via intragastric intubation. Control animals were dosed with water only. Dosing solutions were stored refrigerated until used. Dosing solutions were analyzed 5 times throughout the study. At the 1st time point, samples were analyzed to determine concentration and stability. At the remaining time points, samples were analyzed for concentration verification.

Each dosage group was divided into subchronic toxicity, immunotoxicity, neurotoxicity, and reproductive toxicity subsets (10 animals/sex/subset/concentration). Body weights, clinical observations, and individual food consumption were recorded. Ophthalmoscopic examinations were conducted on all rats prior to the start of the study and on surviving subchronic toxicity rats just prior to scheduled sacrifice.

At approximately midstudy and near the end of the study, blood was collected from each rat designated as subchronic toxicity animals. Fifteen hematologic parameters and 17 clinical chemistry parameters were measured or calculated. On the day prior to each bleeding time, an overnight urine specimen was collected and 12 urine chemistry parameters were measured or calculated. The rats designated for subchronic toxicity evaluations were sacrificed and necropsied at the end of the study. Each rat was given a gross examination, the weights of 6 organs were recorded, and representative samples of 53 tissues were saved for histopathologic examination. All tissues collected (except nasal tissue without gross lesions) from all animals in the control and 600 mg/kg groups were microscopically examined. Liver, kidneys, lungs, and most gross lesions were examined from rats in the intermediate concentration groups.

After 28 days of glycolic acid administration, humoral immune function was evaluated in animals in the immunotoxicity subset. On test day 23, animals designated for immunotoxicity evaluation were injected intravenously with sheep red blood cells (SRBC). Six days after injection, the animals were euthanatized. Following sacrifice, the spleen and thymus were removed and weighed, and serum was collected from each rat and analyzed for SRB-specific IgM antibody. Sera previously collected from rats injected with SRBC and dosed with the known immunosuppressive agent cyclophosphamide served as a positive control.

Rats designated for neurotoxicity evaluation underwent functional observational battery (FOB) assessments (encompassing 34 endpoints) and motor activity (MA) evaluations (encompassing 2 dependent variables) once prior to study start, then near the beginning, middle, and end of the study. Six animals per group were evaluated for neuropathology at the end of the study. Six unexposed control animals per sex were randomly selected as negative controls. Rats were euthanatized followed by whole body perfusion fixation, and 17 tissues were saved. Only tissues from the control and 600 mg/kg group were microscopically examined.

On test day 97, animals of the reproductive toxicity subset were bred within their respective treatment groups and allowed to deliver and rear their offspring until weaning (postpartum day 21). All parental rats were sacrificed and received a gross pathological examination. Additional details for reproductive and pup/weanling information can be found in Section 5.4.

GLP: Yes

Test Substance: Glycolic acid (tested as a 70% solution in water), purity >98%

Results: Concentration verification of the samples from the 1st time point were within acceptable limits ranging from 95.0-109.3% of nominal. The mean measured values were 98.7%, 98.3%, and 107.5% of nominal at 150,300, and 600 mg/kg. Measured values for stability were 97.7-109.3% of nominal concentrations. These data indicated that the test substance was stable in water at room temperature and refrigerated storage conditions; therefore the dosing solutions were considered stable under the conditions of use in this study. Analytical results verifying concentration at the remaining sampling time points showed that percent

nominal concentrations ranged from 92.0-102.7%. The results were within expected variability of the analytical method. These data, together with the concentration verification from the 1st time point, indicate that the test substance was present at the targeted dosing concentrations.

Two compound-related deaths occurred in males at 600 mg/kg. No other compound-related mortality was observed in this study. No effects in body weight, food consumption, or clinical signs were observed in animals dosed with 150 mg/kg glycolic acid. Administration of glycolic acid doses of 300 and 600 mg/kg/day decreased mean body weight, overall body weight gain, food consumption, and food efficiency when compared to their respective controls. The body weight effects observed in the 600 mg/kg/day groups were considered adverse, however, the magnitude of the body weight effect observed at 300 mg/kg was mild, and was not considered adverse. There were no adverse clinical signs indicative of systemic toxicity and no test substance-related ophthalmologic findings observed during this study.

Subchronic Toxicity Subset: Toxicologically significant changes in hematologic measurements were increased neutrophils in male rats dosed with 300 (transient) or 600 mgikg. Toxicologically significant changes in clinical chemistry and urinalysis parameters included increased urea nitrogen, phosphorus, and creatinine, and decreased urine concentration at the end of the study in male rats dosed with 300 (transient) or 600 mg/kg. All other changes were either not compound-related or considered not to be adverse.

Mean kidney weight (absolute and relative to body weight) of male rats in the 300 and 600 mg/kg groups was significantly higher. Those weights and gross fmdings of renal pelvis dilatation correlated with microscopic findings of oxalate crystal nephrosis and unilateral hydronephrosis in the 300 and 600 mg/kg groups. In addition, hyperplasia of the transitional epithelium of the renal pelvis was observed microscopically in males of the 300 and 600 mg/kg groups and was considered secondary to the mucosal irritation created by passage of oxalate crystals from the kidney. There were no organ weight, gross, or microscopic findings indicative of systemic toxicity observed in female rats treated with glycolic acid. A number of microscopic findings in the upper airways and lungs of male and female

rats in all treated groups were considered irritant effects occurring secondary to aspiration (and/or off-gassing) of the acidic gavage material. No other test substance-related changes were noted.

Immunotoxicity: There were no toxicological changes in the immunotoxicity parameters measured.

Neurotoxicity: There were no toxicological changes in the behavioral parameters of neurotoxicity measured. There were no compound-related gross lesions or microscopic findings observed in the tissues of the nervous system or skeletal muscle examined.

Reproduction: There were no toxicological changes in the measures of reproductive function. There were no changes in organ weights or gross pathology of the reproductive system. There were compound-related gross lesions (dilatation of the pelvis, calculus, chronic progressive nephropathy, and pale discoloration) in the kidneys of male rats in the 600 mg/kg/day group that correlated microscopically with oxalate crystal nephropathy similar to that diagnosed in the subchronic toxicity animals. No compound-related gross observations were noted in the P_1 females or the F_1 weanlings. Additional details for the reproductive toxicity subset can be found in Section 5.4.

Reference: DuPont Co. (1999). Unpublished Data, Haskell Laboratory Report No. DuPont- 1597.

Reliability: High because a scientifically defensible or guideline method was used.

Study No. 2

Type: **2-Week Inhalation**

Species/Strain: Rats/Crl:CD®

Sex/Number: Male/ 10 per group

Exposure Period: 2 weeks; 14-day recovery

Frequency of Treatment: 6 hours/day, 5 days/week

Exposure Levels: 0.16, 0.51, 1.4 mg/L

Method: Rats (7-8 weeks old, weighing 237-263 g) were exposed nose-only to glycolic acid 6 hours/day, 5 days/week for 2 weeks. Aerosol atmospheres of glycolic acid were generated into 20-L cylindrical glass exposure chambers using a nebulizer. A small liquid flow was aerosolized off a spherical glass bead by a high-pressure airstream. The aerosol was mixed with dilution air and introduced directly

into the glass exposure &amber. Chamber atmospheric concentrations were determined by gravimetric analysis. Particle size was conducted on the 1st exposure day of the study using a cascade impactor. Chamber temperature was monitored during each exposure.

Body weights and clinical signs were recorded. Clinical laboratory measurements were performed on 10 rats/group following 10 exposures (8 for the 1.4 mg/L group) and on 5 rats/group following the 14-day recovery period. Individual urine samples were collected overnight following the 8th exposure in the high level (1.4 mg/L) and the 9th exposure in the remaimng levels, and 12 urine chemistry parameters were measured or calculated. A similar urine sample was collected and evaluated from animals at all levels at the end of the recovery period.

On the morning after the urine collection, blood was collected from each rat. Fifteen hematologic parameters and 7 clinical chemistry parameters were measured or calculated.

After the 8th exposure, 4 rats from the 1.4 mg/L exposure level were sacrificed and given a gross examination. Weights of 7 organs were recorded, and 24 tissues were examined microscopically. After the 1 0th exposure, 5 rats from the 0, 0. 16, and 0.5 1 mg/L exposure levels were similarly examined. Remaining rats were sacrificed at the end of the recovery period for similar examination.

GLP: Yes

Test Substance: Glycolic acid (tested as a 70% solution in water), purity >98%

Results: The generation of glyoolic acid aerosol was such that the actual mean concentrations attained were 0.16, 0.5 1, and 1.4 mg/L over the entire experiment. These concentrations were presented for glycolic acid; the material tested was 29% water so that the actual concentrations of the material tested were close to the design concentrations of 0.23, 0.72, and 2.0 mg/L. In all of the particle size determinations, over 95% of the particles were less than 10 µm (mean between 1.5-2 µm). Chamber temperatures stayed within 23 ± 2°C in all groups during the experiment.

All rats survived in the control and 0.16 mg/L groups. One rat exposed to 0.5 1 mg/L was sacrificed in moribund condition. Seven rats exposed to 1.4 mg/L glycolic acid were sacrificed *in* extremis. Body weights of rats exposed to

0.16 mg/L glycolic acid were comparable to controls. Statistically significant and severe weight loss were observed throughout the exposure and recovery periods in rats exposed to 0.5 1 and 1.4 mg/L glycolic acid. Clinical signs of toxicity included labored breathing (0.51 and 1.4 mg/L), lung noise (0.5 1 and 1.4 mg/L), ruffled and discolored fur (0.5 1 and 1.4 mg/L), red and clear nasal and ocular discharges (0.5 1 and 1.4 mg/L), poor muscle tone (0.5 1 and 1.4 mg/L), and pallor (1.4 mg/L).

At the end of the exposure period there were no test substance-related clinical pathology changes in rats exposed to 0.16 mg/L of the test substance. Rats exposed to 0.5 1 mg/L had increased serum activities of aspartate aminotransferase and decreased urine volume. These changes had not resolved by the end of the recovery period in this group due to 2 of the rats having elevated alanine aminotrausferase and aspartate aminotransferase levels. Rats exposed to 1.4 mg/L had decreased concentrations of serum protein, increased serum activities of alanine aminotransferase and aspartate aminotransferase, and decreases in urine volume and pH. These changes were interpreted as evidence of a test substance-related effect on the integrity and function of hepatic tissue. These effects were reversible following 14 days of recovery. No other biologically significant changes were observed.

Gross pathological examination following the exposure period revealed no test substance-related changes in rats exposed to 0.16 or 0.5 1 mg/L. In rats exposed to 1.4 mg/L, distended gastrointestinal (GI) tract, small spleen, and small thymus were observed. No effects were observed in rats after the recovery period. Microscopically, a very mild diffise hepatocellular degeneration (eosinophilia and shrinkage) was detected in 1/10 (0/5 following exposure, 1/5 following recovery), 9/10 (5/5 following exposure, 4/5 following recovery), and 7/10 (at sacrifice) rats exposed to 0.16, 0.5 1, and 1.4 mg/L, respectively. Atrophy and degeneration of the thymus were noted in 5110 rats exposed to 0.5 1 mg/L (2/5 following exposure and 3/5 at the end of recovery) and 8/10 rats exposed to 1.4 mg/L (at sacrifice). No other test substance-related microscopic findings were observed.

A comparison of organ and body weights between test and control rats showed no changes in rats exposed to 0.16 mg/L.

Absolute liver, spleen, kidney, and thymus weights were significantly lower following the exposure period in rats exposed to 0.51 and 1.4 mg/L. On an organ/body weight basis, rats exposed to 0.16 mg/L had an elevated mean lung weight ratio. Rats exposed to 1.4 mg/L had elevated organ/body weight ratios for the heart, lung, kidney, and testis, and a decreased thymus/body weight ratio. At the end of the recovery period, rats exposed to 0.5 1 mg/L had significantly lower lung, liver, kidney, and thymus weights. Rats exposed to 1.4 mg/L had significantly lower kidney weights. On an organ/body weight basis, the only difference noted was an increased testis/body weight ratio in rats exposed to 0.5 1 mg/L.

The only effect seen at the low level was a very mild, diffuse hepatocellular degeneration in 1/10 rats 14 days post-exposure, and 0.16 mg/L can be considered for all practical purposes a no adverse effect level.

References:

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DuPont Co. (1982). Unpublished Data, Haskell Pathology Report No. 25-82.

Kennedy, G. L. and B. A. Burgess (1997). Inhal. Tox., 9(5):435-447.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Repeated Dose Toxicity:

Oral

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Krop, S. et al. (1945). J. Am. Pharm. Assoc., 34:86-89.

Richardson, D. E. (1965). Toxicol. Appl. Pharm., 7:507-5 15.

Rose and Carter (1943). Toxicity Study of Glycolic Acid, Central Research Laboratories, General Food Corporation, Hoboken, NJ (March 29).

Silbergeld, S. and H. E. Carter (1959). Arch. Biochem. Biophys., 84:183-187.

Selvarn et al. (1992). Pharmacol. Res., 26:385-394 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Silbergeld, S. (1960). Toxicol. Appl. Pharm., 2:220-224.

Data from these additional sources were not summarized because the test substance was a mixture or otherwise inappropriate.

DuPont Co. (1940). Unpublished Data, Haskell Laboratory Report No. l-40.

Ogawa et al. (1986). Hinyokika Kiyo, 32(8):1127-l 133 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Ogawa et al. (1986). J. Ural., 135:1057-1060 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid'" (October 6)).

Ogawa et al. (1987). Hinyokika Kiyo, 33:1772-1777 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Data from this additional source was not summarized because insufficient study information was available.

Sanchez, I. M. and R. J. Bull (1990). Toxicology, 64:33-46.

Dermal

Data from these additional sources were not summarized because the study design was not adequate.

Argus Research Laboratories, Inc. (2000). Correspondence from D. B. Learn to L. Loretz (CTFA), RE: Protocol 1203-005.

Yu, R. J. and E. J. van Scott (1975). U. S. Patent No. 3879537 (April 22) (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

5.3 Developmental Toxicity

Study No. 1

Type:	***In vivo* Developmental Toxicity**
Species/Strain:	Rats/Crl:CD®BR
Sex/Number:	Females/25 per dose level
Route of Administration:	Gavage
Exposure Period:	Day 7-2 1 of gestation; Cesarean section on Day 22
Frequency of Treatment:	Once/day

Exposure Levels: 0, 75, 150, 300, 600 mg/kg

Method: Solutions of the test material in deionized water were prepared weekly during the study and stored in the refrigerator. Sufficient amounts of solution needed for dose administration were removed from the refrigerated containers daily. Samples of each test solution were taken 3 times during the study. Analysis of the first sampling addressed concentration and stability. For the 2nd and 3rd samplings, analyses addressed concentration.

Females were cohabited with males (1: 1) until copulation was confirmed by the presence of a copulation plug in the vagina or on the cageboard. Checks for copulation plugs were made each morning; the day copulation was confirmed was designated as Day 1 of gestation (Day 1G). Before dosing began, females were randomly assigned to control or experimental groups based on their body weight.

Body weights, clinical signs, and food consumption were recorded. Females were euthanized on Day 22G, and the organs of the thoracic and abdominal cavities were examined for gross pathologic changes. The uterus was removed, weighed, and opened. The types of implants (live and dead fetuses, and resorptions) were counted and their relative positions were recorded. Then the empty uterus was weighed to permit calculation of body weight minus the products of conception. The ovaries were removed and the corpora lutea were counted and recorded. The uterus of each apparently nonpregnant rat was opened and stained to detect very early resorptions.

Live fetuses were weighed, sexed, and examined for external alterations. The first live fetus and thereafter every other fetus in each litter was decapitated and examined for visceral alterations and the sex verified. The heads were fixed and examined. The remaining fetuses were euthanized. All fetuses were fixed, stained, and examined for skeletal alterations.

GLP: Yes

Test Substance: Glycolic acid, purity 99.6%

Results: Measured concentrations of glycolic acid in dosing formulations at the 1st sampling time point (fresh sample) ranged from 98.6-103% of nominal. These data indicate that the test substance was at an acceptable level in all formulations. Measured concentrations of glycolic acid in dosing formulations at the 1" sampling point, refrigerated for

7 days, and then analyzed were from 95.7-99.8% of nominal. These data indicate that the test substance was stable for the storage conditions of the study. Measured concentrations for the 2nd and 3rd sampling points were 99.8-103 and 97.5-102% of nominal, respectively. These data indicate that the test substance was at an acceptable level in all formulations.

Pregnancy ratios were 25/25, 25/25, 24/25, 23/25, and 23/25 at 0, 75, 150,300, and 600 mg/kg, respectively. There were no mortalities observed at any dose level. One female in the 150 mg/kg dose group delivered early. A summary of other reproductive outcomes (means/litter) are provided in the table below.

Dose (mg/kg)	0	75	150	300	600
Corpora Lutea:	16.3	16.3	15.8	17.4	17.0
Implantations:	15.4	15.0	14.7	15.3	15.9
Total No. of Resorptions:	0.7	0.8	0.7	0.6	0.6
Total No. of Fetuses:	14.6	14.2	14.0	14.7	15.3
Total No. of Live Fetuses:	14.6	14.2	14.0	14.7	15.3
Mean Fetal Weight	5.02	5.20	5.17	5.05	4.38
Sex Ratio (No. male fetuses/No. live fetuses):	0.44	0.49	0.50	0.50	0.48

There was no evidence of either maternal or developmental toxicity at either 75 or 150 mg/kg.

Marginal evidence of both maternal and developmental toxicity was detected at 300 mg/kg. Regarding maternal toxicity, lung noise similar to that observed at 600 mgikg was observed in 2 of 25 dams. Developmental toxicity was evident only as a slight, but not statistically significant, increase in the incidence of skeletal malformations (fused ribs and fused vertebra). No other maternal or developmental parameters were affected.

Compound-related, adverse maternal and developmental toxicity was observed at 600 mg/kg. Maternal effects included significant reductions in maternal body weights and food consumption. Adverse clinical observations were

significantly increased at this level as well, and included abnormal gait/staggering, lung noise (wheezing and/or rattling), irregular respiration, and lethargy. There were no remarkable postmortem findings in these dams. Developmental toxicity was evident at this level in significantly reduced mean fetal weight, a significant increase in the incidence of fetal malformations (fused and absent ribs, fused and hemivertebra, and abnormally fused and cleft/non-fused sternebra), and increased fetal variations (misaligned and incompletely ossified sternebra and incompletely ossified vertebra).

A summary of gross, soft tissue, and skeletal anomalies are provided in the table below. Data are presented as number of fetuses (litters) affected.

Dose (mg/kg)	0	75	150	300	600
Skeletal, Number examined	366(25)	354(25)	321(23)	339(23)	351(23)
Fused ribs	0(0)	0(0)	0(0)	2(2)	9(9)
Absent ribs	0(0)	0(0)	0(0)	0(0)	3(3)
Fused vertebra	0(0)	0(0)	0(0)	2(2)	6(6)
Hemi-vertebra	0(0)	1(1)	0(0)	1(1)	8(8)
Abnormally fused sternebra	0(0)	0(0)	0(0)	0(0)	3(3)
Cleft/non-fused sternebra	1(1)	0(0)	0(0)	1(1)	6(5)
Misaligned sternebra	1(1)	1(1)	0(0)	1(1)	13(9)
Incompletely ossified sternebra	14(6)	4(2)	13(2)	12(3)	60(14)
Incompletely ossified vertebra	95(19)	119(21)	68(17)	114(22)	204(21)

Thus, the maternal and developmental no-observed-effect level (NOEL) was 1 50 mg/kg/day. Therefore, the results of this study indicate that glycolic acid is not likely to be uniquely toxic to the rat conceptus.

Reference:

DuPont Co. (1996). Unpublished Data, Haskell Laboratory Report No. 191-96 (also cited in TSCA fiche OTS0572155-1).

Munley, S. M. and M. E. Hurtt (1996). Teratology, 53(2):117 (Abstract No. P54).

Munley, S. M. et al. (1999). Drug Chem. Toxicol., 22(4):569-582.

Reliability: High because a scientifically defensible or guideline method was used.

Study No. 2

Type: ***In vitro* Developmental Toxicity**

Species/Strain: **Rat/Sprague Dawley**

Sex/Number: Rat embryo/10 per concentration (Experiment 1); 12 per concentration (Experiment 2)

Route of Administration: *In vitro* culture

Exposure Period: 46 hours

Exposure Levels: **0, 0.5, 2.5, 12.5, 25, 50 mmol/L**

Method: Adult female time-mated Sprague Dawley rata, obtained from Charles River Breeding Laboratory, supplied the embryos used in this study. Day 10.5 conceptuses (day of sperm-positive vaginal smear or copulation plug was designated as day 0.5) were dissected free of decidual tissue and Reichert's membrane, leaving the visceral yolk sac and ectoplacental cone intact. Early somite stage embryos were then transferred to culture bottles (2 embryos/bottle) containing pre-warmed, pm-gassed test or control culture media. The culture bottles were maintained in a continuous gas flow rotating culture unit at 37°C for 46 hours. The culture medium was comprised of 75% immediately centrifuged, heat-inactivated serum collected from adult rats and 25% Dulbecco's Modified Eagle's Medium.

In Experiment 1, groups of 10 embryos were cultured in media containing the test substance for 46 hours. An additional group of 10 embryos was cultured with sodium valproate (1.O mM) and served as positive controls. In Experiment 2, groups of 12 embryos were cultured for 46 hours in 1 of 4 media: control medium at pH 7.41, control medium titrated to pH 6.74 with HCl, medium containing 12.5 mM glycolic acid (pH 6.74), or medium containing 12.5 mM sodium glycolate (pH 7.42).

Upon completion of the culture period, embryos were evaluated for the presence of a beating heart and an active visceral yolk sac circulation. Embryos with a beating heart were considered viable embryos. Morphology was evaluated using Brown-Fabro scoring. Growth was assessed by measurement of visceral yolk sac diameter, crown-rump

The percentage of dysmorphic embryos was significantly increased in the glycolic acid 12.5 and 25 mM groups. The most commonly observed morphological alteration was a striking, bilateral, cystlike enlargement of the maxillary process. At 12.5 mM, several rostro-medial structures of the midfacial region were observed, which included an apparent absence of olfactory rudiments, irregular protrusions extending from an area just above the expected region of the nasal process, and hypoplastic and/or widely spaced telencephalic hemispheres. Other effects observed included dysmorphogenesis of the optic vesicles and an irregular pattern of somite segmentation. Similar effects were observed in the surviving embryos exposed to 25 mM glycolic acid. In addition, a disorganized pattern of visceral yolk sac vessels was observed in embryos exposed to 25 mM glycolic acid. Exposure of embryos to the positive control agent resulted in abnormal somite segmentation, altered neural tube development (characterized by a wavy or kinked neural suture line), incomplete closure of the otic vesicles, disorganized vitelline (visceral yolk sac) vessels and other abnormalities.

Embryo viability was not affected by any of the treatments in Experiment 2. However, the percentage of embryos with active yolk sac circulation was slightly, but not significantly decreased in both the 12.5 mM glycolic acid (pH 6.74) and acidified medium (pH 6.74) groups. The effects observed on the growth of embryos cultured in 12.5 mM glycolic acid (pH 6.74) were virtually identical to those observed in Experiment 1, with all parameters significantly different from pH 7.41 controls. The same measures were also affected by culture with 12.5 mM sodium glycolate at pH 7.42, although to a slightly lesser degree. In contrast, only the protein contents of embryo and visceral yolk sac and embryo head length were significantly affected in embryos cultured in control medium titrated to pH 6.74. Both treatment with 12.5 mM glycolic acid (pH 6.74) and 12.5 mM sodium glycolate (pH 7.42) resulted in a significant increase in the percentage of dysmorphic embryos. The type of alterations were similar, and as seen in Experiment 1, were predominantly craniofacial. Again the maxillary process and midfacial region were the principle sites affected.

In Experiment 1, the pH of representative media samples (without embryos) were in the physiological range at the

start of the culture, and remained relatively stable during the 46-hour culture period. In Experiment 2, relatively slight changes in pH occurred in the 12.4 mM glycolic acid, 12.5 mM sodium glycolate, and acidic control groups. Osmolalities of 299,396, and 377 mOsmol/kg H_2O were noted for the control, 12.5 mM glycolic acid, and 12.5 mM sodium glycolate medium, respectively. Differences between osmolality for the serum-based media used in the study versus theoretical values predicted for dilute aqueous solutions were likely due to interactions among serum components, as well as pH influences on the ionization of such components.

References:

Carney, E. W. et al. (1996). Teratology, 53:38-46.

Carney, E. W. et al. (1995). The Toxicologist, 15(1): 163 (Abstract No. 866).

Dow Chemical Company (1995). Correspondence to U. S. EPA, OTS Office, 8E Communication (April).

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Developmental Toxicity:

Data from these additional sources support the study results summarized above. These studies were not chosen for detailed summarization because the data were not substantially additive to the database.

Breslin, W. et al. (1997). The Toxicologist, 36 (1, Part 2):100 (Abstract 511).

Carney, E. W. et al. (1999). Toxicol. Sci., 50:117-126 (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

Carney, E. W. et al. (1997). Unpublished Data, Dow Chemical Company, Study ID K-0025558-012 (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

DuPont Co. (1995). Unpublished Data, Haskell Laboratory Report No. 96-95 (also cited in TSCA fiche OTS0572155).

5.4 Reproductive Toxicity

Species/Strain:	Rats/Crl:CD®(SD)IGS BR
Sex/Number:	Male and female/l0 per sex per dose group
Route of Administration:	Cavage
Exposure Period:	90 days of feeding plus 1 -generation reproduction
Frequency of Treatment:	Daily
Exposure Levels:	0, 150, 300, 600 mg/kg
Method:	Rats (40/sex/dose group) were administered solutions that contained 0, 150,300, or 600 mg/kg glycolic acid daily for 90 days. Each dosage group was divided into subchronic toxicity, immunotoxicity, neurotoxicity, and reproductive toxicity subsets (10/sex/subset/concentration). Details for the subchronic, immunotoxicity, and neurotoxicity subsets can be found in Section 5.2.

During the 90-day feeding phase of the study, all rats were weighed, clinical observations were recorded, and food consumption was measured. On test day 97, animals of the reproductive toxicity subset were bred within their respective treatment groups. Each female was continually housed on a 1: 1 basis with a randomly selected male of the same dose level until copulation was observed (designated as day 0 of gestation) or until 2 weeks bad elapsed. The presence of an intravaginal or extruded copulation plug was considered evidence of copulation. Females were allowed to deliver and rear their offspring until weaning (postpartum day 21). During the mating, gestation, and lactation phases of the study, body weights and clinical observations were recorded for male and female rats, and food consumption was recorded only for female rats during gestation. Live and dead pups in each litter were counted, and body weights and clinical observations of pups were recorded. On Day 4 postpartum, the litters were culled randomly to 8 (4/sex when possible). Extra pups from this culling were euthanatized and did not receive pathological evaluation. Litters of 8 pups or less were not reduced. All parental rats were sacrificed and received a gross pathological examination. The testes of each male rat were weighed. The uteri of all cohabited female rats were examined for the presence and number of implantation sites. Offspring that were found dead during the lactation period underwent gross pathological evaluation. Weanlings were sacrificed on postpartum day 2 1 and underwent gross pathological

evaluation. Gross lesions from some weanlings were evaluated microscopically. Reproductive parameters recorded or calculated included gestation length, mating index, fecundity index, gestation index, litter survival, implantation site numbers, implantation efficiency, sex ratio, percent born alive, viability index, and lactation index.

GLP: Yes

Test Substance: Glycolic acid (tested as a 70% solution in water), purity >98%

Results: Results of the 90-day subchronic portion of the study can be found in Section 5.2. Results of reproductive performance are detailed below.

Significant decreases in mean body weight of females during gestation was observed in the 300 and 600 mg/kg dose groups. In addition, a significant decrease in mean body weight was observed in the 600 mg/kg dose group on lactation day 0. Since there were no statistically significant differences in overall mean body weight gain for these females during gestation (days 0-21), and there was an overall body weight gain during the 2 1 -day lactation period for the 600 mg/kg females, it was concluded that these effects were due to preexisting body weight deficits established during the premating period. There were no differences in maternal food consumption or food efficiency during gestation; clinical observations during gestation or lactation; mating, fecundity, or gestation indices; implantation efficiency; or gestation length in rats dosed with any concentration of test substance. There were no test substance-related effects on litter size, pup survival, pup weight, or pup clinical signs. A summary of reproductive outcomes is provided in the table below.

Dose (mg/kg)	0	150	300	600
Mating Index(%):	80.0	90.0	100.0	90.0
Fecundity Index (%):	75.0	88.9	90.0	66.7
Gestation Length (days):	22.3	22.6	22.4	22.7
Implantations:	13.8	13.6	13.8	13.3
Implantation efficiency (%):	84.4	97.8	88.0	87.1
Gestation Index:	100.0	100.0	100.0	100.0
Mean % Born Alive:	100.0	100.0	100.0	98.6
0-4 Day Viability % :	97.5	98.3	l,oo.o	100.0
Lactation Index (%):	100.0	100.0	98.6	100.0
Litter Survival (%):	100.0	100.0	100.0	100.0
Sex Ratio (males):	0.58	0.52	0.41	0.48

There were no changes in organ weights or gross pathology of the reproductive system. There were compound-related gross lesions (dilation of the pelvis, calculus, chronic nephropathy, and pale discoloration) in the kidneys of male rats in the 600 mg/kg/day group that correlated microscopically with oxalate crystal nephropathy similar to that diagnosed in the subchronic toxicity animals. No compound-related gross observations were noted in the P_1 females or the F_1 weanlings.

Reference: DuPont Co. (1999). Unpublished Data, Haskell Laboratory Report No. DuPont- 1597.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for Reproductive Toxicity: None Found.

5.5 Genetic Toxicity

Type: In *vitro* Bacterial Reverse Mutation Assay

Tester Strain: *Salmonella typhimurium* TA97a, TA98, TA100, TA1535 *Escherichia coli* strain WP2 *uvr*A (pKM101)

Exogenous Metabolic Activation: With and without Aroclor®-induced rat liver S9

Exposure Concentrations: *Salmonella typhimurium* strain TA 100 and *Escherichia coli*

strain WP2 *uvrA* (pKM101): 1, 5, 10, 50, 100,500, 1000, 2500, 5000 µg/plate

Salmonella typhimurium strains TA97a, TA98, TA1535: 10, 50, 100, 500, 1000, 2500, 5000 µg/plate

Method: Concentrations of glycolic acid were evaluated in comparison to negative (solvent) controls using *Salmonella typhimurium* strain TA100 and *Escherichia coli* strain WP2 *uvrA* (pKM101). Concentrations of *Salmonella typhimurium* strains TA97a, TA98, and TA1535 were subsequently tested to complete the first trial. In a second independent assay, concentrations of glycolic acid were tested in comparison to negative (solvent) controls.

Solutions of the test substance were prepared immediately prior to treatment, and were presumed to be stable under the conditions of the study. Treatment and control solutions were not analyzed for concentration, uniformity, or stability. The stock solution used for preparation of the dosing solutions was corrected for a purity value of 70.58%.

This study consisted of 2 independent trials that assessed test substance mutagenicity. For each trial, 3 replicates were plated for each tester strain in the presence and absence of the exogenous metabolic activation system at each test substance concentration. Phosphate buffered saline (PBS) was used as the test substance solvent, diluent, and negative control. Positive controls included the following: 2-nitrofluorene (2NF), N-ethyl-N-nitro-N-nitroguanidine (ENNG), sodium azide (NAAZ), ICR 191 acridine mutagen (ICR 191), 9,10-dimethyl-1 ,2-benzanthracene (DMBA), and 2-aminoanthracene (2AA). Treatments with the exogenous metabolic activation system were conducted by adding negative or positive control or test substance solution, metabolic activation system, and overnight culture containing approximately $1x10^8$ bacteria to top agar containing L-histidine, D-biotin, and L-tryptophan. Treatments in the absence of the metabolic activation system were the same as those in the presence of the exogenous metabolic activation system, with the exception that sterile buffer was used as a replacement for the exogenous metabolic activation system. After pouring onto the surface of minimal glucose agar plates, the top agar was allowed time to solidify, and the individually labeled plates were inverted and incubated at approximately 37°C for approximately 48 hours. When necessary, plates were

refrigerated at 4 ± 3°C prior to evaluation and counting of revertant colonies.

Bacterial background lawns were evaluated for evidence of test substance toxicity and precipitation. Evidence of toxicity was scored relative to the concurrent negative control plates and recorded. Revertant colonies for a given tester strain and condition were counted by an automated colony counter, unless the plate exhibited excessive toxicity. Plates with test substance precipitation that interfered with the automated colony counting were counted manually, when possible.

A test substance was classified as positive (mutagenic) if the mean number of revertants in any strain at any test substance concentration was at least 2 times greater than the mean of the concurrent vehicle control and there was a concentration-related increase in the mean revertants per plate in that same strain. A test substance was classified as negative (not mutagenic) if there were no test substance concentrations with a mean number of revertants that were at least 2 times greater than the mean of the concurrent vehicle control or there was no positive concentration-related increase in the mean revertants per plate in that same strain. The test article was classified equivocal if there was no consistent evidence for either a positive or negative evaluation.

GLP:	Yes
Test Substance:	Glycolic acid (tested as a 70% solution in water), purity >98%.
Results:	Negative
Remarks:	In all assays, toxicity was observed in the bacterial background lawns, with and without S9, usually at 1000 µg/plate and above. No evidence of mutagenic activity was detected in either of 2 independent trials.
Reference:	DuPont Co. (1998). Unpublished Data, Haskell Laboratory Report No. DuPont-1301.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional References for In *vitro* Bacterial Reverse Mutation Assay:

Data from these additional sources support the study results summarized above. The studies were not chosen for detailed summarization because the data were not substantially additive to the database.

DuPont Co. (198 1). Unpublished Data, Haskell Laboratory Report No. 608-8 1.

Hoechst AG (1992). Unpublished Data, Report No. 92.0588 (cited in IUCLID (1998). IUCLID Data Sheet "Glycolic acid" (October 6)).

Microbiological Associates (1994). Unpublished Data, submitted by CTFA, Study No. G94AT72.330 (95-AHA-42), Washington, DC, Cosmetic Ingredient Review (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

Yamaguchi, T. and K. Nakagawa (1983). Agric. Biol. Chem., 47(11):2461-2465.

Type:	***In vitro* Mouse Lymphoma Forward Mutation Assay**
Cell Type:	Mouse lymphoma cells (L5 178Y; TK locus)
Exogenous Metabolic Activation:	With and without Aroclor®-induced rat liver S9
Exposure Concentrations:	Initial assay: 39.3, 78.5, 157, 313, 625, 1250, 2500, 5000 µg/mL Confirmatory assay: 250, 500, 1000, 2000, 2500, 3000, 4000, sooo µg/mL
Method:	The vehicle for the test substance was water in the cytotoxicty assay and was changed to Fischer's medium for the mutation assays to aid pH adjustment. Concurrent vehicle controls were performed for each portion of the assay, both with and without metabolic activation. Three vehicle control cultures were initiated in the mutation assays. The positive control substances were methyl methanesulfonate (MMS) and methylcholanthrene (MCA) for the assays without and with exogenous metabolic activation, respectively. Preparations of test substance in the vehicle were prepared fresh each day. The stock solution used for preparation of the dosing solutions was corrected for a purity value of 70.58%. Initial and confirmatory assays were performed without exogenous metabolic activation, In the initial assay, 8 concentrations were analyzed for mutant induction. A confirmatory assay was performed with concentrations clustered at the high end of the concentration range. In the presence of S9 metabolic activation, an initial and confirmatory assay were also performed. The assay conditions consisted of vehicle controls in triplicate, 2 positive controls, and 10 different test substance dose

levels using 1 culture per dose level. Treated cultures were eliminated during the expression period so that 8 dose levels were left for analysis of mutant induction. The appearance of the treated cultures was recorded both at the time of treatment and after the 4-hour treatment period. A standard expression period of 2 days was used to allow for mutant recovery, growth, and expression of the $TK^{+/-}$ phenotype. Cell densities were determined on day 1 and were adjusted to $3x10^5$ cells/mL in 20 mL of growth medium. If the cells in a culture failed to multiply to a density of 4x 1 0^5 on the first day after treatment, the culture was not subcultured. On day 2, cell counts were again determined, and appropriate cultures were selected for cloning and mutant selection. Cultures with cell densities less than approximately $3x10^5$ cells/mL were deemed unacceptable due to cytotoxicity, and were not considered for selection. A total of $3x10^6$ cells from each selected tube was suspended in selection medium in soft agar to recover mutants. This sample was distributed into 3 dishes (100 mm each). All dishes were placed in an incubator at approximately 37°C with approximately 5% CO_2:95% humidified air. After 12 or 13 days in the incubator, the colonies were counted. The mutant frequency was calculated as the ratio of the total number of mutant colonies found in each set of 3 mutant selection dishes to the total number of cells seeded, adjusted by the absolute selection cloning efficiency.

The test substance was evaluated as positive, negative, or equivocal in this assay. The test substance was classified positive (induced gene mutations) if dose-dependent increases of 2-fold or greater in mutant frequency were obtained over the concurrent background mutant frequency (average mutant frequency of the vehicle control cultures). It was desirable to obtain this relationship for at least 3 doses, but this goal depended on the dose steps chosen for the assay and toxicity at which mutagenic activity appeared. The dose dependent requirement was waived if a large increase in mutant frequency (4-fold or higher) was obtained for a single dose at or near the highest testable toxicity. However, for the test substance to be evaluated as positive, any increases must have been repeated in the 2nd trial.

The test substance was classified negative in a single trial if a 2-fold increase in mutant frequency was not observed for (1) a range of doses that extended to toxicities causing 10-20% relative total growth, (2) for relative nontoxic test

	substances, a range of doses that extended to the maximum concentration of 5 mg/mL, (3) a range of doses that extended to a level approximately twice the solubility limit in culture medium, or (4) the increase(s) were not repeatable in a confirmatory trial. The test article was classified equivocal if there was no consistent evidence for either a positive or negative evaluation.
GLP:	Yes
Test Substance:	Glycolic acid (tested as a 70% solution in water), purity >98%.
Results:	Equivocal: Without S9 metabolic activation: Negative. With S9 metabolic activation: Negative at concentrations of 26 mM and below. Positive with metabolic activation at concentrations of 33 mM and above. See remarks for additional information.
Remarks:	The test substance did not induce forward mutations at the TK locus in L5178Y mouse lymphoma cells under the nonactivation conditions. The test substance produced increases in mutant frequency in the presence of S9 metabolic activation at high concentrations only (2500-5000 µg/mL), which corresponds to 33-66 mM concentrations. However, no increases in mutant frequency were observed at or below 2000 µg/mL (26 mM). The recommended maximum concentrations specified in the OECD testing guideline is 10 mM for this assay. Therefore, the positive response was only observed at excessively high concentrations. The average cloning efficiencies for the vehicle controls varied from 93.9% and 77.7% without activation to 95.0% to 77.2% with activation. The positive control cultures, MMS (nonactivation) and MCA (activation) induced large increases in mutant frequency that were greatly in excess of the minimum criteria.
Reference:	DuPont Co. (1998). Unpublished Data, Haskell Laboratory Report No. DuPont-1616.
Reliability:	High because a scientifically defensible or guideline method was used.

Additional Reference for In *vitro* Genetic Toxicity Assays:

Data from this additional source supports the study results summarized above. This study was not chosen for detailed summarization because the data were not substantially additive to the database.

Microbiological Associates (1994). Unpublished Data, submitted by CTFA, Study No. G94AT72501 (95-AHA-41), Washington, DC, Cosmetic Ingredient Review (cited in NICNAS (2000). Glycolic Acid: Priority Existing Chemical Assessment Report No. 12, National Industrial Chemicals Notification and Assessment Scheme, Commonwealth of Australia).

Type:	*In vivo* **Mouse Micronucleus** Assay
Species/Strain:	Mice/Crl:CD-1®(ICR)BR
Sex/Number:	Male and female/5 per sex for the low and mid doses; 10 per sex for the control; 15 males and 13 females for the high dose
Route of Administration:	Oral intubation
Exposure Concentrations:	300, 600, 1200 mg/kg (low, mid, and high doses, respectively) for males 400, 800, 1600 mg/kg (low, mid, and high doses, respectively) for females
Method:	Immediately prior to dosing, glycolic acid solutions, adjusted for purity, were prepared in water. The stock solution used for preparation of the dosing solutions was corrected for a purity value of 70.58%. The corresponding vehicle control was water, and the positive control was cyclophosphamide (CP). All mice were dosed by intragastric intubation. The number of mice in the high dose groups exceeded 10 mice/sex to ensure a minimal number survived for evaluation of micronuclei in the event of mortality. Body weights and clinical signs were recorded. Bone marrow smears were prepared from 5 mice/sex from the control and all treatment groups 24 hours post-dosing, and from the control and high-dose treatment groups 48 hours post-dosing. Bone marrow smears were examined using incident light fluorescence microscopy. Color was used to distinguish PCEs (polychromatic erythrocytes) from NCEs (normochromatic erythrocytes). PCEs (2000 per animal) were evaluated for the presence of micronuclei. Cellular inclusions that were irregularly shaped or stained, or out of the focal plane of the cell, were considered artifacts and were not included in the micronuclei counts. The unit of scoring was the micronucleated cell; therefore, PCEs with more than 1 micronucleus were scored as a single MNPCE. Micronucleated NCEs were counted in each optic field while scoring the 2000 PCEs. Additionally, the number of PCEs among 1000 erythrocytes was recorded for each animal.

For the test substance to be judged negative, no statistically significant increases in MNPCEs above the concurrent vehicle control values could occur at any dose level or sampling time. In order for a test substance to be judged positive, statistically significant increases in MNPCEs above concurrent vehicle control values must have been observed at more than one sampling time, or in both sexes. However, the final analysis was based on scientific judgement and results not meeting the indicated criteria for positive or negative findings were evaluated on a case-by-case basis.

GLP: Yes

Test Substance: Glycolic acid (tested as a 70% solution in water), purity >98%.

Results: Negative

Remarks: A total of 5 males and 3 females from the highest dose groups (1200 and 1600 mg/kg, respectively) were found dead 1 or 2 days post-dosing. There were no statistically significant decreases in body weight gain in either male or female mice administered glycolic acid. Within approximately 2 hours post-dosing, clinical signs of systemic toxicity, including lethargy, moribundity, and/or abnormal gait were observed in a few mice from the groups that received the highest doses of glycolic acid (5/15 males in the 1200 mg/kg group, and 2/13 females in the 1600 mg/kg group). Lethargy and/or moribundity continued to be observed at a low frequency in these groups up to 2 days post-dosing. There were no clinical signs of toxicity or statistically significant body weight gain decrements in CP-treated mice of either sex.

No statistically significant increases in micronucleated PCE frequency were observed in any test substance-treated group at either time point. The proportions of PCEs among 1000 erythrocytes were decreased approximately 18 and 25% below concurrent control values in the high dose male and female mice, respectively, at the 48-hour time point. Although not statistically significant, the depressions in this parameter might be indicative of bone marrow toxicity. Glycolic acid did not induce a statistically significant increase in micronucleated PCEs in mouse bone marrow. As expected, there were statistically significant increases in MNPCE frequency in male and female mice treated with CP. No statistically significant depressions in the PCE/NCE ratio were found in either CP-treated male or female mice.

Reference: DuPont Co. (1998). Unpublished Data, Haskell Laboratory

Report No. DuPont- 1197.

Reliability: High because a scientifically defensible or guideline method was used.

Additional References for *In vivo* Mouse Micronucleus Assay: None Found.