EPA 560/11-79-006

Investigation of Selected Potential Environmental Contaminants: Ethylene Glycol, Propylene Glycols and Butylene Glycols

By:

Lynne M. Miller

May 1979

Final Report

EPA Contract No. 68-01-3893

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Project Officer:

Robert Carton

Prepared For:

Office of Toxic Substances

U.S. Environmental Protection Agency

Washington, D.C. 20460

Franklin Research Center

A Division of The Franklin Institute

The Benjamin Franklin Parkway, Phila., Pa. 19103 (215) 448-1000

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PREFACE

This report is a survey and summary of the literature available through November 1978 on ethylene glycol, 1,2-propanediol, 1,3-propanediol, 1,2-butanediol, 2,3-butanediol, 1,3-butanediol, and 1,4-butanediol. Major aspects of properties, reactions, production, use, environmental exposure, biological effects and regulations are reviewed. A list of sources employed in the literature search appears in the appendix.

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EXECUTIVE SUMMARY

This report reviews aspects of production, use, environmental exposure and biological effects of ethylene glycol, two isomers of propylene glycol (1,2- and 1,3-propanediol) and four isomers of butylene glycol (1,3-, 1,4-, 2,3-, and 1,2-butanediol). About 3.7 billion pounds of ethylene glycol were produced in 1977 in the U.S. for use primarily in antifreeze and polyester fiber. Domestic production of 1,2-propanediol (propylene glycol) is about 0.5 billion pounds which goes mainly into polyester resins, food, pharmaceuticals, and cellophane. 1,3-Propanediol is of only minor commercial importance. Domestic demand for 1,4-butanediol is 0.17 billion pounds for the production of tetrahydrofuran and acetylenic chemicals. 1,2- and 1,3-butanediol are used to produce polymeric plasticizers while the 2,3-isomer is used as a solvent, humectant, and coupling agent; production figures are unavailable.

Limited monitoring data make it difficult to adequately assess environmental exposure to the glycols. The major source of contamination by ethylene glycol and 1,2-propanediol is probably from the disposal of spent antifreeze and de-icing fluids. The glycols are capable of being degraded by a variety of acclimated and unacclimated soil, water, and sewage microorganisms. Under different testing conditions, complete degradation usually occurred within 3-20 days.

In humans, ethylene glycol intoxication, usually as a result of accidental ingestion of antifreeze, may result in nausea, hypertension, tachycardia, cardiopulmonary failure, renal impairment, and coma. The oral lethal dose in humans is about 1.4-1.6 g/kg and in laboratory

animals, 6-15 g/kg. This toxicity is due to a metabolite of ethylene glycol, glycolate. Microscopic findings in humans and laboratory animals often include deposition of calcium oxalate crystals in the kidney. Significant inhalation exposure is likely only when the glycol is at elevated temperatures. Only one occupationally-related case report is available in the literature involving ethylene glycol inhalation. Intermittent exposure to 10 or 57 mg/m^3 for 90 days was without effect to several laboratory animals while continuous exposure to 12 mg/m^3 caused eye irritation. Continuous exposure to 256 mg/m^3 of monkeys resulted in some impairment of sensory discrimination. No carcinogenic potential has been noted in mice given a single s.c. injection, in mice by lifetime skin painting, or in rats given twice weekly s.c. injections for one year.

1,2-Propanediol is a generally-recognized-as-safe (GRAS) food additive. In laboratory animals, the oral LD_{50} ranges between about 14-30 g/kg. Large doses result in a loss of equilibrium, central nervous system depression and respiratory failure. No consistent chronic effects were noted in rats fed up to 10% in the diet or dogs fed up to 20%. No teratogenic effects were noted in mice, rats, hamsters, or rabbits given 1,2-propanediol during gestation. 1,2-Propanediol was not carcinogenic when administered by single or multiple injection, by chronic dietary addition or by lifetime skin painting. No mutagenic effects were detected in a host-mediated assay, cytogenetic assay, or dominant lethal gene test.

In one study, 1,3-propanediol was twice as toxic as 1,2-propanediol by subacute dietary feeding.

1,3-Butanediol has been extensively studied as a synthetic metabolizable source of dietary energy. The oral LD_{50} in mice and rats ranges from 23 to 30 g/kg. At large doses, narcosis results from muscle relaxation. Some investigators reported a decrease in body weight gain at high levels of 1,3-butanediol in the diet (often 20% or more) but no histological changes have been attributed to this diol. A gradual decrease in reproductive rate was noted in a multigeneration study in rats fed up to 24% in the diet. No teratogenic effects were observed in litters from rats, dogs, or rabbits given butanediol prior to and/or during pregnancy. Furthermore, no adverse effects were noted in a dominant lethal test and in a cytogenetic test in rats.

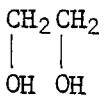
Few studies are available on 1,2- , 2,3- , and 1,4-butanediol. In laboratory animals, the oral LD_{50} averages 16 g/kg, 8.9 g/kg, and 1.2-2.5 g/kg, respectively, for these isomers; the 1,4- isomer is the more acutely toxic isomer, acting as a central nervous system depressant.

I. PHYSICAL AND CHEMICAL DATA

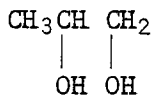
A. Chemical Structure

Glycols are compounds containing two hydroxyl groups (—OH) attached to carbon atoms in an aliphatic carbon chain. The glycols discussed in this report have the following structures:

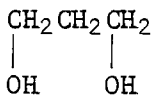
1,2-Ethanediol (ethylene glycol)



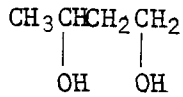
1,2-Propanediol (propylene glycol)



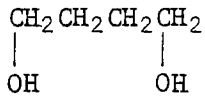
1,3-Propanediol



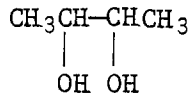
1,3-Butanediol



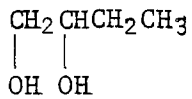
1,4-Butanediol



2,3-Butanediol



1,2-Butanediol



Synonyms and other identifiers of these glycols appear in Table 1. The term propylene glycol is often used in the literature to refer to 1,2-propanediol; the latter term is used throughout this report.

Table 1

Nomenclature and Other Identifiers of Ethylene Glycol, Propylene Glycols, and Butylene Glycols

Chemical Abstracts Service (CAS) 10th Collective Index Name	CAS Registry No.	EPA Toxic Substances Control Act List No.	Synonyms	Molecular Formula	Wiswesser Line Notation
ethylene glycol	107-21-1	A806-1653	1,2-dihydroxyethane 1,2-ethanediol ethane-1,2-diol ethylene alcohol ethylene dihydrate glycol glycol alcohol monoethylene glycol	$C_2H_6O_2$	Q2Q
1,2-propanediol	57-55-6	B450-5740	propylene glycol methylethylene glycol methyl glycol monopropylene glycol propane-1,2-diol alpha-propylene glycol 1,2-propylene glycol trimethyl glycol 1,2-dihydroxypropane sirlene	$C_3H_8O_2$	QY1Q

Table 1 (Continued)

Chemical Abstracts Service (CAS) 10th Collective Index Name	CAS Registry No.	EPA Toxic Substances Control Act List No.	Synonyms	Molecular Formula	Wiswesser Line Notation
			2,3-propanediol 2-hydroxypropanol		
1,3-propanediol	504-63-2	B451-0531	1,3-dihydroxypropane trimethylene glycol 1,3 propylene glycol Beta-propylene glycol 2-deoxyglycerol	$C_3H_8O_2$	Q3Q
1,3-butanediol	107-88-0	A322-3373	Beta-butylene glycol 1,3-butylene glycol 1,3-dihydroxybutane methyl trimethylene glycol butane-1,3-diol	$C_4H_{10}O_2$	QY2Q
1,4-butanediol	110-63-4	A322-3510	1,4-butylene glycol 1,4-dihydroxybutane 1,4-tetramethylene glycol tetramethylene glycol butane-1,4-diol	$C_4H_{10}O_2$	Q4Q

Table 1 (Continued)

Chemical Abstracts Service (CAS) 10th Collective Index Name	CAS Registry No.	EPA Toxic Substances Control Act List No.	Synonyms	Molecular Formula	Wiswesser Line Notation
2,3-butanediol	513-85-9, 35007-63-7, 6982-25-8, 24347-53-8, 5341-95-7, 19132-06-0	A322-3843	2,3-dihydroxybutane dimethylene glycol 2,3-butylene glycol pseudobutylene glycol sym-dimethylene glycol	$C_4H_{10}O_2$	QY,YQ
1,2-butanediol	584-03-2	A322-3155	1,2-butylene glycol 1,2-dihydroxybutane ethyl ethylene glycol	$C_4H_{10}O_2$	

B. Properties of the Pure Material

Ethylene glycol is a colorless, practically odorless, relatively involatile, hygroscopic liquid. Some of its important physical properties are listed in Table 2. Ethylene glycol is miscible in all proportions with water and the lower aliphatic alcohols, aldehydes, and ketones, but is almost insoluble in hydrocarbons (Curme and Johnston, 1952). It is an excellent permanent antifreeze because it is miscible with water and has such a low freezing point. Ethylene glycol is considered a slight fire hazard when exposed to heat or flame and a slight explosion hazard when exposed to flame (Sax, 1975). The lower flammable limit is 3.2% (Table 2).

1,2-Propanediol is a colorless, odorless, slightly sweet tasting liquid. As it contains an asymmetric carbon atom, it occurs in two optically active forms (levorotatory and dextrorotatory isomers). Data on physical properties, which appear in Table 3, were determined on the racemic mixture. 1,2-Propanediol is completely miscible with water and most lower molecular weight aliphatic compounds containing oxygen or nitrogen; most aromatic and halogenated compounds are only partly miscible in 1,2-propanediol (Curme and Johnston, 1952). It is considered a moderate fire hazard when exposed to heat or flame and a moderate fire hazard when exposed to flame (Sax, 1975).

1,3-Propanediol is a viscous, colorless, hydroscopic, odorless liquid possessing a brackish irritating taste. It is soluble in water, alcohol, and ether (Curme and Johnston, 1952). Physical properties of 1,3-propanediol are listed in Table 3.

Table 2

Physical Properties of Ethylene Glycol (Dow, 1978a, Union Carbide, 1978 and 1976; Perl et al., 1976; Curme and Johnston, 1952)

Property	Data
appearance	colorless liquid mild odor
boiling point, 760 mm Hg	197.6°C
density, 20°C	1.11336 g/ml
flash point	241°F
flammable limits	lower 3.2%
freezing point, 760 mm Hg	−12.7°C
heat of combustion, 20°C	−283.3 kcal/mol
molecular weight	62.07
saturated vapor at 20°C	79 ppm (204 mg/m^3)
solubility in water at 20°C	complete
vapor density (air = 1)	2.14
vapor pressure at 20°C	0.06 mm Hg
refractive index, n_D^{20}	1.4318
% volatiles by volume	Nil
weight/U.S. gallon, 20°C	9.28 lbs
conversion factors (25° C; 760 mm Hg)	1 ppm = 2.74 mg/m^3 1 mg/ℓ = 394 ppm
olive oil/water partition coefficient, 37°C	34×10^{-4}

Table 3
Physical Properties of Propylene Glycols (Dow, 1978b; Union Carbide, 1978; Dow, 1966; Perl et al., 1976; Curme and Johnston, 1952)

Property	1,2-Propanediol	1,3-Propanediol
appearance	colorless liquid	colorless liquid
boiling point, 760 mm Hg	187.3°C	210-211°C
density (20°C), g/ml	1.0363	1.0597
flash point	214°F	--
flammable limits	lower: 2.6%; upper: 12.5%	--
freezing point, 760 mm Hg	-60°C	--
heat of combusion, 20°C	435.9 kcal/mol	--
molecular weight	76.10	76.10
refractive index n_D^{20}	1.4326	--
solubility in water at 20°C	complete	complete
vapor density (air = 1)	2.62	2.6
vapor pressure at 25°C	0.22 mm Hg	--
saturated vapor at 20°C	299 ppm (917 mg/m^3)	--
weight/U.S. gallon, 25°C	8.62	--
conversion factors (25° C, 760 mm Hg)	1 ppm = 3.11 mg/m^3 1 mg/ℓ = 322 ppm	1 ppm = 3.11 mg/m^3 1 mg/ℓ = 322 ppm
olive oil/water Partition coefficient, 37°C	23 x 10^{-4}	24 x 10^{-4}

There are four butanediols: 1,3-, 1,4-, 2,3-, and 1,2-butanediol. Physical properties of these isomers are listed in Table 4. Butanediols are usually viscous, colorless, odorless liquids which are soluble in water. 1,3-Butanediol is also soluble in dibutylphthalate, methyl ethyl ketone and other solvents, but insoluble in straight chain hydrocarbons (Wagner, 1966). 1,4-Butanediol is completely soluble in water, methanol, ethanol, and acetone and moderately soluble in acetate and only slightly soluble in hydrocarbons (GAF, n.d.). The meso form of 2,3-butanediol is moderately soluble in diisopropyl ether, while the d,l form is very soluble in this ether (Windholz, 1976). 1,3-Butanediol has been classed as a slight fire hazard, while the other butanediols present moderate fire hazards when exposed to heat or flame (Sax, 1975).

C. Properties of the Commercial Material

Specifications for industrial grade (99.0% pure) and polyester grade ethylene glycol are listed in Table 5. Impurities in both grades include acetic acid, ash, and diethylene glycol.

Specifications for U.S.P (99.5% pure) and industrial grade 1,2-propanediol appear in Table 6. Both grades contain acetic acid.

1,4-Butanediol is available in a technical (97% pure) or an anhydrous grade (98.5% pure); the technical grade contains a maximum of 0.4% water while the anhydrous grade contains 0.04% water (Freifeld and Hort, 1966). Specifications are shown in Table 7. Impurities include butenediol and butyrolactone.

Table 4
Physical Properties of Butylene Glycols (Perl et al., 1976; Sax, 1975; Weast, 1974; Budke and Banerjee, 1971; Wagner, 1966; Freifeld and Hort, 1966)

	1,3-Butanediol	1,4-Butanediol	2,3-Butanediol	1,2-Butanediol
appearance	colorless liquid	colorless liquid	viscous liquid or solid	colorless liquid
boiling point, °C	--	221-231	--	--
(l)	107-110	--	178	94-96
(d)	204	--	180-182	192-194
(m)	--	--	182	--
(d,l)	207.5		177	190.5
density, 20°C		1.0171		
(l)	1.005	--	0.9869	--
(d)	1.0053	--	0.9872	1.0059
(m)	--	--	1.0003	--
(d,l)	1.0053		1.0003	1.0024
molecular weight	90.12	90.12	90.12	90.12
flash point	250°F	>250°F (open cup)	185°C (open cup)	104°F
refractive index		1.4446	--	--
(l)	--		1.4318	--
(d)	1.4418		1.4306	1.4375
(m)	--		1.4325	--
(d,l)	1.4410		--	1.4378
solubility in water	complete	complete	complete	complete

Table 4 (Continued)

	1,3-Butanediol	1,4-Butanediol	2,3-Butanediol	1,2-Butanediol
conversion factors (25° C, 760 mm Hg)	1 ppm = 3.68 mg/m^3 1 mg/ℓ = 272 ppm	1 ppm = 3.68 mg/m^3 1 mg/ℓ = 272 ppm	1 ppm = 3.68 mg/m^3 1 mg/ℓ = 272 ppm	1 ppm = 3.68 mg/m^3 1 mg/ℓ = 272 ppm
olive oil/water Partition coefficient, 37°C	--	84×10^{-4}	--	--
vapor pressure	0.06 mm Hg at 20°C	--	--	--
saturated vapor at 20°C	79 ppm (296 mg/m^3)			

The specifications for commercially available 1,3- and 2,3-butanediols are listed in Table 7.

D. Chemical Reactions Involved in Use

The most important commercial reaction of the glycols is esterification (Miller, 1966). Esterification is carried out with organic and inorganic acids, acid halides, or acid anhydrides. The reaction of a glycol with monocarboxylic acids, such as acetic acid, produces

Table 5
Specifications for Industrial Grade and Polyester Grade Ethylene Glycol (Union Carbide, 1978)

	Industrial Grade	Polyester Grade
purity, % by weight, minimum	99.0	--
acidity, % by weight, maximum as acetic acid	0.005	0.005
water, % by weight, maximum	0.2	0.08
ash, % by weight, maximum	0.005	0.005
odor	mild	mild, practically none
specific gravity at 20/20°C	1.1151-1.1156	1.1151-1.1156
suspended matter	substantially free	substantially free
water solubility	miscible in all proportions at 25°C	miscible in all proportions at 25°C
diethylene glycol, % by weight, maximum	0.5	0.08
iron, ppm maximum	--	0.07

primarily mono- or diesters depending on the molar ratios of the reactants. An example of this is the reaction of ethylene glycol with acetic acid:

Table 6
Specifications for Industrial Grade and U.S.P. 1,2-Propanediol (Dow, 1975, 1978b)

	Industrial Grade	U.S.P.
purity, % by weight, minimum	--	99.5
acidity, ppm maximum as acetic acid	20	20
water, % by weight, maximum	0.2	0.2
ash, % maximum, sulfated	--	.005
odor	characteristic odor	practically none
taste	--	slight characteristic
specific gravity 20/20°C	1.0377-1.0390	1.0376-1.0389
suspended matter	--	substantially free
water solubility	complete	complete
chlorides, ppm maximum	1	1
heavy metals, ppm maximum as lead	--	5
arsenic, ppm maximum at As_2O_3	--	1
iron, ppm maximum	0.5	0.3

Table 7
Specifications for Butylene Glycols

	1,4-Butanediol[a] (GAF, n.d.; Freifeld and Hort, 1966)	1,3-Butanediol (Budke and Banerjee, 1971; Celanese, 1977)	2,3-Butanediol (Budke and Banerjee, 1971; Curme and Johnston, 1952)
purity, %, minimum	(b)	99.0	--
color, APHA maximum	20	--	--
appearance at 25°C	clear liquid	--	--
boiling point	--	--	182°C[(c)]
solidification point, °C, minimum	19.0		
water content, % maximum	(a)	0.50	--
solidification point, °C, minimum	19	--	--
carbonyl number, mg KOH/g, maximum	1.5	--	--
distillation range, 760 torr	--	200-215°C	174-186°C
acidity, as acetic acid, % maximum	--	0.005	0.01
specific gravity 20/20°C	--	1.004-1.006	1.006-1.010
butenediol (%)	<0.05	--	--
butyrolactone (%)	0.1	--	--

[a]Two grades are available, regular (0.4% water, maximum) and anhydroug (contains less than 0.04% water).

[b]Technical grade: 97% pure anhydrous grade: 98.5% pure.

[c]Mixture of 85% meso and 15% dextro-levo isomers.

$$HOCH_2CH_2OH + CH_3COOH \rightarrow CH_3COOCH_2CH_2OH + H_2O$$

ethylene glycol monoacetate

$$HOCH_2CH_2OH + 2CH_3COOH \rightarrow CH_3COOCH_2CH_2OOCCH_3 + 2H_2O$$

ethylene glycol diacetate

Cyclic or linear polyesters are formed by the reaction with dicarboxylic acids, an example of which is given below:

$$HOCH_2CH_2OH + HOOCRCOOH \rightarrow (OCH_2CH_2OOCRCO)_n + 2H_2O$$

Commercial applications of low-molecular weight organic-acid esters of ethylene glycol include use in solvents. Glycol esters of acrylic and methacrylic acids are used to prepare polyacrylate resins. The terephthalate ester of ethylene glycol is used to make polyester fiber. Fatty acid esters of propylene glycol are used in cosmetics and pharmaceutical preparations. Polyesters of 1,3-butanediol are made by reaction with oxalic, succinic, glutaric, or adipic acids or with maleic or phthalic anhydrides. Esters of 1,4-butanediol are used in thermoplastic polymers; polyesters are used as plasticizers (Miller, 1966; Wagner, 1966; Freifeld and Hort, 1966).

Another commercially important reaction of the glycols is etherification. An example is heating ethylene glycol with a dehydration catalyst (H_2SO_4) to form dioxane, a cyclic diether.

Acetals and ketals of glycols are formed by condensation reactions with appropriate aldehydes and ketones. These have applications as solvents.

II. ENVIRONMENTAL EXPOSURE FACTORS

Aspects of manufacture, use, waste, handling, environmental contamination, degradation, and analytical detection methods are considered in the following sections.

A. Production

1. Production Processes

a. Ethylene Glycol

Two methods are currently used in the U.S. to manufacture ethylene glycol. The more widely used process involves the hydration of ethylene oxide. A method for the direct production of ethylene glycol from ethylene was recently put into commercial operation by Oxirane Corporation.

Figure 1 shows a flow chart for the production of ethylene glycol from ethylene oxide. In a widely used method of producing ethylene oxide, ethylene and oxygen are fed into an isothermal catalytic

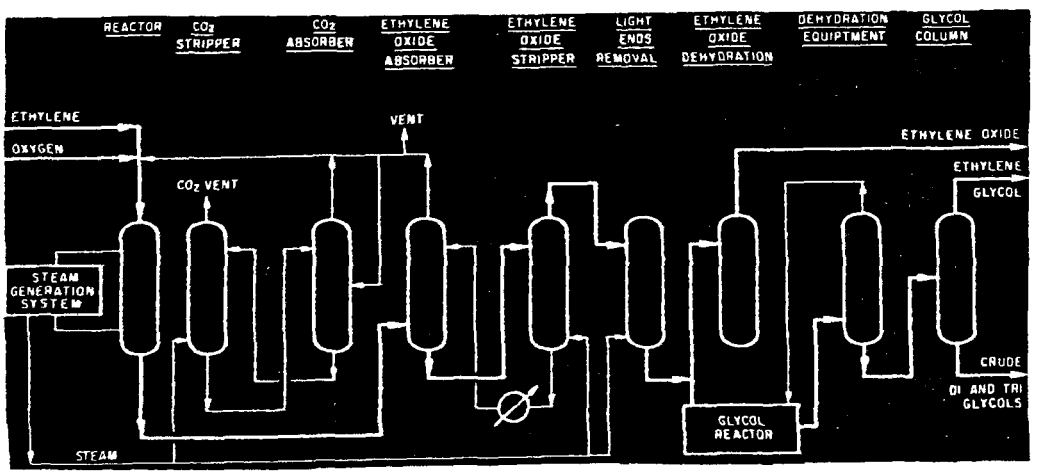


Figure 1. Production of ethylene oxide and ethylene glycol, licensed by Shell Development Co. (Anon., 1977a). Reprinted by permission from Gulf Publishing Co., Houston, Texas

reactor; the selective silver catalyst highly favors ethylene oxide formation. About 60-70% of the ethylene is converted to ethylene oxide at reaction temperatures of 270-290°C. The reactor effluent gas containing the ethylene oxide product is cooled, then the ethylene oxide is recovered by absorption in water; unabsorbed gases are recycled. Recycle gas is scrubbed to remove excess CO_2. The ethylene oxide is stripped from the water, then distilled to remove light ends. To produce ethylene glycol, ethylene oxide is then hydrated in acid or by pressure in a tower reactor. Acid hydration requires a 30 minute contact at 50°-70°C in a 0.5-1.0% sulfuric acid solution. In pressure hydration, 185 psi and a contact time of one hour at 195°C are required. Using either hydration process, diethylene glycol and triethylene glycol are formed as by-products, which can be separated from ethylene glycol by vacuum distillation (Anon, 1977a & b; Lowenheim and Moran, 1975).

A new process of manufacturing ethylene glycol directly from ethylene by acetoxylation was developed by Halcon International, Inc. and put into commercial use at the Oxirane plant in Channelview, Texas, which came on stream in early 1978 (Anon., 1977c). The first step in the Halcon process is the catalyzed liquid-phase oxidation of ethylene in acetic acid to a mixture of mono- and diacetates of ethylene glycol. The acetates are then hydrolyzed to ethylene glycol at 107-130°C and 1.17 atm pressure; acetic acid is recycled (Hatch and Matar, 1978a). The overall ethylene glycol yield by this process is 95%, compared to 67% via ethylene oxide hydration (Brownstein, 1974).

Union Carbide has obtained a patent on the production of ethylene glycol from synthesis gas. If this process were commercialized, ethylene glycol could be manufactured from a variety of raw materials; production would then be independent of natural gas and petroleum supply (Hatch and Matar, 1977). The reaction is carried out at 200°C and 8,000 psi and is as follows:

$$3CO + 5H_2 \rightarrow HOCH_2\text{-}CH_2OH + CH_3OH$$

Methanol is a by-product, the amount depending on the reaction conditions. This process is predicted to be of major importance in the mid-1980's (Hatch and Matar, 1978a).

Three other processes to produce ethylene glycol have been employed commercially in the past: a) the reaction of carbon monoxide and formaldehyde; this method was discontinued in 1968 by duPont; b) the fermentation of molasses was a not widely used method which was discontinued in the early 1970's; c) vapor-phase oxidation of propane; this was discontinued by Celanese in 1975 (Lowenheim and Moran, 1975).

b. Propylene Glycols

1,2-Propanediol is manufactured commercially by the hydrolysis of propylene oxide. This process, shown in Figure 2, is analogous to that used to produce ethylene glycol from ethylene oxide (Lowenheim and Moran, 1975). Propylene oxide yields 1,2-propanediol by acid or pressure hydration in a tower reactor. Hydration occurs at elevated temperatures (EPA, 1975). Reaction products are then passed from the reactor to evaporation and drying towers where excess water

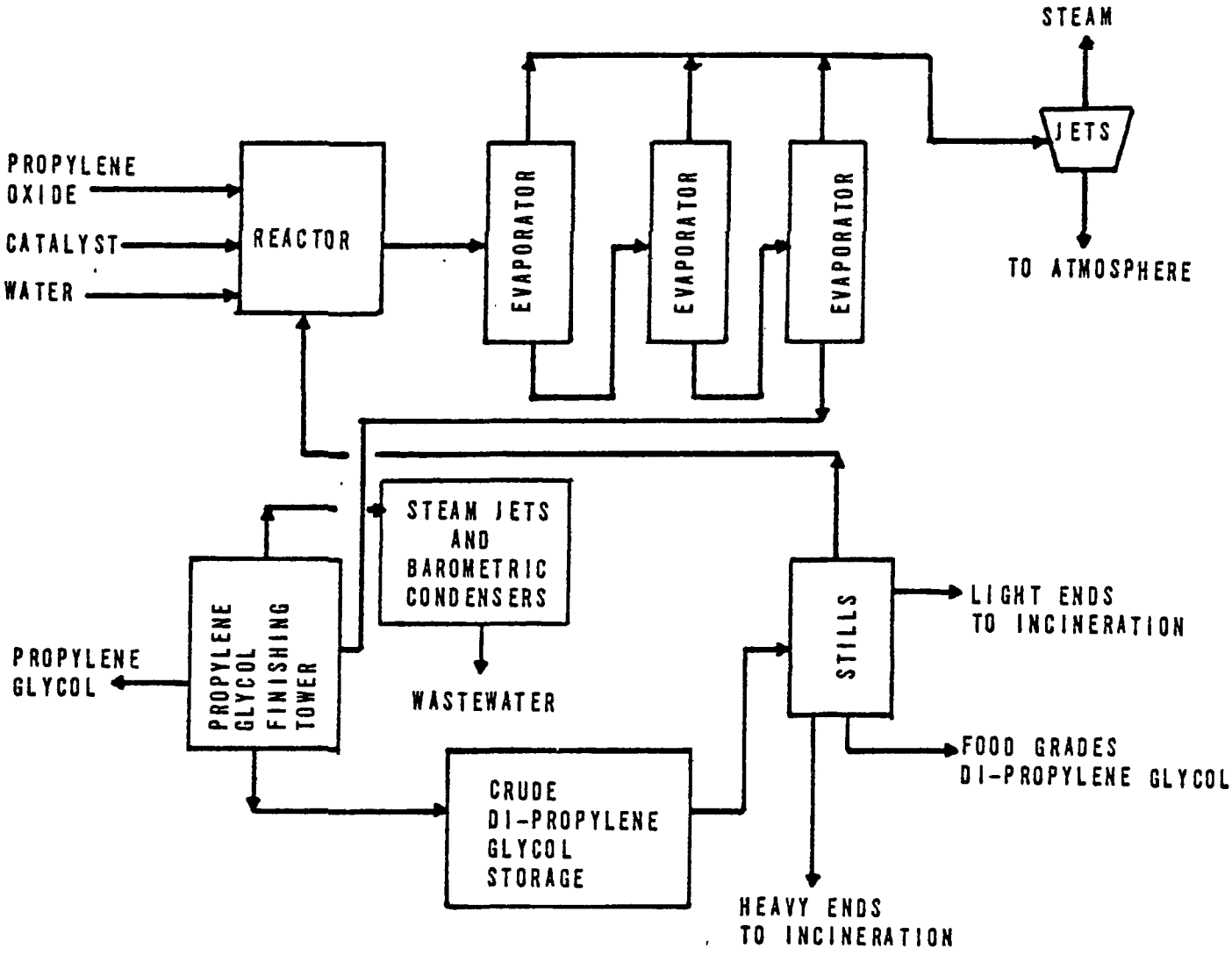


Figure 2. Manufacture of 1,2-Propanediol from propylene oxide (EPA, 1975).

is removed. Crude 1,2-propanediol is then passed to a series of fractionators where water and light ends are removed; then industrial grade 1,2-propanediol is separated and condensed. Dipropylene glycol is obtained as a by-product.

1,3-Propanediol is only of minor commercial importance. It is

primarily recovered in commercial glycerol plants only when there is enough demand. 1,3-Propanediol has also been prepared by heating γ,γ-dihydroxydipropyl ether with hydrobromic acid then hydrolyzing the reaction product with sodium hydroxide (Budke and Banerjee, 1971).

c. Butylene Glycols

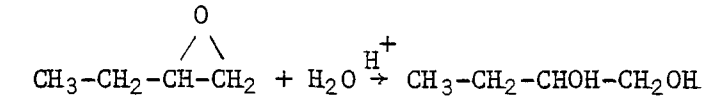
1,4-Butanediol is manufactured at GAF and BASF by the condensation of acetylene with formaldehyde via cupric acetylide catalysts (Brownstein and List, 1977). The copper acetylide is formed by the reaction of acetylene with copper salts such as ammonical cuprous hydroxide. Reaction of formaldehyde with copper acetylide under 5-15 atm. pressure at 90-100°C gives the butynediol in 95% yield. The butynediol is hydrogenated over Raney nickel catalysts at 40-120°C and 75-300 psig to give a 85-90% yield of 1,4-butanediol. Alternate feedstocks for 1,4-butanediol, including maleic anhydride, propylene, and butadiene have been proposed but have not been commercialized in the U.S.

The major commercial method for manufacturing 1,3-butanediol is the catalytic hydrogenation of acetaldol (Wagner, 1966). Catalysts used include Raney nickel, copper, and platinum oxide. Temperatures of 65-120°C and a pressure of 700 psi are employed. From the hydrogenation product, low boiling materials are removed; these include ethyl alcohol, water, and n-butanol. The reaction product is then filtered to remove precipitated salts and catalyst and is redistilled to purify the 1,3-butanediol.

Various bacteria produce 2,3-butanediol through fermentation and have been used in the commercial preparation of this glycol. Vergnaud

(1950) described in a patent the process of making 2,3-butanediol by fermentation of sugar or molasses using bacteria of the genus Mesentericus. 2,3-Butanediol can also be produced by fermentation of potatoes, wheat mash, or enzyme mash (Curme and Johnston, 1952). The proportion of optical isomers produced is a function of the bacteria used. Fermentation products depend on the strain of bacteria employed; these products may include (besides 2,3-butanediol) lactic acid, ethanol, glycerol, formic acid, hydrogen, and carbon dioxide. 2,3-Butanediol is recovered by distillation, solvent extraction, dialysis or steam stripping. 2,3-Butanediol can also be made from gaseous mixtures containing isobutylene and normal butenes; this mixture is combined with hydrogen peroxide and formic acid; then, the reaction product is distilled to remove fractions containing 2,3- and 1,2-butanediols (Cosby, 1957). Keith et al. (1961) described the preparation of 2,3-butanediol in 55% yield by oxidation of 2-butene.

1,2-Butanediol is produced from butylene oxide (Hatch and Matar, 1978b). The oxide is produced from 1-butene by chlorohydrination with hydrochlorous acid, followed by epoxidation. Butylene oxide is then hydrolyzed to 1,2-butanediol, as shown below:



2. Quantity Produced

Production of ethylene glycol is the U.S. during 1977 was 3.7 billion pounds. This represents an 80% increase in production in the last decade, during which time production increased from 2.0

billion pounds in 1968; production peaked at 3.8 billion pounds during 1972 and 1975 (Table 8). Ethylene glycol production during January-October 1978 was 3.25 billion pounds (U.S. Int. Trade Commission, 1978) and year end totals are expected to exceed 3.7 billion pounds (Anon, 1977d). Production is currently less than 60% of the in-place design capacity of manufacturing units (Anon, 1977d).

Total domestic production of 1,2-propanediol was about 0.5 billion pounds during 1977, an increase of 40% during the last decade; during this time, maximum production occurred in 1972 and 1976 (Table 8).

The U.S. International Trade Commission does not list production figures for 1,3-propanediol or for the butanediols. Estimates of plant capacity are discussed in the next section.

3. Domestic Producers and Production Sites

There are 12 producers of ethylene glycol in the United States. Based on announced capacities and trade estimates, the total capacity for 1978 is 6.7 billion pounds (Table 9). More than one billion pounds of capacity were added during 1977 and a 0.8 billion pound capacity plant (Oxirane) was added during 1978 (Anon, 1977d). The largest producer of ethylene glycol is Union Carbide, with a total capacity of about 2.3 billion pounds. Of the 16 sites where ethylene glycol is produced, 7 are in Texas, 5 in Louisiana, 2 in Puerto Rico, 1 in Kentucky, and 1 in Illinois. ICI Americas has announced construction of an ethylene glycol/ethylene oxide plant "at a Texas site" which will be completed in 1981 (Anon, 1978a). Another ethylene glycol/ethylene oxide plant will be built in Texas City, Texas; Union Carbide

Table 8

U.S. Production and Sales of A) Ethylene Glycol and B) 1,2-Propanediol (U.S. International Trade Commission 1973-1978; U.S. Tariff Commission 1968-1972)

	Production (thousand pounds)	Sales (thousand pounds)	Unit Value of Sales, cents per pound
A. Ethylene Glycol			
1978	(3,252,824)[a]	--	--
1977	3,675,461	2,958,366	0.19
1976	3,334,587	2,525,135	0.20
1975	3,809,003	2,847,976	0.21
1974	3,340,695	2,699,075	0.14
1973	3,277,639	2,828,598	0.07
1972	3,761,143	3,113,931	0.06
1971	3,070,007	2,630,826	0.06
1970	3,037,501	2,209,675	0.07
1969	2,570,947	1,936,013	0.06
1968	2,042,846	1,627,336	0.07
B. 1,2-Propanediol			
1978	(345,760)[a]	--	--
1977	489,064	487,152	0.25
1976	516,932	469,850	0.26
1975	390,836	365,513	0.27
1974	510,206	476,450	0.21
1973	501,808	520,298	0.09

Table 8 (Continued)

	Production (thousand pounds)	Sales (thousand pounds)	Unit Value of Sales, cents per pound
1972	562,583	538,037	0.08
1971	421,446	427,311	0.09
1970	428,181	395,459	0.09
1969	460,565	411,173	0.09
1968	352,876	333,055	0.09

[a]Preliminary; production from January 1-October, 1978.

has announced construction of a 700 million pound/year ethylene glycol facility there by 1981 (Anon, 1977e).

There are five domestic producers of 1,2-propanediol with a total capacity of 0.8 billion pounds (Table 10). The largest producers are Dow Chemical (0.40 billion pounds) and Oxirane Chemical Co. (0.25 billion pounds). Production is at six sites: three in Texas, and one each in Louisiana, Kentucky, and West Virginia. The limiting factor for production of 1,2-propanediol is the availability of propylene oxide; expansions of propylene oxide capacity have been announced by Dow and Oxirane (Anon, 1977f).

1,3-Propanediol is manufactured by the Guardian Chemical Corporation (Eastern Chemical Division) in Hauppauge, N. Y. (SRI, 1975); the capacity of this plant is not available.

Table 9
Ethylene Glycol Producers (MCP, 1977; Anon, 1977e)

Producer	Capacity[a] (millions of pounds per year)
BASF Wyandotte Corp.	
Geismar, Louisiana	250
Calcasieu Chemical Corp.	
Lake Charles, Louisiana	230
Celanese Corp.	
Clear Lake, Texas	500
Dow Chemical USA	
Freeport, Texas	330
Plaquemine, Louisiana	350
Jefferson Chemical[a]	
Port Neches, Texas	360
Northern Petrochemical	
Joliet, Illinois	350
Olin Corp.	
Brandenburg, Kentucky	50
Oxirane	
Channelview, Texas	800
PPG Indust., Inc.	
Beaumont, Texas	200
Guaynilla, Puerto Rico	400
Shell Chemical Co.	
Geismar, Louisiana	200
Texas Eastman	
Longview, Texas	180
Union Carbide Corp.	
Ponce, Puerto Rico	730
Seadrift, Texas	870
Taft, Louisiana	700
Total	6,700

[a]Capacities are probably overstated and include total glycols, for example, triethylene glycol.

Table 10
1,2-Propanediol Producers (Anon, 1977f)

Producer	Capacity (millions of pounds per year)
Dow Chemical	
Freeport, Texas	250
Plaquemine, Louisiana	150
Jefferson Chemical Co.	
Port Neches, Texas	40
Olin Corp.	
Brandenburg, Kentucky	45
Oxirane Chemical Co.	
Bayport, Texas	250
Union Carbide Corp.	
S. Charleston, West Virginia	100
Total	835

Production data for butylene glycols are listed in Table 11. Producers of 1,4-butanediol are duPont, GAF Corp. and BASF Wyandotte Corp. Total capacity is in excess of 0.2 billion pounds (figures for GAF are unavailable) at two sites in Texas, one in New Jersey and one in Louisiana. The U.S. International Trade Commission (1977) lists Celanese Corp. and duPont as producers of 1,2- and 1,3-butanediols; plant capacities have not been disclosed. Optically active (D)(-)

Table 11

Butylene Glycol Producers (SRI, 1975; Anon, 1976a; 1977g; U.S. Int. Trade Comm., 1977)

Producer	Capacity (millions of pounds per year
I. 1,4-Butanediol	
E. I. duPont de Nemours and Co., Inc. LaPorte, Texas	162, estimated[a]
GAF Corp. Calvert City, Kentucky Linden, New Jersey Texas City, Texas	capacity not disclosed
BASF Wyandotte Corp. Geismar, La.	55
II. 1,2- and 1,3-Butanediols	capacity not disclosed
Celanese Corp. Bishop Texas	
E. I. duPont de Nemours and Co.	
III. 2,3-Butanediol	capacity not disclosed
Burdick and Jackson Labs. Subsidiary of Hoffman LaRoche, Inc. Muskegon, Mich.	

[a]Capacity figures are not available from duPont; this estimate of 162 million pounds is based on an estimate of 90 million pound capacity in 1976 plus 80% of 90 million pounds; duPont announced in 1976 an 80% increase in capacity by 1978 (Anon, 1976a).

2,3-butanediol is manufactured by Hoffmann-LaRoche; total capacity has not been disclosed.

4. Imports and Foreign Producers

Imports of ethylene glycol into the U.S. during 1976 totalled about 45 million pounds and came primarily from Japan (36.2%) and the Netherlands (34.7%); other sources included Belgium, Canada, the United Kingdom, and West Germany (Table 12). As shown in Table 12, total imports since 1972 have been quite variable. A peak level was reached during 1975 when imports exceeded 371 million pounds, coming from Belgium (32.5%), Japan (30.2%), and the Netherlands (23.1) among other countries. In 1973, only 23 billion pounds were imported.

According to a study by Monkman-Rumsey on worldwide ethylene oxide supply and demand, Western Europe and the Far East will be the major exporters of ethylene glycol into the U.S. through 1980 (Taylor, 1976). There is no cushion in ethylene oxide capacity in the U.S., so imports may be needed to relieve some tightness in the ethylene glycol market. Worldwide capacity of ethylene glycol is expected to grow faster than demand until 1980, making export markets very competitive. Antifreeze sales are expected to lag worldwide but use of ethylene glycol in polyester fiber will increase (Taylor, 1976).

The U.S. Bureau of the Census does not list import figures separately for propylene glycol and butylene glycol (isomers are not specified). As shown in Table 13, imports of both propylene glycol and butylene glycol into the U.S. during 1976 exceeded 23.5 million pounds. The major sources were West Germany (53.1%), France (19.5%) and Japan

Table 12

Imports of Ethylene Glycol into the United States[a] (U.S. Bureau of the Census, 1972-1976)

	1976	1975	1974	1973	1972
total quantity (lbs)	45,339,410	371,225,119	132,088,298	23,448,848	92,043
country of origin (%)					
Belgium	11.2	32.5	17.5	9.5	--
Brazil	--	--	0.7	--	--
Canada	0.8	--	3.1	11.2	--
Finland	--	--	--	--	1.7
France	--	0.3	2.7	0.1	--
Italy	--	--	1.1	--	--
Japan	36.2	30.2	14.1	0.1	44.6
Netherlands	34.7	23.1	30.4	17.7	--
Sweden	--	--	0.2	--	--
Switzerland	--	0.1	--	--	--
United Kingdom	2.4	4.8	15.1	9.4	50.3

Table 12 (Continued)

	1976	1975	1974	1973	1972
West Germany	14.2	8.9	15.1	52.0	3.4
other countries	0.5	0.1	--	--	--

[a]Commodity number 4,283,400.

Table 13
Imports of Propylene Glycol and Butylene Glycol into the United States[a]
(U.S. Bureau of the Census 1972-1976)

	1976	1975	1974	1973	1972
total quantity (lbs)	23,663,699	17,304,595	22,831,220	7,152,068	1,722,487
country of origin (%)					
Belgium		--		--	--
Brazil		--		--	--
Canada	6.8	--	3.8	1.3	1.1
Finland	--	--	--	--	--
France	19.5	25.8	14.1	0.6	--
Italy	--	--	--	--	--
Japan	16.3	43.1	38.9	13.2	44.9
Netherlands	3.4	1.7	37.0	76.9	--
Sweden	--	--	--	--	--
Switzerland	--	--	--	--	--
United Kingdom	--	0.3	4.5	0.6	--
W. Germany	53.1	28.9	--	7.4	54.0
other countries	0.9	0.2	1.7	--	--

[a]Commodity Number 4,283,000. Source: U.S. Bureau of the Census 1972-1976.

(16.3%). Imports have increased considerably since 1972, when the total quantity was 1.7 billion pounds.

5. Market Price

Table 14 lists the current market price of the glycols available from representative domestic producers and distributors. Bulk price refers to tank truck quantities while drum price refers to 55 gallon drums. The quantities quoted by Aldrich (1978) are considered research amounts.

Table 8 lists the price trend during the last decade for ethylene glycol and 1,2-propanediol. In 1968 the price of ethylene glycol was $0.07/lb; the price remained near this level until 1974, when it increased to $0.14/lb. In 1977, the average price was $0.19/lb. The price of 1,2-propanediol increased from $0.08-0.09/lb during 1968-1973 to $0.21/lb in 1974; in 1977, the average price was $0.25/lb.

B. Use

1. Ethylene Glycol

a. Current Demand

End uses of ethylene glycol include the following: antifreeze (45%), polyester fiber (35%), exports (8%), alkyd and polyester resins (4%), latex paints and other emulsions (1%), as well as a variety of miscellanedous uses (7%) (MCP,1977).

The low volatility and low molecular weight of ethylene glycol as well as its low solvent action on automobile finishes accounts for its major use as a base for all-winter automobile anti-freeze and

Table 14
Market Price of the Glycols in the United States

Product	Quotation (dollars)	Source
ethylene glycol	$0.245 per pound, bulk	Dow, 1978c
	0.305 per pound, drums	
1,2-propanediol		Dow, 1978c
industrial grade	0.265 per pound, bulk	
	0.325 per pound, drums	
U.S.P. grade	0.03 per pound, bulk	
	0.36 per pound, drums	
1,3-propanediol	7.50 per 100 g	Aldrich, 1978
1,4-butanediol		GAF, 1977
regular	0.55-0.58 per pound, bulk	
	0.62-0.67 per pound, drums	
anhydrous	0.97 per pound, bulk	
	1.01-1.06 per pound, drums	
1,2-butanediol	10.00 per 250 g	Aldrich, 1978
1,3-butanediol	0.43 per pound, bulk	Celanese, 1978
	0.495 per pound, drum	Celanese, 1978
	14.40 per 3 kg	Aldrich, 1978
2,3-butanediol	7.45 per 100 g	Aldrich, 1978

coolant. Related uses involve application in aircraft and runway defrosting and de-icing formulations. Producers of ethylene glycol are the major suppliers of antifreeze (Kallgren, 1963).

Use of ethylene glycol in polyester fiber is expanding, and currently accounts for about one-third of demand. Ethylene glycol is used as a raw material by all polyester fiber manufacturers in the U.S. except for Tennessee Eastman; this company uses 1,4-cyclohexanedimethanol to produce Kodel II. The first step in polyester manufacture involves the reaction of dimethyl terephthalate with a slight excess of ethylene glycol over a temperature range of 150-210°C in the presence of a catalyst (Shumeyko and Mansfield, 1975). Trade names and producers of polyester are listed in Table 15.

About 4% of ethylene glycol demand is for use in alkyd and polyester resins. These resins are thermosetting plastics formed by addition polymerization reactions; the resins are cured, set or hardened into a permanent shape. Numerous raw materials, including ethylene glycol, are used to produce alkyd and polyester resins. A typical reaction to produce a polyester resin is shown below (Harper, 1975):

1. $OH\text{-}CH_2CH_2\text{-}OH + HO\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH{=}CH\text{-}\overset{O}{\overset{\|}{C}}\text{-}OH \rightarrow$

   ethylene glycol — maleic acid

   $$H_2O + HO[CH_2CH_2\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}CH{=}CH\text{-}\overset{O}{\overset{\|}{C}}\text{-}O\text{-}CH_2CH_2]_nOH$$

   ethylene glycol maleate polyester

2. The polyester polymer units then react with styrene monomer in the presence of catalyst and/or heat to obtain styrene-polyester copolymer resin, a cured polyester.

Table 15

Trade Names and Producers of Polyester Fiber
(Shumeyko and Mansfield, 1975[a])

Trade Name	Company
Anavor	Dow Badische Co.
Angelrest	Fiber Industries Inc.
Avlin	FMC Corp.
Dacron	duPont
Esterweld	American Cyanamid
Fortrel, Fortrel 7	Fiber Industries, Inc.
Fybrite	Celanese Fibers Marketing Co.
Golden Touch	American Enka Co.
Kodel	Eastman Kodak Co.
Quintess	Phillips Fibers Corp.
Serene	Fiber Industries, Inc.
Spectran	Monsanto Textiles Co.
Strialine	American Enka Co.
Textura	Rohm and Haas Co.
Trevira	Hoechst Fibers, Inc.

[a]All but Kodel manufactured using ethylene glycol as a raw material.

Alkyds are formulated from polyester-type resins. Typical uses of these resins are in moldings, laminated or reinforced structures, and coatings (Harper, 1975).

Exports in 1977 accounted for 8% of total demand and exceeded 253 million pounds. They went primarily to the Netherlands (33.1%), Taiwan (22.1%), and Belgium (10.3%). Export trends during the past six years are shown in Table 16.

Miscellaneous uses of ethylene glycol include applications in: latex paints and other emulsions to prevent freezing; brake and shock absorber fluids to counteract swelling of rubber and to help dissolve inhibitors; fire retardant lubricants as a coupler; solvent for dyes and colorants; textile fibers, paper, leather, adhesives, and glue as a humectant; electrolytic capacitors as a suspending medium and solvent; and in the production of ethylene glycol dinitrate, a component in low temperature dynamites (MCP, 1977; Dow, 1978a).

b. Market Trends

During the period 1964-1974, ethylene glycol showed an annual growth rate of 6% (Anon, 1976b). Growth in the 1970's has been modest, averaging less than 2% per year. Future growth has been forecasted at 3% annually through the early 1980's (MCP, 1977).

Demand for antifreeze-grade ethylene glycol was estimated to be between 195-215 million gallons during 1977, up from 150 million gallons in 1976. In 1975, demand was about 200-218 million gallons, reflecting hoarding by distributors and consumers due to an anticipated antifreeze shortage (Anon, 1977h; Anon, 1977d). Antifreeze

Table 16

Exports of U.S. Ethylene Glycol[a] (U.S. Bureau of the Census 1972-1977)

	1977	1976	1975	1974	1973	1972
Total quantity (lbs)	253,032,950	253,565,853	97,166,231	163,407,637	174,001,552	232,942,355
Where Exported (%)						
Canada	2.4	6.0	35.2	16.9	9.3	7.5
Mexico	0.8	0.5	2.5	19.7	3.4	
Colombia	0.3	2.6	10.1	4.4	5.6	2.7
Venezuala	3.5	3.3	6.1	3.0	2.7	1.8
Peru	0.5	1.8	--	--	--	--
Chile	0.4	--	--	--	--	--
Brazil	7.7	8.9	1.6	4.9	15.5	11.3
Argentina	4.1	--	9.6	8.4	9.1	8.3
Netherlands	33.1	51.3	14.6	9.0	31.9	37.3
Belgium	10.3	10.5	--	--	--	20.0
Spain	0.5	1.4	--	--	--	

Table 16 (Continued)

	1977	1976	1975	1974	1973	1972
France	--	--	--	--	--	2.1
Turkey		1.6				
Switzerland	--	--	--	2.3	1.9	--
Malaysa	--	--	--	--	--	--
Philippines	--	--	--	1.1	--	--
Korean Republic	--	3.5				
China, Taiwan	22.1	4.6	16.8	11.3	7.1	4.8
Japan	5.6	--	--	16.1	12.5	--
Other	8.7	4.5	3.5	2.9	1.0	--

[a]Commodity Number 5120910.

consumption is forecasted to remain at about 200 million gallons per year through 1982 (MCP, 1977). Although there are more cars on the road, less antifreeze is required in the increasing number of smaller cars.

Demand in polyester fiber is the fastest growing end use of ethylene glycol. Forecasted growth in polyester demand is about 8% per year. However, this figure is about 50-100% less than the annual polyester demand increase during the early 1970's (Anon, 1977d).

2. Propylene Glycols

a. Current Demand

The major use of 1,2-propanediol (45%) is in polyester resins. Other uses include exports (12%), pet food (12%), food and pharmaceuticals (11%), cellophane (7%), tobacco humectant (7%) as well as miscellaneous uses (6%) (Anon, 1977f).

In polyester resins, 1,2-propanediol is esterified with diabasic acids such as maleic and fumaric acids. These resins are used, for example, in sports equipment, appliances, furniture, boat hulls, luggage, aircraft parts, and automobile bodies (MCP, 1976).

About 23% of 1,2-propanediol production goes into pet food, human food, and pharmaceuticals, in which this diol functions as a solvent, humectant and preservative. For example, U.S.P. grade 1,2-propanediol is used as a solvent for flavoring materials, extract preparations, and food colors (Dow, 1978b). It is a humectant for baked goods and packaged goods, such as shredded coconut. 1,2-Propanediol goes into products coming in contact with foods, such as cork seals, bottle-cap linings, and cellulose coatings for sausage and cheese.

It is also used as an intermediate for pharmaceuticals and cosmetics, as a vehicle for drugs and as a solvent for medicinal chemicals, vitamins, dyes, and perfumes (Dow, 1978b).

Seven percent of the 1,2-propanediol produced is used to soften cellophane. This market used to be the second largest consumer of propylene glycol, but use of cellophane has declined (MCP, 1976). About 7% is used as a humectant for tobacco formulations.

Exports comprise 12% of 1,2-propanediol production. Total exports exceeded 36 million pounds during 1977, going primarily to Venezuela (14%), Argentina (12.3%), the Netherlands (12.4%), and Japan (10.6%). Exports during 1977 were at the lowest level in recent years; for example, exports totalled 64.1 billion pounds in 1976 and 107.7 billion pounds in 1972 (Table 17).

Miscellaneous applications include use in: polymeric plasticizers (in vinyl compounding); and brake and hydraulic fluids as a solvent, lubricant and coupling agent (MCP, 1976). 1,2-Propanediol is also formulated into some antifreeze and de-icing solutions. Because of the lower toxicity of 1,2-propanediol compared to ethylene glycol, it is often used in antifreeze which may accidently come into contact with food (such as in the refrigeration systems in breweries, dairies, food plants, and packing houses) (Budke and Banerjee, 1971).

b. Market Trends

Growth of 1,2-propanediol production volume was 5.6% annually from 1967-1976. A growth rate of 7-8% per year has been forecasted through 1981 (Anon, 1977f). The major growth area for 1,2-propanediol is in polyester resins. These resins are expected to grow at about 12-15%

Table 17
Exports of U.S. 1,2-Propanediol (U.S. Bureau of the Census, 1972-1977)

	1977	1976	1975	1974	1973	1972
Total quantity (lbs)	36,480,073	64,147,544	38,619,686	67,725,527	58,614,441	107,765,835
Where exported (%)						
Canada	0.7	--	1.3	5.7	8.8	2.7
Costa Rica	0.8	--	--	--	--	--
Mexico	0.6	--	10.8	4.4	--	--
Equador	0.8	1.4	1.2	--	--	--
Colombia	7.8	1.2	3.3	2.2	3.0	1.6
Panama	--	--	--	2.2	--	--
Venezuela	14.0	5.5	8.9	4.4	4.8	1.6
Peru	0.7	--	1.6	--	--	--
Chile	1.3	--	--	--	--	--
Brazil	8.7	31.7	25.5	13.3	17.2	9.3
Argentina	12.3	12.2	4.2	7.0	5.5	62.0
Netherlands	12.4	10.8	--	11.9	13.1	51.9

Table 17 (Continued)

	1977	1976	1975	1974	1973	1972
Belgium	--	--	--	--	--	
Singapore	3.2	5.8	8.8			
Spain	--	--	--	--	--	1.1
Italy	--	--	--	--	--	--
Australia	7.3	5.0	2.8	6.4		4.3
New Zealand	5.6	4.7	2.3	2.3	1.2	--
Switzerland	--					
HongKong	--	--	--	--	2.3	--
Korean Republic	--	3.5	--	--	--	--
Republic of S. Africa	8.4	2.2	7.3	--		4.2
China Taiwan	--	--	--	--	1.2	
Philp Rep	--	--	--	2.3	1.3	--
W. Germany	--	--	--	1.7	--	--
Japan	10.6	9.8	16.9	24	36.0	14.6
Poland	--	--	--	1.7	--	--
others	4.8	6.2	8.0	10.5	5.6	6.7

[a]Commodity Number 5120912. Source: U.S. Bureau of the Census 1972-1977.

per year (Anon, 1977f), but growth here is particularly sensitive to economic conditions in the construction, automotive, and recreational sectors (MCP, 1976). Consumption in other end uses will probably remain steady, with increases in humectants offset by decreases in cellophane and specialty antifreeze (MCP, 1976).

3. Butylene Glycols

1,3-Butanediol is used primarily as an intermediate in the manufacture of polyester plasticizers, particularly in polyvinyl chloride but also in synthetic rubbers, nitrocellulose, polyvinyl acetate, ethylcellulose, and polyvinyl butyral resins. 1,3-Butanediol is also used as a gelling agent for gelatin, proteins, and cellulose nitrate. High purity 1,3-butanediol (99.00%) serves as a solvent for several natural and synthetic flavoring substances such as spearmint, peppermint, and orange oils (Wagner, 1966). It functions in some hand cleansers, lotions, and other cosmetic formulations (Budke and Banerjee, 1971). Pyroborate and boronate esters of 1,3-butanediol are used in jet-fuel to improve high temperature stability; these esters also inhibit the growth of microorganisms in jet fuels. The sulfite ester can be used to stabilize cellulosic esters (Wagner, 1966).

The major market for 1,4-butanediol in the U.S. is in the preparation of tetrahydrofuran (57%). Tetrahydrofuran is combined with CO_2 to form adipic acid and is also used as an intermediate for other chemicals. Other applications include use in acetylenic chemicals (25%), polyurethanes (9%), polybutylene terephthalate (PBT, 7%), as well as miscellaneous markets (1%). Current domestic demand for 1,4-butanediol is 175 million pounds (Brownstein and List, 1977). DuPont predicts

that demand for 1,4-butanediol will increase rapidly over the next few years for use in engineering plastics and polyurethanes. DuPont employs 1,4-butanediol capitively in the manufacture of tetrahydrofuran and, since 1975, also in polybutylene terephthalate resin (trade name "Rynite") (Anon, 1976a). BASF uses 1,4-butanediol to produce polybutylene-terephthalate and to make polyurethanes injection molded thermoplastics and shoes (Anon, 1977i).

2,3-Butanediol is used as a solvent for dyes, as a humectant and as a coupling agent (Budke and Banerjee, 1971). 1,2-Butanediol is used in the production of polymeric plasticizers (Hatch and Matar, 1978b).

C. Possible Alternatives to Use

A major use of ethylene glycol is in polyester fiber. To retain the special qualities of polyester, a suitable substitute might not exist. In all polyester formulations, ethylene glycol is used as the raw material, with the exception of Kodel II which uses 1,4-cyclohexanedimethanol. Kodel II has a somewhat higher melting point, and has bulkier and deeper-dyeing fibers than polyester made from ethylene glycol (Shumeyko and Mansfield, 1975).

Other raw materials besides 1,2-propanediol and ethylene glycol are currently used to produce alkyd and polyester resins (Harper, 1975). These include a variety of organic alcohols, such as neopentyl glycol, which could be used in place of ethylene and propylene glycols. Use of 1,2-propanediol in food and pharmaceuticals would be a difficult market for which to find suitable substitutes. Other polyols, such as glycerine, sorbitol, and mannitol, which are also used as food additives have some-

what overlapping properties as 1,2-propanediol and might substitute for it. Use of 1,2-propanediol as a solvent in pharmaceuticals would be particularly difficult to substitute because of its relatively low toxicity.

D. Entry into the Environment

Only limited monitoring data on the glycols are available. These are reviewed in the following section on sources of entry into the environment.

1. From Production

Ethylene glycol and 1,2-propanediol have been identified as components of the wastewater from production facilities (Zeitoun and McIlhenny, 1971). In 51 samples at two ethylene glycol plants, the concentration of ethylene glycol in the wastewater ranged from 680-2,300 ppm and averaged between 1,003-1,306 ppm. In a similar number of samples at two 1,2-propanediol plants, the level of this glycol ranged from 355-2,550 ppm and averaged between 960-1,140 ppm. Other components of the wastestreams are described in the section on waste handling. As discussed in the section on waste handling, these wastestreams can be handled by biological treatment, in which case the glycols would not be entering the environment.

A source of air pollution during 1,2-propanediol manufacture is the venting of excess vapor from the evaporation and drying towers, as shown in Figure 2 (EPA, 1975). It is not known whether 1,2-propanediol is a component of this vented vapor.

Other minor sources of environmental contamination might be from fugitive emissions at valves, seals, and vents (the glycols would be volatile, however, only at elevated temperatures) and from accidental leaks and spills.

The potential for environmental contamination will certainly depend on the design of a given production facility and to what extent spent glycol is recycled (see section on waste handling) and treatment of waste streams is practiced. As such data are unavailable, it is difficult to accurately estimate the environmental hazards from production facilities in general.

2. From End Product Manufacture

Ethylene glycol was identified as a constituent of the wastewater of a polyester fiber plant in Poland. The level of ethylene glycol ranged from 200-440 mg/ℓ and averaged 220 mg/ℓ (Grabinska-Loniewska, 1974a).

3. From Use and Disposal

The major source of environmental contamination by ethylene glycol and 1,2-propanediol is likely from the disposal of spent antifreeze, but no estimates are available assessing the magnitude of this problem. The upper limit of this contamination is based on antifreeze use and the assumption that all is discarded to the environment.

Another source of environmental contamination by glycols is runoff of de-icing fluids. Aircraft de-icing fluids, for example, are sprayed on airplanes and the runoff can enter the airport sewer collection system or contaminate surface waters. The composition of de-icers available from two manufacturers contained 16 and 38% 1,2-propanediol and 32 and 56% ethylene glycol; other characteristics of de-icers appear in Table 18 (Jank et al., 1974).

Table 18
Composition of De-Icers (Jank et al., 1974)

	Dow	UCAR
Composition (%)		
water	50	5
ethylene glycol	32	56
propylene glycol (1,2-propanediol)	16	38
inhibitor package	2	1
Characteristics		
TOC[a] (mg/ℓ)	261,000	460,000
BOD[b] (mg/ℓ)	362,000	712,000
pH	8.0	8.7

[a]TOC = total organic carbon.

[b]BOD = biological oxygen demand.

Measurements at the Montreal International Airport revealed that de--icers are used about 150 days of the year. Drainage is into two manholes (storm sewer); during February-March 1972, the glycol content in the runoff ranged from 0-4,780 mg/ℓ. The BOD of the waste ranged from 200,000-400,000 mg/ℓ (Schulz and Comerton, 1974). Jank et al. (1974) studied the biological treatment of de-icing runoff on a laboratory scale. An activated sludge system treating de-icing fluid and sewage at less than 10°C resulted in an effluent having a BOD of less than 20 mg/ℓ and TSS* of less than 25 mg/ℓ. The authors caution that growth of filamentous microorganisms might cause a problem in full-scale plants.

4. From Transportation

Transportation accidents are another possible source of environmental contamination. Estimates of the safety of ethylene glycol transport by barge, rail, and truck were provided by Arthur D. Little, Inc. in 1974. Estimates were based on one selected route: the shipment of ethylene glycol from Belle, West Va. to Pittsburgh, Pa., covering 335 miles by barge, 290 miles by rail, or 200 miles by truck. According to the U.S. Army Corps of Engineers, the quantity of ethylene glycol shipped annually between this origin and destination exceeds 100,000 tons. Based on past accidents, the number of trips made by each mode of transport and other factors, the following estimates were made of the probable annual number of accidents causing release of cargo: 0.0018 by barge; 0.014 by truck; and 0.055 by rail. These figures represent the hypothetical situation where the entire commodity would be transported by each mode. Arthur D. Little, Inc. also took this model further and estimated the spill pool radius, the hazardous radius, population exposure, probability

*total suspended solids

of ignition, annual property damage and the recurrence interval. These estimates are listed in Table 19. Based on these estimates, rail transport will occur more frequently, expose more people, have a greater hazard area and will damage more property than the other two modes of transportation.

5. From Microorganisms

2,3-Butanediol occurs in the environment as an endproduct of fermentation by various strains of enteric bacteria (Enterobacteriaceae) such as Aerobacter, Klebsiella, and Serratia (Brock, 1970). Typical end products of fermentation by Aerobacter are:

	moles product/100 moles glucose fermented
2,3-Butanediol	66.5
CO_2	172
H_2	36
formic acid	18
acetic acid	0.5
lactic acid	3
ethyl alcohol	70

Serratia marcescens produces 2,3-butanediol from agricultural waste materials (Bahadur and Dube, 1959). The acid hydrolyzates from wheat straw, wheat bran, rice straw, and rice polishings gave yields of 31-40% butanediol on the basis of sugar consumed.

An actively growing culture of Bacillus polymyxa produced 2,3-butanediol, but the quantity decreased over a 60-day period (Bahadur and

Table 19
Hazards of Ethylene Glycol Transportation[a]
(A. D. Little, Inc., 1974)

	Barge	Truck	Rail
spill pool radius (feet)	NA	56	104
hazard radius (feet)	NA	56	104
hazard area (acres)	.04[b]	.22	.78
relative exposure (%) urban/rural	16/84	16/84	6/94
expected number of annual spills	.0018	.014	.055
expected annual number of people exposed urban/rural[c]	0	.001/.0002	.006/.004
expected property damage $[c] urban/rural	0	20/4	103/60
recurrence interval[d] (years)	555	71.4	18.2

[a]Calculations are based on the assumption that each mode handles 100% of the quantity shipped.

[b]For spills into water which do not ignite the water toxicity hazard distance (feet) measured downstream from spill location for a 500 feet wide, 10 feet deep river flowing at 2.3 feet per second. Assumes vertical dispersion rate at 1.0 feet per minute until uniform mixing is achieved.

[c]Although ethylene glycol is not considered flammable or capable of chemical decomposition, its potential to cause hazards is assessed in terms of number of people exposed and dollar value of exposed property. It is, however, recognized that this approach is conservative. In any event, it provides a basis for comparing relative damages associated with transportation by alternative modes.

[d]Average number of years between accidents.

Ranganayaki, 1961). Several strains of lactobacilli and staphylococci produce 2,3-butanediol, which is then further metabolized (Cantoni et al., 1965).

Filamentous fungi, such as Rhizopus nigricans and Penicillium expansum, also produce 2,3-butanediol (Fields and Richmond, 1967). In a laboratory experiment, the amount of 2,3-butanediol identified after 5-14 days incubation of R. nigricans on an artificial or apple juice medium ranged from 43.0-230.0 µg/ml. For P. expansum levels ranged from 104.0-343.0 µg/ml.

6. From Other Sources

Ethylene glycol and ethylene chlorohydrin are degradation products of ethylene glycol; these compounds are found as residues after sterilization and fumigation of various organic materials and synthetic objects with ethylene oxide (Gardner, 1978).

Ethylene glycol, 2,3-butanediol and 1,2-propanediol were identified as three of 479 water-soluble components of cigarette smoke (Schumacher et al., 1977).

E. Waste Handling

1. Characteristics of Waste Stream

Characterization of waste streams from ethylene glycol manufacture appears in Table 20. Data for flow, biological oxygen demand (BOD) and chemical oxygen demand (COD) were submitted by ten manufacturers to EPA during 1975 or earlier. These values are quite disparate; flow ranged from 9.4-14,300 gal/1,000 lbs, BOD from 0.34-27.7 lb/1,000 lbs and COD from 0.80-209.0 lb/1,000 lbs. Data from three manufacturers (Dow,

Table 20

Flow, Biological Oxygen Demand (BOD) and Chemical Oxygen Demand (COD) of Waste Streams Generated at Various Plants During Ethylene Glycol Manufacture (Train, 1975)[a]

Source	Flow gal/1,000 lb	BOD lb/1,000 lb	COD lb/1,000 lb
Dow Chemical Co. Freeport, Tex.[b]	584	0.34	8.76
Union Carbide Corp. Ponce, P.R.	29	0.5	0.80
Jefferson Chemical Co. Port Neches, Tex.	178	1.02	2.18
Union Carbide Corp. Taft, La.[b]	66	3.5	9.7
Shell Chemical Co. Houston, Tex.	5,430	10.5	22.6
Olin Corp. Brandenburg, Ky.	7,000	12.4	209.0
Texas Eastman Co. Longview, Tex.	9.4	27.7	48.6
Union Carbide Port Lavaca, Tex.	272	7.6	10.4
Houston Chemical Co. Houston, Tex.[b]	14,300	11.3	12.2
Citgo Corp. Lake Charles, La.[c]	128	0.07	11.3

[a]Data received by EPA from the individual manufacturers; data were generally collected over a 30-day period or longer.

[b]Combined load for ethylene glycol and ethylene oxide production.

[c]According to Citgo, these data are suspect due to possible incorrect analysis.

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Union Carbide, and Houston Chemical) are for combined process wastes from both ethylene glycol and ethylene oxide production. According to EPA (1974), a source of waste streams is the condensate from the dehydrator, which is only partly recycled (refer to Figure 1). Additional measurements of waste water generated during ethylene glycol manufacture at two plants were made by Zeitoun and McIlhenny (1971) of the Dow Chemical Company, as shown below:

	Average values
COD[a], ppm	1,630-1,850
TOD[b], ppm	1,730-1,920
NaCl, %	10.72-12.90
total dissolved solids, %	11.12-13.30
ethylene glycol, ppm	1,003-1,306
ethylene oxide, ppm	60
ethylene dichloride, ppm	16
ethylene chlorohydrin	15
dichloroethyl ether	29

[a]Chemical oxygen demand.

[b]Total oxygen demand.

In 1,2-propanediol manufacture, waste waters are generated, for example, during the evaporation-drying operation and the distillation processes (refer to Figure 2) (EPA, 1975). Measurement of waste water at one plant yielded the following:

flow	660 gal/1,000 lb
BOD_5	0.016 lb/1,000 lb
COD_5	0.055 lb/1,000 lb
total organic carbon	0.006 lb/1,000 lb

Zeitoun and McIlhenny (1971) of Dow Chemical Co. provided additional data on waste water generated during 1,2-propanediol manufacture at two plants (one a pilot plant) tabulated below:

	Average values
COD, ppm	2,138-3,086
TOD, ppm	2,198-4,398
% NaCl	9.8-10.3
total dissolved solids	10.1-10.65
propylene glycol (1,2-propanediol)	960-1,140
propylene oxide	28-196
epichlorohydrin	25-138
propylene chlorohydrin	42

2. Treatment of Waste Stream

Measurements by Zeitoun and McIlhenny (1971) reveal that at both ethylene glycol and 1,2-propanediol production facilities, the wastewater is characterized by a high salt content (10-13%), excess alkalinity (0.05-0.45%, as sodium hydroxide) and the presence of several organic compounds. Zeitoun and McIlhenny tested several alternative treatment

methods to handle these wastes, which are briefly described below.

i. Solvent Extraction -- Solvent extraction of glycol wastewater with secondary or tertiary amines produced: a) a raffinate that was low in glycol and was salt saturated (this could be recycled for use in hydrolysis) and b) a product enriched with glycol and almost free of salt (glycol would be recovered). The authors found this system to be uneconomical.

ii. Carbon Adsorption -- Adsorption on activated carbon was not feasible because of the low capacity of activated carbons for glycols.

iii. Membrane Separation -- Cellulose acetate membranes did not efficiently separate the salt and the glycol.

iv. Biological Treatment -- This was the preferred method of treatment. Organisms from natural saline environments were screened for their capacity to utilize glycols. The biodegradability of glycols is discussed in the next section on fate and persistence. Biological oxidation of propylene glycol wastewater in batch and continuous laboratory units gave a total oxygen demand (TOD) removal efficiency of 86-88% at a residence time of 12 hours. An activated sludge pilot plant was built which removed more than 90% of the TOD at a residence time of 8.0 hours. Design parameters for this pilot plant are presented by Zeitoun and McIlhenny (1971).

Grabinska-Loniewska (1974a) found that removal of ethylene glycol (0.11-0.50 mg/mg/day) wastes generated during polyester fiber production was 80-100% complete using activated sludge. The percent removal depended

on the initial sludge load; efficiency decreased with increasing sludge load (100-500 ml/g total sludge volume tested).

Japanese investigators Kawami and Torikai (1976) described the electrolytic treatment of a synthetic effluent (COD = 20,000-30,000 ppm) containing 5% ethylene glycol. The effluent was electrolyzed using a platinum or lead dioxide anode. Products of decomposition were CO and O_2 when using the platinum anode and CO_2 when using the lead dioxide anode. The decrease in COD was 73 and 90%, respectively, for the two anodes.

3. Diol Recovery

Cox and Wilkes (1975) in a patent assigned to PPG Industries, Inc. described a method for recovering ethylene glycol used in the manufacture of polyesters. In one step of this manufacturing process, ethylene glycol is esterified with dimethyl terephthalate or terephthalic acid. Depending on the nature of the process used, the residual glycol stream (or "spent glycol") can be contaminated with ethylene glycol, dimethyl terephthalate, salts of terephthalic acid, methanol, water, acetals, higher glycols, as well as other solid and liquid contaminants. The glycol stream may contain 40-90 weight percent ethylene glycol, so the recovery of this glycol plays an important role in the economics of polyester manufacture. Recovery involves subjecting the spent glycol to a sequential flash evaporation-distillation or distillation-flash evaporation-distillation procedure. Dimethyl terephthalate impurities are rendered non-volatile by the addition of alkali metal hydroxide prior to flash evaporation. Ethylene glycol that is recovered from spent glycol can be used in antifreeze compositions or, if pure enough, it can be reused in the polyester manufacturing processes.

Mattia (1971) in a patent assigned to Day and Zimmermann, Inc. developed a process for recovering organic compounds present in aqueous streams at levels between 50-5,000 ppm. He suggested this method is applicable for the recovery of ethylene glycol from polyester plant effluent streams. The recovery process utilizes a system of absorbers to strip organic compounds from the aqueous stream. Steam desorption is accomplished by a thermocompressor, which recycles regenerating steam through the adsorbers.

F. Fate and Persistence in the Environment

1. Biological Degradation

The glycols are capable of being degraded by a variety of bacterial strains. Several investigators identified those strains which can utilize the glycols as sole carbon sources. Other investigators studied the rate of biodegradation under controlled laboratory conditions. Both types of studies are discussed for each glycol.

a. Ethylene Glycol

1) Microbial Metabolism

Grabinska-Loniewska (1974a) isolated strains of bacteria capable of decomposing ethylene glycol from activated sludge used to treat polyester fiber plant wastes. Among other constituents, these wastes contained ethylene glycol (200-440 mg/ℓ), methanol (215-450 mg/ℓ), and formaldehyde (60-68 mg/ℓ). Of 44 strains of bacteria isolated from activated sludge which degraded the three compounds, Pseudomonas bacteria were most prevalent. Less numerous were Achromobacter, Flavobacterium, Mycobacterium, and Xanthomonas. In another study, Grabinska-

Loniewska (1974b) examined each of the 44 strains as sole carbon sources for various compounds, ranking growth as excellent, good, fair, or poor. The following summarizes data obtained for ethylene glycol:

Species of Organism	No. Strains	Growth on ethylene glycol				
		excellent	good	fair	poor	No
Acetobacter	1	1				
Achromobacter	4	3		1		
Alcaligenes	1		1			
Arthrobacter	1		1			
Flavobacterium	2	1	1			
Micrococcus	1			1		
Mycobacterium	3	3				
Pseudomonas	26	10	7	4	1	4
Sarcina	1	1				
Xanthomonas	4	1	2		1	1

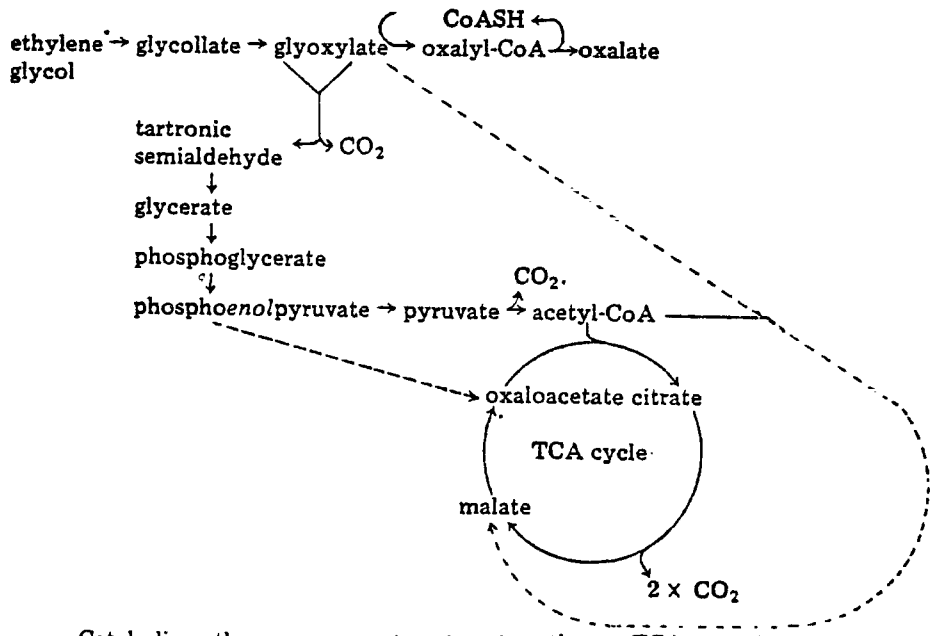
Excellent or good growth was obtained with most (70%) of the strains tested.

Gonzalez et al. (1972) isolated a bacterium (ATCC 27042) capable of using ethylene glycol as a sole carbon source from a brine pond. This gram-negative nonmotile rod required a medium containing at least 0.85% NaCl for growth but tolerated up to 12% NaCl.

Haines and Alexander (1975) isolated a species of microorganism from soil (Pseudomonas aeruginosa) capable of degrading ethylene glycol. Based on measurements of O_2 consumption, ethylene glycol (added at 1.0 mg carbon per bottle) was degraded in two days.

Jones and Watson (1976) studied the catabolism of ethylene glycol by a bacterium (possibly Acinetobacter) isolated from sewage. Cell-free extracts of the bacterium grown on ethylene glycol contained high (0.175 μmol/min/mg protein) ethylene glycol dehydrogenase activity; ethanol and 1-butanol were also oxidized. NAD^+ and $NADP^+$ were utilized. In addition, bacteria grown on ethylene glycol showed a 40-fold increase of a NAD^+-dependent glycolaldehyde dehydrogenase activity and an increase in glycerate-pathway enzyme activity.

Child and Willetts (1978) described the metabolism of ethylene glycol by a species of Flavobacterium (NCIB 11171). This bacterium, isolated from pond water, is capable of using ethylene glycol as its sole carbon source, optimal growth was obtained at 30 mM ethylene glycol. Several experimental procedures were used to identify the metabolic pathway for ethylene glycol metabolism, including a) assaying for specific metabolites and enzymes, b) comparison of oxidation by various substrates, c) measuring incorporation of ^{14}C-labeled ethylene glycol into the ethanol-soluble fraction of washed suspensions. The following pathway was suggested by the results of these experiments.



——, Catabolic pathway; – – –, Anaplerotic pathway. TCA, tricarboxylic acid.

2) Rate of Degradation

Evans and David (1974) evaluated the biodegradation of ethylene glycol in river water under controlled laboratory conditions. Samples from four types of river waters were used: a) major watercourse with a constant slow flow rate; b) major tributary with a varied flow running through agricultural land; c) fast running river originating in an upland stream; d) slow flowing river passing through agricultural land. To the samples were added 2 or 10 mg/ℓ ethylene glycol. Biodegradation was monitored over 14 days at 4, 8, or 20°C. Remaining glycol was determined by oxidation with acidified permanganate to an aldehyde and subsequent reaction with 3-methylbenzothiazolone hydrazone hydrochloride to give chromogens measured at 630 nm. Ethylene glycol biodegraded completely within three days in all river waters tested at 20°C. On day one, 0-1.8 mg/ℓ ethylene glycol remained when 2 mg/ℓ had been added; 1.8-9.1 mg/ℓ remained in samples to which 10 mg/ℓ had been added. At 8°C, biodegradation was complete within 14 days for each river sample; the rate of degradation in rivers a) and b) was slow for the first seven days but increased thereafter. At 4°C, the rate of degradation was low; only about 0.2 mg/ℓ per day were degraded. In most samples tested at this temperature, partial degradation occurred by day seven but degradation was not complete by day 14.

The theoretical oxygen demand for ethylene glycol is 1.30 mg/mg. This value represents the oxygen needed for complete conversion to CO_2 and H_2O. The actual chemical oxygen demand is 1.29 mg/mg, as calculated by Price et al. (1974).

Lamb and Jenkins (1952) studied the biological oxygen demand in a

solution of ethylene glycol over a 20 day period at 20°C. Ethylene glycol (2.5 mg/ℓ) was added to a BOD bottle with mineralized dilution water and settled sewage seed. The percent of theoretical BOD after 5, 10, 15, and 20 days was 12.5, 51.8, 71.0, and 78.0%, respectively.

Pitter (1976) determined the biodegradability of ethylene glycol based on measurements of chemical oxygen demand. About 1,000-1,500 ml ethylene glycol were added to adapted activated sludge so that the initial COD was 200 mg/ℓ. Ethylene glycol was the only source of carbon provided. Over 120 hours, 96.8% of the ethylene glycol had been degraded. Expressed as a rate, 41.7 mg COD were degraded per gram per hour. According to the author, ethylene glycol is readily decomposed.

Bedard (1976) evaluated the biodegradation of ethylene glycol, antifreeze, and other organics over a 30-40 day period. The quantitative measure used was the Refractory Index (RI) which is defined as a ratio of the oxygen required for biological stabilization in a long-term Warburg Respirometer (the ultimate Biochemical Oxygen Demand or BOD) to the amount of oxygen required for complete oxidation to end products of CO_2, H_2O, and NO_3^-(the ultimate oxygen demand or UOD). Domestic raw sewage was used as seed. Compounds having a high R.I. value degrade readily and are judged safe for disposal into municipal biological sewage systems. Bedard cautions, however, that a high R.I. is a function of the favorable environment of the Warburg flask and similar results may not be obtained in the natural environment in such a short time. Both ethylene glycol and antifreeze had high R.I.: 0.76 and 1.12, respectively, as shown in Table 21.

Table 21
Biodegradation of Ethylene Glycol, Antifreeze, and 1,2-Propanediol (Bedard, 1976)

	Ultimate Biochemical Oxygen Demand (BOD_u)[a] (mg/ℓ)	Ultimate Oxygen Demand (UOD)[b] (mg/ℓ)	Refractory Index (R.I. = BOD_u/UOD)
ethylene glycol	207	271	0.76
antifreeze	301	268	1.12
propylene glycol	326	420	0.78
(1,2-propanediol)	220	419	0.52

[a]Measures quantity of O_2 used by bacteria originating from a domestic raw sewage seed as an energy and growth supply over a 30-40 day period.

[b]Amount of oxygen needed for complete oxidation to end products of CO_2, H_2O, and NO_3^-.

Price, Waggy, and Conway (1974) determined the biodegradability of ethylene glycol and other petrochemicals in freshwater. Settled domestic wastewater (seed material) and aerated water were added to BOD bottles. The test chemicals were added to yield a final concentration of 3, 7, and 10 mg/ℓ. Dissolved oxygen was monitored over 20 days. The percent bio-oxidation was calculated on day 5, 10, 15, and 20 using this equation:

$$\% \text{ bio-oxidized} = \frac{100(O'_g - O_b)}{C_x \cdot ThOD}$$

where O'_g = cumulative oxygen uptake in the sample from day zero to the day of interest

O_b = cumulative oxygen uptake in a blank (containing the same amount of seed material) from day zero to the day of interest

C_x = initial concentration of the compound

ThOD = theoretical oxygen demand per mg of compound for complete conversion of the compound to CO_2 and H_2O

As shown in Table 22, the bio-oxidation for ethylene glycol was 34%, 86%, 92%, and 100% after 5, 10, 15, and 20 days, respectively.

Price et al. (1974) also determined the biodegradation of ethylene glycol in synthetic seawater. The seed used was from seawater taken from Lavaca Bay, Texas. Using the formula described above, the bio-oxidation was 20, 60, 65, and 77% after 5, 10, 15, and 20 days, respectively (Table 22). That is, rate of degradation was slower in seawater.

b. Propylene Glycols

1) Microbial Metabolism

Gorban and Petrenko (1972) identified several species of Pseudomonas capable of using 1,2-propanediol as a sole source of carbon. They established a maximum permissible concentration of 700 mg/ℓ of 1,2-propanediol for biological degradation to procede.

Morihara (1965) determined that Pseudomonas aeruginosa (Strain IFO 3455) is capable of good growth and high protinease production when 1,2-propanediol was supplied as the sole source of carbon; optimal growth was obtained in a 5% solution.

Yagi and Yamada (1969) isolated 60 strains of 1,2-propanediol-utilizing microorganisms from 150 soil samples. Thirty strains were bacteria, 29 were molds and one was an actinomycete. One strain, Arthrobacter

Table 22
Biodegradation of Ethylene Glycol and 1,2-Propanediol
(Price et al., 1974)

	Ethylene glycol	1,2-Propanediol
theoretical oxygen demand (mg/mg)	1.30	1.68
measured chemical oxygen demand (mg/mg)	1.29	1.63
biodegradability (% bio-oxidation)		
Freshwater		
Day 5	34	62
10	86	68
15	92	75
20	100	79
Salt Water[a]		
Day 5	20	55
10	60	72
15	65	73
20	77	83

[a]Synthetic seawater.

oxydans produced lactic acid from 1,2-propanediol.

The response of mycobacteria, many species of which occur in the soil, to 1,2-propanediol was studied by Tsukamura and Tsukamura (1968). Growth on a number of strains from fourteen species of mycobacteria exposed to

5% 1,2-propanediol was compared to growth in nonexposed controls over 2-4 weeks. In eleven species, growth in 1,2-propanediol and in controls was comparable. However, three species were intolerant to 1,2-propanediol (Mycobacterium tuberculosis, M. bovis, and M. kansasii) and did not grow.

Resting cells of the yeast Hasenula miso IFO 0146 grown on ethanol are capable of oxidizing dl-1,2-propanediol to acetol and 1,3-propanediol to β-hydroxypropionic acid (Harada and Hirabayashi, 1968). Two ml of a 1% solution of each glycol were tested. Oxidation products were identified by paper chromatography.

2) Rate of Degradation

1,2-Propanediol was designated as having a "high degradability" by Bedard (1976) based on its high refractory index (R.I.). As defined in Table 20, the refractory index is the ratio of the ultimate biochemical oxygen demand to the ultimate oxygen demand. In two replicate analyses, the R.I. of 1,2-propanediol was 0.78 and 0.52.

The theoretical oxygen demand for 1,2-propanediol is 1.68 mg/mg. This value is the oxygen required for complete conversion to CO_2 and H_2O. Price et al. (1974) measured the actual chemical oxygen demand to be 1.63 mg/mg.

Lamb and Jenkins (1952) followed the biological oxygen demand of 2.5 mg/ℓ 1,2-propanediol added to a BOD bottle with mineralized dilution water and settled sewage seed. The percent of theoretical BOD satisfied after various days is as follows:

Day	% theoretical BOD
5	2.2
10	59.8
15	61.5
20	66.4
30	64.0
40	72.2
50	68.0

Price et al. (1974) determined the biodegradability of 1,2-propanediol in freshwater over 20 days using the procedure described for ethylene glycol in the previous section. The data appear in Table 22 and show that after 5, 10, 15, and 20 days, the percent of 1,2-propanediol bio-oxidized was 62%, 68%, 75%, and 79%, respectively.

Using synthetic seawater, Price et al. (1974) determined the biodegradability of 1,2-propanediol to be 55% after five days and 83% after 20 days, comparable to degradation in freshwater (Table 22).

c. Butylene Glycols

1) Microbial Metabolism

Tsukamura (1966) showed that some strains of mycobacteria are capable of using butanediols as sole sources of carbon. Of 132 strains tested, 56 showed growth with 1,3-butanediol, 8 with 1,4-butanediol, and 59 with 2,3-butanediol.

Resting cells of the yeast Hansenula miso IFO 0146 grown on ethanol oxidized meso-2,3-butanediol, dl-1,3-butanediol and 1,4-butanediol to acetoin, β-hydroxybutyric acid and α-hydroxybutyric acid, respectively (Harada and Hirabayashi, 1968). These products were identified using paper chromatography. The diols were tested using 2 ml of a 1% solution.

2,3-Butanediol at 0.1 or 1.0 molar concentration was not inhibitory to the growth of Pseudomonas fragi (Pinheiro et al., 1968).

2) Rate of Degradation

1,4-Butanediol is readily degradable. Pitter (1976) added about 1,000-1,500 ml to activated sludge adapted for 20 days. During 120 hours, 98.7% of the glycol had been degraded based on reduction of initial COD. The rate of degradation was expressed as 40.0 mg COD/g/hour.

2. Chemical Degradation

The glycols are quite stable compounds. As discussed in the previous section, they are all readily oxidized by microorganisms, and would be expected to be biodegraded before chemical degradation became significant.

3. Transport Within and Between Media

The subject glycols are soluble in water in all proportions, and are denser than water. When spilled in a body of water, they would sink, then dissolve.

The glycols have a very low vapor pressure at ambient temperatures (Tables 2-4) so evaporation from water or land to the atmosphere will

occur slowly. Runoff of spent antifreeze or de-icing fluids can occur; for example, the runoff of deicing fluids, which contain ethylene and/or propylene glycol, can enter airport sewer collection systems or contaminate surface waters (see section II-D-3).

4. Persistence and Bioaccumulation

The glycols are subject to moderately rapid breakdown by both acclimated and unacclimated soil, water, and sewage microorganisms, as discussed in section II-F-1, thus precluding persistence in the environment. There is no evidence to suggest that the glycols would bioaccumulate.

G. Analytical Methods

Various methods are available for the identification and separation of glycols. Chemical and chromatographic methods used during the last few years are reviewed in this section. The reader is referred to Budke and Banerjee (1971) for a comprehensive review of older papers.

Colorimetry

A number of chemical methods have been developed for detecting glycols in aqueous solutions or in biological material. These methods, in most cases, involve the oxidation of the glycol with subsequent reaction with a reagent. In some tests, bromine water or potassium permanganate is used to oxidize ethylene glycol to glycolic aldehyde and propylene glycol to acetol. Adding the reaction product to Fehlings solution, ammoniacal silver nitrate or Nessler's reagent will produce a positive test. With phenolic reagents (such as resorcinol, thymol,

and codeine) in sulfuric acid, characteristic color for ethylene and propylene glycol are obtained (Budke and Banerjee, 1971).

Ethylene and propylene glycols are oxidized by periodates to aldehydes which can be quantitated colorimetrically. For example, Rajogopal and Ramakrisnan (1975) used sodium metaperiodate ($NaIO_4$) to oxidize ethylene glycol to formaldehyde for determinations of ethylene glycol in blood and tissue. Excess periodate was reduced by arsenite after which chromotropic acid was added; the purple color was developed in a boiling water bath, and measured at 550 nm. From 98-100% of known amounts added to blood and liver homogenate were measured by this method. Russell, McChesney and Golberg (1969) also oxidized ethylene glycol with periodate for determinations in biological material. A protein- and carbohydrate-free filtrate was prepared, then oxidized with periodate. The formaldehyde which was produced is converted to a dihydrolutidine derivative. The absorbance of the solution was read in a spectrophotometer at 412 mμ. The precision of this method was 3-4% in tests with known amounts of ethylene glycol in urine, serum, and tissue. In this method, metabolites of ethylene glycol do not interfere.

Another method using oxidizing action of ethylene glycol with periodate was described by Sunshine (1969) for determinations in blood or urine. The oxidation product was condensed with Schiff's reagent to give a characteristic colored product whose absorbance is read at 555 nm. Recovery was 100 ± 5%.

Efstathiou and Hadjiioannou (1975) developed a method for determining the rate at which ethylene glycol, 1,2-propanediol, or 2,3-butanediol is oxidized with periodate. The reaction rate is followed with a perchlorate ion selective electrode; the time is measured for the reaction

to consume a fixed amount of periodate (and therefore for the potential to increase) which is related to the glycol concentration. Measurements were made over 3-18 mg/28 ml of glycol with a relative error of 0.7%.

Evans and Dennis (1973) described a test for mono-, di-, and triethylene glycols based on the reaction with sulfuric acid and potassium permanganate. This step oxidizes the glycols to aldehydes. The latter are converted with 3-methylbenzothiazol-2-one hydrazone hydrochloride (MBTH) to green cationic chromagens which are measured spectrophotometrically at 630 nm. This method was used to determine low levels of ethylene glycols in surface waters. Recovery was in the range of 1-5 mg/ℓ with a precision of 7%.

Chromatographic Methods

In addition to chemical tests, chromatographic procedures have been developed for determining glycols in various media.

Reid and Ivery (1975) developed a rapid procedure using pyrolysis-gas chromatography for measuring ethylene or propylene glycol in serum, gastric, and urine samples. The sample was introduced into the chamber of a pyrolyzer and flash vaporized at 270°C. The vapors were swept into a GC column maintained at 250°C. Recovery of glycol ranged from 96-104% at 50 mg/dl levels and 98-104% at 100 mg/dl levels.

Holman and Mundy (1976) used gas chromatography (GC) to measure ethylene glycol in mouse plasma. Normal constituents of plasma did not interfere with GC peaks of ethylene or propylene glycols.

GLC determination of propylene glycol using Chromosorbiol as a column packing, resulted in 95-108% recovery in cosmetic samples containing 20.0-40.0 mg propylene glycol (Champion, 1970).

A potential problem of using gas chromatography for determining ethylene glycol is ghosting, a desorption process in which a small amount of solute which had been injected in the GC column is removed from the column by subsequent injections of a solvent that does not contain this solute (Spitz, 1972). As long as an ethylene glycol standard used is the same concentration range as that in the sample, ghosting will not be a problem.

Belue (1974) described a high-pressure liquid chromatographic method for the separation and identification of related polyhydric alcohols such as ethylene glycol, glycoaldehyde, glycerol, and isoerythritol; methyl ethyl ketone-water-acetone was used as a solvent.

III. BIOLOGICAL EFFECTS

The biological effects of ethylene glycol, propylene glycols, and butylene glycols are considered separately in the sections which follow.

A. Ethylene Glycol

1. Humans

a. Acute Toxicity

During the 1920's and 1930's, ethylene glycol was not recognized as a potentially toxic material. In 1917 Bachem drank 45 ml of ethylene glycol without any noticeable effects and in 1927 Page drank 15 ml, also without ill effect. Hanzlik et al. concluded in 1931 that ethylene glycol was "comparatively innocuous as a solvent for medicinals." The first recognition in the U. S. that ethylene glycol can be hazardous when ingested was a report by a physician that two men died from drinking Prestone antifreeze (Anon., 1930). Since that time, numerous cases have been reported. Haggarty (1959) attributed 40-60 deaths per year to ethylene glycol intoxication. In most cases, ingestion of ethylene glycol, usually as antifreeze, is accidental. For example, Pons and Custer (1946) described 16 fatal cases in soldiers who drank antifreeze. Gaultier et al. (1976) reported on six patients who, lost in the desert, drank a mixture of antifreeze in water. Friedman et al. (1962) described four cases of toxicity in young adults who mistook ethylene glycol for ethanol.

In humans, the lethal dose of ethylene glycol is about 100 grams or about 1.4-1.6 g/kg. This is equivalent to 100 ml of 100% ethylene glycol or 105-110 ml of commercial antifreeze (Lavelle, 1977). With supportive therapy, patients ingesting up to 970 ml have been successfully treated (Gaultier et al., 1976).

The clinical course of ethylene glycol poisoning can be divided into three stages (Berman et al., 1957; Friedman et al., 1962; Parry and Wallach, 1974):

i) Central Nervous System Manifestations.

Within 0.5-12 hours after ingestion of ethylene glycol, the patient appears intoxicated. Nausea, vomiting, mild hypertension, tachycardia, and low grade fever may occur during the early stages. Coma, convulsions, and death may follow with large doses.

Laboratory tests may reveal a normal hematocrit and moderate leukocytosis (10,000-40,000/mm^3), with polymorphonuclear cells predominating. Acidosis is a frequent finding (serum bicarbonate <10 meq/ℓ; anion gap >20) due to organic acids, such as oxalic acid, produced during metabolism. Hypocalcemia is usually observed, possibly due to chelation of the calcium ion by oxalate to form calcium oxalate crystals.

The urine usually contains oxalate crystals 4-6 hours after ingestion and shows a low specific gravity with excess protein. If death occurs during the first 24 hours, the major change observed is the presence of calcium oxalate crystals in the kidney, brain, leptomeninges, vessel walls, and/or perivascular spaces.

ii) Cardiopulmonary Failure

Twelve to 18 hours after ingestion of ethylene glycol, cardiopulmonary failure, accompanied by tachypnea, tachycardia, mild hypertension and cyanosis, may occur. According to Parry and Wallach (1974), recent cases have not reported this stage, probably because of rapid recognition and treatment of acidosis and hypocalcemia. Death during this stage can be attributed to pulmonary edema, cardiac dilation, and bronchopneumonia.

iii) Renal Failure

If the patient survives the first two stages, renal impairment, ranging from proteinuria to anuria, may ensue. Oxaluria usually occurs soon after intoxication. Oliguria may occur approximately 12 hours after intoxication.

iv) Other Changes

Central hydropic degeneration or fatty metamorphosis of the liver with focal necrosis has been observed in cases of ethylene glycol poisoning (Friedman et al., 1962). Smith (1951) reported inflammation of the diaphragm and Friedman et al. (1962) found inflammation of skeletal muscle. Petechial hemorrhage of the gastrointestinal tract may occur (Levy, 1960), but major gastrointestinal bleeding has not been reported (Parry and Wallach, 1974).

b. Occupational Exposure

Although many deaths have resulted from acute ingestion of ethylene glycol, few cases exist of chronic occupationally-related toxicity. Ethylene glycol is a compound of low volatility (Table 2), so inhalation exposure is usually not significant. However, in one case, workers were exposed to an aerosol generated from heating ethylene glycol. Another case involved dermatitis in a worker having skin contact with ethylene glycol.

1) Aerosol Inhalation

Troisi (1950) described exposure of electrolytic condenser factory workers to ethylene glycol at elevated temperatures. The operation

involved the manual spreading of a heated mixture (105°C) of 40% ethylene glycol, 55% boric acid and 5% ammonia on a strip of paper using a paintbrush. Of 38 women exposed in this manner for several years, nine frequently both lost consciousness and had nystagmus while five had only nystagmus. Lymphocytosis was observed in five workers. Affected workers had been exposed to this procedure for 1-5.5 years. No abnormalities were found in the urine of any worker. The attacks disappeared when the process was mechanized with no further exposure to the women. According to the author, there was no evidence to implicate boric acid or ammonia as causative agents; further elaboration was not given.

The Russian investigators Dubeikovskaya et al. (1973) reported that in the manufacture of electrolytic condensers, workers are exposed to an average level of 44.8 mg/m^3 ethylene glycol (range 17-96.2 mg/m^3). No signs of toxicity were noted in exposed workers.

2) Dermal Exposure

A 17-year-old male developed eczematous dermatitis four months after working in a factory where eyeglasses were made (Dawson, 1976). He burnished glass lenses by bathing the lenses in a fluid made of one part ethylene glycol to three parts water. Patch tests with 3% ethylene glycol in ethanol were strongly positive at 72 hours; no reaction occurred with ethanol alone.

c. Controlled Studies

A group of 20-30 year old male volunteer prisoners (number not given) was exposed to aerosolized ethylene glycol for periods up to 28 days (Harris, 1969). Psychomotor, psychological, and psychiatric tests were

performed. In addition, blood chemistry and excretion of urea and creatinine were monitored. Volunteers exposed to 25 ppm (63.5 mg/m^3) were unaware of the presence of ethylene glycol; no changes in any tests were detected. Volunteers exposed to 50 ppm (127.0 mg/m^3)"for short periods of time" were able to detect the presence of ethylene glycol; they tasted its sweetness and experienced an irritation in the pharyngeal area. When the level was raised to 75 ppm (190.5 mg/m^3), without their knowledge, several volunteers were awakened from their sleep, unable to tolerate the exposure.

2. Nonhuman Vertebrates

a. Absorption, Distribution, and Excretion

1) Rat

McChesney et al. (1971) studied the biological fate of ethylene glycol in male albino rats which received intravenous injections of 139 mg/kg ^{14}C-labeled ethylene glycol. The excretion and tissue distribution 1, 4, and 24 hours following treatment are shown in Table 23. The output of $^{14}CO_2$ amounted to about 1.5% of the dose hourly for four hours; by 24 hours, 14.4% of the dose had been eliminated as CO_2. Urinary excretion in 24 hours totalled about 46% of the dose. There was a wide distribution of ^{14}C in various tissues, as shown in Table 23. The level of ^{14}C in the liver remained relatively constant while the level in the body as a whole decreased; this probably reflects the entry of ethylene glycol metabolites into cellular metabolism.

The urinary excretion by rats following oral dosing of ^{14}C-labeled ethylene glycol in 0-8, 8-24, and 0-24 hour urine samples is shown in

Table 23

Tissue Distribution and Excretion of ^{14}C-labelled Ethylene Glycol (139 mg/kg, i.v.) in Rats (McChesney et al., 1971)

Material analyzed	Excretion or tissue distribution (% of dose) in rat no.			
	1	2	3	4
Body weight (g)	220	198	290	280
Dose of ^{14}C (μC)	2.5	5.0	3.5	2.0
Time before sacrifice (hr) .	1	1	4	24
expired air	1.3	1.7	5.8	14.4
feces	0.2	0.2	0.4	1.1
urine	--	--	37.7	46.5
blood[a]	5.8	4.5	4.1	5.0
bladder wall	0.1	0.1	1.1	0.1
heart	0.4	0.4	0.1	0.5
lungs	0.9	0.9	0.4	0.8
spleen	0.3	0.3	0.6	0.7
liver	8.7	6.4	9.2	8.5
kidneys	0.6	1.2	1.0	1.3
brain	0.7	0.7	0.4	0.2
ileum	5.1	5.7	4.5	4.9
colon	4.0	5.8	2.9	3.3
carcass	81.0	58.3	37.3	13.3
Recovery (% of dose)	109	86	106	101

[a]Blood volume assumed to be 5.4% of body weight.

Table 24. In 24 hours, an average of 56% of the ^{14}C dose was excreted; of this, 57% was unmetabolized.

Table 24
Urinary Excretion of ^{14}C-Labeled Ethylene Glycol by Male Rats (McChesney et al., 1971)

Time after ethylene glycol administration (hr)	Percent of dose[a] excreted as	
	ethylene glycol[b]	^{14}C[b]
0-8	27.8 ± 1.0	45.9 ± 0.3
8-24	3.8 ± 0.5	9.8 ± 2.7
0-24	31.7 ± 1.5	55.7 ± 2.4

[a]dose of 1 ml/kg orally, as the labeled compound.

[b]Data expressed as mean ± SEM; results from three rats.

The approximate ratio of glycolic and oxalic acids in the 0-8 hour urine was about 13:1 by weight; in a pooled 8-24 hour sample, the ratio was about 8:30. This is in contrast to the monkey, in which the ratio is about 80:3 in 8-24 hour urine (Section 2-a-4); the monkey converts less ethylene glycol to oxalate than does the rat.

Gessner et al. (1961) found that in the albino rat, excretion of ^{14}C-labeled ethylene glycol at 24 hours was 21% of a 0.1 g/kg dose and 58% of a 1.0 g/kg dose; $^{14}CO_2$ in the expired air decreased from 23% of

the dose in 24 hours at 0.1 g/kg to 2.4% in 12 hours at 10 g/kg.

In Sprague-Dawley male rats given an i.p. injection of 4 ml/kg (4.4 g/kg) of ethylene glycol, 1.50 ml/kg (1.66 g/kg) was recovered in the urine during day one and 0.35 ml/kg (0.39 g/kg) was recovered on day two, (Peterson et al., 1963).

2) Rabbit

In Chinchilla rabbits given 0.1-2.0 g/kg of ^{14}C-labeled ethylene glycol, orally or by i.v. injection, about 20% of the radioactivity was excreted in the urine in two days (Gessner et al., 1971). At doses of 2.5 and 5.0 g/kg, radioactivity in the urine increased to about 50%. Gessner et al. (1971) identified the following metabolites in three rabbits given 25 mg/kg orally: oxalic acid (0.01-0.11% of dose), urea (0.65-1.5% of dose) and unchanged ethylene glycol (6.0-15.1% of dose).

3) Dog

The blood glycol content in two dogs (breed and sex not reported) given 2 ml/kg ethylene glycol (2.2 g/kg) by i.v. and oral routes is shown below (Hanzlik et al., 1939a):

	Blood glycol, mg%	
	i.v.	gastric
2 hours	337	310
4 hours	270	283
6 hours	202	240

4) Monkey

McChesney et al. (1971) studied the metabolism of ethylene glycol

in the rhesus monkey (Macaca mulatta). In one experiment, two females received an intravenous injection of ^{14}C-labeled ethylene glycol. The excretion and tissue distribution of label at one and four hours are shown in Table 25. After four hours, about 10% of the label had been eliminated in the urine and 5% in expired air; only 0.1% had been found in the feces. At four hours, the highest proportion of ^{14}C was found in the carcass (69%), which includes muscle, skin, and bone, in the liver (6.3%) and in the blood (4.7%). The rest of the ethylene glycol was widely distributed (Table 25).

In another experiment, the plasma half-life and rate of urinary excretion were determined. Unlabeled ethylene glycol was given to one male and two females (1 ml/kg or 1.1 g/kg) by stomach tube. A peak blood level of 125 mg/100 ml was reached at 1-2 hours. The plasma half-life was 2.7-3.7 hours.

The urinary excretion of ethylene glycol in three female rhesus monkeys is shown in Table 26. In the period 0-24 hours, 23.5% of the dose was excreted as unchanged ethylene glycol; no additional ethylene glycol was excreted at 24-48 hours. During the period 0-48 hours, other metabolic products accounted for a mean of 22.2% of the dose. Most of the metabolic products was excreted in the 8-24 hour period.

In a preliminary study of metabolism in chimpanzees, two females were given ^{14}C-labeled ethylene glycol intravenously (McChesney et al., 1971). One female given 2 ml/kg (2.2 g/kg), died after nine hours; 4% of the ^{14}C was identified in the urine at nine hours (40% of this was as ethylene glycol). The other female was given 1 ml/kg (1.1 g/kg). During the first eight hours, 28% of the administered label was excreted (30%

Excretion and Tissue Distribution of ^{14}C Labeled Ethylene Glycol[a] in Female Rhesus Monkeys (McChesney et al., 1971)

Material analyzed	Excretion or tissue distribution (% of dose) in monkey no.	
	1	2
Body weight (kg)	3.3	3.3
Dose of ^{14}C (μC)	41.3	41.3
Time before sacrifice (hr)	1	4
expired air	1.3	5.0
feces	0.1	0.1
urine	4.3	10.4
blood[b]	5.4	4.7
bile	0.02	0.04
bladder wall	0.1	0.1
heart	0.9	0.7
lungs	1.6	1.2
spleen	0.2	0.2
liver	4.5	6.3
kidneys	0.8	0.7
brain	2.8	2.6
adrenals	0.02	0.02
stomach	0.9	0.5
ileum	3.7	3.5
colon	2.7	2.6
carcass	78.8	69.0
Recovery (% of dose)	108	108

[a] 139 mg/kg administered i.v.

[b] Blood volume assumed to be 5.4% of body weight.

Table 26
Urinary Excretion of Ethylene Glycol and ^{14}C by Female Rhesus Monkeys (McChesney et al., 1971)

Time after ethylene glycol administration (hr)	Percentage of dose excreted as	
	ethylene glycol[b]	^{14}C[b]
0-8	17.9 ± 2.9	25.9 ± 5.1
8-24	5.6 ± 2.3	19.0 ± 4.6
24-48	0	0.8 ± 0.4
0-48	23.5 ± 1.3	45.7 ± 4.9

[a]Dose 1 ml/kg (1.1 g/kg) orally, as the labeled compound.

[b]Data expressed as mean ± SEM; results from three monkeys.

as ethylene glycol). In the 8-24 hour period, an additional 11% of the ^{14}C was excreted (17% as ethylene glycol).

Squirrel monkeys (Saimiri sciurea, 450-750 g) were given an i.p. injection of 3.2 ml/kg (3.5 g/kg) ethylene glycol (Peterson et al., 1963). By 24 hours after the injection 0.20 (S.D. = 0.09) ml/kg (0.22 g/kg) of the dose had been recovered in the urine. All died 14-30 hours after ethylene glycol administration.

b. Metabolism

The pathway of ethylene glycol metabolism in the rat is shown in Figure 3. Ethylene glycol is oxidized to glycolaldehyde, which is further

oxidized to glycolate. Glycolate is metabolized to oxalate and CO_2 and also to glycine and then serine (Chou and Richardson, 1978). Numerous studies were conducted to elucidate this pathway and to identify enzymes catalyzing the reactions. Some of the more recent major papers are

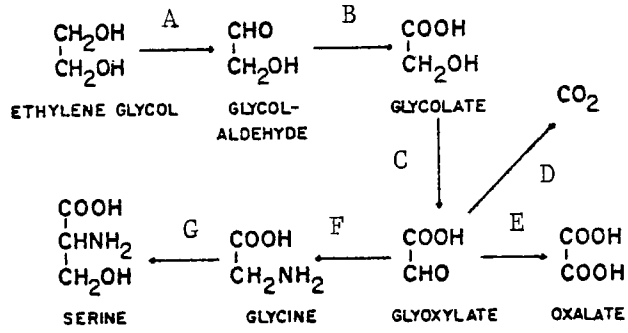


Figure 3. Pathway of ethylene glycol metabolism in the rat (Chou and Richardson, 1978).

The enzymes which catalyze the lettered reactions are: A. alcohol dehydrogenase; B. aldehyde dehydrogenase; C. glycolic acid oxidase and lactic dehydrogenase; D. 2-oxoglutarate: glyoxylate carboligase; E. xanthine oxidase, lactic dehydrogenase, and glycolic acid oxidase; F. alanine: glyoxylate aminotransferase, and ornithine:glyoxylate aminotransferase; G. serine hydroxymethyltransferase.

summarized in this section; in these papers, matabolites were isolated and possible toxic products were identified.

Although some investigators have attributed the acute toxic effects of ethylene glycol to the alcohol itself (Pons and Custer, 1946; Rowe, 1963), the majority have attributed these effects to the metabolites. Milles (1946) suggested the metabolite oxalate to be the toxic

product, but other investigators (Wiley et al., 1938; Roberts and Seibold, 1969; McChesney et al., 1972) have suggested that oxalate plays only a minor role. Others have implicated the oxidation products of ethylene glycol, such as glycolaldehyde, glycolate, and glyoxylate (Bachmann and Golberg, 1971; Richardson, 1973). Recently, unequivocal evidence has been presented that the metabolite glycolate is the specific toxic agent in ethylene glycol poisoning in the rat (Chou and Richardson, 1978) and the monkey (Clay and Murphy, 1977).

There appears to be a sex-related difference in the metabolism of ethylene glycol. Richardson (1965) found that the oxidation of glycolic acid to glyoxylic acid, and of glyoxylic acid to oxalic acid occurs twice as rapidly in liver homogenates of male rats compared to female rats. In male rats, the level of glycolic acid is 30% higher than in females (Richardson, 1964). Male rhesus monkeys are more sensitive to ethylene glycol than females (Roberts and Seibold, 1969).

1) Rat

Richardson (1973) showed that the toxicity of ethylene glycol is likely due to metabolic products such as oxalate and glyoxalate. Male Wistar rats (140-160 g) were partially hepatectomized (about 1/3 or 2/3 of the liver was removed) and maintained on a vitamin B_6-dificient diet (to enhance urinary oxalate excretion). An oral dose of 2 ml of ethylene glycol resulted in fewer deaths in hepatectomized than in intact rats. Urine was collected for 48 hours and assayed for oxalate and glycolate. Hepatectomized rats given ethylene glycol showed no change in the level of urinary oxalate. Liao and Richardson (1972) showed that isolated perfused rat liver is capable of oxidizing ethylene glycol to oxalate.

Since removal of part of the liver, which would decrease the metabolic rate of ethylene glycol, lowered the toxicity of ethylene glycol, the authors infer that this glycol is not toxic in itself. Rather, oxidation products such as oxalate and glyoxylate are likely responsible.

Chou and Richardson (1978) demonstrated that the metabolite glycolate is the specific toxic agent in acute ethylene glycol poisoning in Wistar rats. They administered alcohol dehydrogenase inhibitors, pyrazole and 4-methylpyrazole, prior to or with a lethal dose (10 ml/kg or 11.1 g/kg) of ethylene glycol. Alcohol dehydrogenase catalyzes the metabolic conversion of ethylene glycol to glycolaldehyde. The resulting mortality and urinary metabolites were determined. As shown in Table 27, administration of 3 mmol pyrazole/kg eight hours before or at the time of ethylene glycol administration, reduced mortality from 100% to 0%. Pyrazole was less effective when given 4-12 hours after ethylene glycol. The amount of ethylene glycol and glycolate excreted in the urine varied with the time of pyrazole administration; the excretion of glycolaldehyde, glyoxylate, and oxalate remained relatively constant (Table 27). In addition, the mortality varied inversely with the amount of ethylene glycol in the urine and directly with the duration of pyrazole treatment, and the amount of glycolate in urine. Similar results were obtained when 4-methylpyrazole was administered.

Chou and Richardson (1978) also administered to rats other enzyme inhibitors, in addition to pyrazole. Inhibitors of the enzyme catalyzing the initial step in the metabolism of ethylene glycol, glycolaldehyde, glycolic acid, and glyoxylic acid were given, as follows:

Table 27

Effect of Pyrazole on Ethylene Glycol Toxicity and Metabolism in the Rat[a]
(Chou and Richardson, 1978)

Pyrazole (3 mmol/kg) administration time compared to ethylene glycol feeding[a] (hr)	Mortality (dead/total)	Content in 48-hr urine collection[b]				
		Ethylene glycol (% recovery)	Glycol-aldehyde (mg/100 g)	Glycolic acid (mg/100 g)	Glyoxylic acid (mg/100 g)	Oxalic acid (mg/100 g)
--[c]	6/6	--[d]	--	--	--	--
-8	0/2	66 ± 4	2.0 ± 0.8	37.9 ± 15.9	0.08 ± 0.03	15.6 ± 0.4
-4	0/6	86 ± 10	4.0 ± 0.9	17.4 ± 2.6	0.10 ± 0.02	9.7 ± 2.3
0	0/6	88 ± 9	3.2 ± 0.4	20.2 ± 6.1	0.15 ± 0.01	9.3 ± 0.9
+4	1/6	73 ± 22	3/4 ± 0.9	73.3 ± 12.6	0.11 ± 0.02	12.7 ± 1.7
+6	2/6	66 ± 16	4.2 ± 0.7	96.7 ± 18.8	0.17 ± 0.03	17.6 ± 1.1
+8	2/6	44 ± 8	4.2 ± 1.2	72.2 ± 8.3	0.23 ± 0.08	11.1 ± 2.1
+10	3/6	63 ± 1	3.5 ± 1.1	133.8 ± 20.7	0.21 ± 0.17	16.3 ± 1.4
+12	4/6	47 ± 11	3.8 ± 0.5	143.7 ± 14.3	0.13 ± 0.07	7.0 ± 5.1

[a] Each rat was fed 10 ml of ethylene glycol/kg.
[b] Values are given as the mean ± SD.
[c] No pyrazole administered.
[d] Control rats all died within 48 hours.

Substrate (g fed/kg)	Inhibitor (administered/kg)	Mortality within 48 hr (dead/total)
ethylene glycol	pyrazole (mg)	
8.5	0.0	3/6
8.5	204.0	0/6
glycolaldehyde	butyraldoxime (mg)	
3.0	0.0	3/6
3.0	130.0	6/6
glycolic acid	DL-phenyllactate (g)	
5.0	0.0	3/6
5.0	3.0	6/6
glyoxylic acid	DL-phenyllactate (g)	
2.0	0.0	3/6
2.0	3.0	6/6

Only pyrazole, an inhibitor of alcohol dehydrogenase which catalyzes the initial oxidation of ethylene glycol, prevented deaths from ethylene glycol. Thus, the lethal toxicity is not due to ethylene glycol per se. The lethal toxicity of the metabolites, however, was dependent on the compounds themselves; enzyme inhibitors lowered the LD_{50} values.

Chou and Richardson (1978) also determined the level of metabolic intermediates in the plasma of rats following a dose of [U-^{14}C] ethylene glycol. The major constituents were ethylene glycol and glycolate; small amounts of oxalic acid were detected. The level of ethylene glycol

By 48 hours, 34.2% of the label was excreted in the urine; in another experiment, three monkeys averaged about 46% ^{14}C. After unchanged ethylene glycol, the next most important excretory product was glycolic acid; little oxalic acid was present. The authors consider that the unidentified compounds included primarily glycolic acid and also hippurate.

In another study, McChesney et al. (1972) investigated the metabolism of glycolic and glyoxylic acids in the rhesus monkey to further elucidate the metabolism of ethylene glycol. Two females weighing 3 kg were given an oral dose of 500 mg/kg 1-^{14}C glycolic acid; two other females weighing 3.5 kg were given 500 mg/kg [1-^{14}C] glyoxylic acid. Urinary excretion of label accounted for 37-52% and 34-69% of the administered glycolate and glyoxylate, respectively, within 96 hours. Fecal excretion averaged about 1% following administration of glyoxylate and 3% following glycolate. Individual labeled acids in the urine were then analyzed. Following a dose of 500 mg/kg glycolate, 34-44% of the dose was excreted unchanged, 0.3-2.2% was excreted as glyoxylate, 0.3% as hippurate and 0.3-1.3% as oxalate; 6% was not accounted for by these acids.

With a dose of 500 mg/kg glyoxylate, 24-59% was excreted unchanged, 0.1% as hippurate, 3% as oxalate and 2% as glycolate; 7-16% of the urinary label was unaccounted for. Urinary samples were similarly analyzed in another experiment in which two females were given 60 mg/kg

decreased with time; the oxalate levels increased with time. Glycolic acid concentration remained constant. These data appear below:

Sacrifice time (hr)	Percentage of dose recovered in plasma		
	Ethylene glycol	Glycolic acid	Oxalic acid
2	2.48	0.71	6.70×10^{-3}
4	1.81	0.61	5.13×10^{-3}
6	0.70	0.60	3.55×10^{-2}
8	0.34	0.79	3.12×10^{-1}
10	0.22	0.73	4.76×10^{-1}

2) Monkey

The rate of urinary excretion of metabolites of ethylene glycol in a female rhesus monkey, who received an oral dose of 1 ml/kg (1.1 g/kg) ^{14}C-labeled ethylene glycol is shown below (McChesney et al., 1971):

Time of ethylene glycol administration (hr)	Percentage of dose[a] excreted as				
	glycolic acid	oxalic acid	ethylene glycol	^{14}C	unidentified compounds
0-8	7.8	0.09	15.1	25.4	2.4
8-24	3.1	0.15	2.0	7.9	2.7
24-48	0.5	0.03	tr	0.9	0.4
0-48	11.5	0.27	17.1	34.2	5.5

[a]Dose of 1 ml/kg (1.1 g/kg) orally as the ^{14}C-labeled compound.

glyoxylate. Now, only 20% of the ^{14}C appeared in the urine within 96 hours and only 1-1.5% of the dose was excreted unchanged. Oxalate was the primary metabolite, accounting for 70% of the total label; hippurate was a minor metabolite. McChesney et al. (1972) suggest that small doses (i.e., 60 mg/kg) of glyoxylate can be metabolized efficiently, but with large doses, such as 500 mg/kg, there is considerable loss by excretion in the urine.

Bachmann and Golberg (1971) hypothesized an adaptive shift in the metabolism of ethylene glycol after prolonged exposure, based on preliminary results in rhesus monkeys exposed almost continuously to an aerosol (600 mg/m^3) for up to 215 days. Liver mitochondrial function (measured as respiratory activity and oxidative phosphorylation) was impaired after five months' exposure, but partial restoration of mitochondrial function was observed by months 6-7. The number of monkeys used was not specifically stated but apparently was small. The authors suggest two hypothetical adaptive processes: a) one involving easier disposal of glyoxylate by reactions avoiding condensation with keto-acid intermediary metabolites or b) one in which another pathway ethylene glycol metabolism assumes greater importance, by-passing glyoxylate.

c. Acute Toxicity

1) Oral Administration

a) Lethal Dose Values

The acute oral lethal dose (LD_{50}) averaged 8.3-15.3 g/kg in mice, 6.1-8.54 g/kg in rats and 6.61-8.1 g/kg in guinea pigs (Table 28).

Table 28
Oral Lethal Dose Values for Ethylene Glycol.

Species/strain	Sex/No.	LD_{50}			
		Reported value	Deviation	Converted value (g/kg)	Reference
mouse/white	NR/4 per dose	7.5 cm^3/kg	--	8.3	Latven and Molitor, 1939
mouse/NR	NR	13.79 cm^3/kg[a]	--	15.3	Fisher et al., 1949
mouse/NR	M&F/10-20 per dose	13.1 ml/kg	range: 11.8-14.6	14.5	Laug et al., 1939
rat/NR M&F	M&F/7-20 per dose	5.5 ml/kg	range: 5.00-6.05	6.1	Laug et al., 1939
rat/Wistar	M/10 per dose	8.54 g/kg[b]	95% C.L.: 7.31-9.99	8.54	Smyth et al., 1941
guinea pig/NR	M&F/5-10 per dose	7.35 ml/kg	range: 6.53-8.27	8.1	Laug et al., 1939
guinea pig/NR	M&F/10 per dose	6.61 g/kg[b]	95% C.C.: 5.06-8.63	6.61	Smyth et al., 1941

NR = not reported.

[a] LD_{50} determined after 24 hours.

[b] LD_{50} determined after 14 days.

b) Signs

Laug et al. (1939) administered large oral doses of ethylene glycol to mice, guinea pigs and rats; the sex and strains used were not reported. Signs of intoxication included weakness, loss of muscular coordination, prostration, coma, and death.

The clinical signs of dogs dying from ethylene glycol ingestion are summarized in Table 29. During the initial stages of intoxication, signs of ataxia, tachycardia, hyperpnea, and tachypnea were consistently observed. Terminal signs included bradycardia and coma (Kersting and Nielson, 1966). No sexual differences were apparent; younger dogs of either sex were less affected than older dogs.

c) Tissue and Organ Changes

Mice, rats, and guinea pigs of unreported strain or sex given fatal oral doses of ethylene glycol showed pulmonary congestion and hemorrhage (Laug et al., 1939). At larger doses, the stomach was also hemorrhagic. Microscopic changes included hydropic degeneration of cells lining the cortical convoluted tubules in the kidney and focal necrosis of the liver.

Pulmonary edema and hyperemia and also gastric or intestinal mucosa hyperemia were observed in most dogs (mixed breeds) receiving acute fatal oral doses of ethylene glycol (Kersting and Nielson, 1966). Calcium oxalate crystals were found throughout the renal tubules and the renal cortex. Occlusion of the tubules was usually observed. In five dogs recovering from a nonfatal dose of ethylene glycol (4.4-6.6 ml/kg or 4.9-7.3 g/kg), biopsies revealed the presence of oxalate

Table 29
Signs of Intoxication in Ten Dogs (Mixed Breed) Dying from Ingestion of Ethylene Glycol (Kersting and Nielson, 1966)[a]

Signs	Onset (hr)	Frequency (%)
ataxia	2-4	100
hyperpnea	2-4	100
tachycardia	2-4	100
tachypnea	2-4	100
anorexia	6-35	100
polydipsia	6-35	100
depression	10-40	100
emesis	intermittent	1
miosis	12-45	100
bradycardia	18-55	100
coma	18-55	100
convulsions	26-48	4
death	26-64	100

[a]Ten dogs of mixed breeds given 6.6-13.2 ml EG/kg (7.3-14.6 g/kg).

crystals in renal tubules at days 3-4; these crystals disappeared after 16-85 days. In two dogs, no crystals were detected. In all dogs, there was no evidence of permanent damage or impaired renal function.

d) Metabolic Acidosis

Clay and Murphy (1977) studied the effect of ethylene glycol

on metabolic acidosis in one male dog (17.7 kg) of an unreported strain. A dose of 6 g/kg ethylene glycol was given via a nasogastric tube. Severe metabolic acidosis occurred; from 0 to 5 hours after ethylene glycol administration, the blood pH had decreased 2.4%, blood P_{CO_2} had decreased 27%, and blood HCO_2 had decreased 53%. This is comparable to acidosis observed in pigtail monkeys given ethylene glycol by injection (section 2-c-2) as in monkeys, acidosis in the dog was caused by the accumulation of blood glycolate. At five hours, 10.1 meq/l glycolate were detected in the blood; prior to ethylene glycol administration, no glycolate was found.

2) Dermal and Ocular Application

According to Rowe (1963) ethylene glycol produces no significant irritation of the skin. Severe prolonged exposure may result in a slight macerating action.

McDonald et al. (1972) evaluated the ocular toxicity of ethylene glycol in New Zealand rabbits (1.5-2.2 g). Multiple topical or multiple intraocular (anterior chamber) applications of a 0.40% or 0.04% solution was nonirritating and nontoxic. Solutions containing 4 and 40% applied to the eyes produced irritation, which consisted of chemosis, swelling, and conjunctival redness. All eyes were normal after seven days. No signs of systemic toxicity were observed. Latven and Molitor (1939) reported that instillation of 0.5 ml of ethylene glycol into the eye caused mild edema and hyperemia after 24 hours.

3) Parenteral Administration

a) Lethal Dose Values

As shown in Table 30, the acute LD_{50} values for ethylene glycol

Table 30
Median Lethal Doses for Ethylene Glycol Administered Subcutaneously, Intravenously, or Intraperitoneally.

Species/strain	Sex/No.	Route	LD_{50} Reported value	LD_{50} Deviation	LD_{50} Converted value (g/kg)	Reference
mouse/Carworth Farms	F/60	i.p.	5.04 ml/kg	S.E. = 1.52	5.6	Karel et al., 1947
mouse/White	NR/4 per dose	i.v.	4.0 cm^3/kg	--	4.4	Latven and Molitor, 1939
mouse/White	NR/4 per dose	s.c.	6.0 cm^3/kg	--	6.7	Latven and Molitor, 1939
rat/Fischer	M&F/20 per dose	s.c.	5,300 mg/kg	95% C.L. = 3,857-7,478	5.3	Mason et al., 1971
rat/Sprague-Dawley	M/10 per dose	i.p.	5.8 ml/kg[a]	--	6.4	Peterson et al., 1963

NR = not reported.

[a] LD_{50} determined after five days.

in mice averaged 5.6 g/kg i.p., 4.4 g/kg i.v., and 6.7 g/kg s.c. In rats, the LD_{50} averaged 5.3 g/kg s.c. and 6.4 g/kg i.p. These values are comparable to those obtained after oral administration (Table 28).

b) Signs

Intramuscular or intravenous injection of ethylene glycol at doses higher than 1.1-1.5 g/kg caused respiratory acceleration, depression, and sometimes death to rabbits and white mice (Hanzlik et al., 1931).

Injection of 3-4 g/kg ethylene glycol in female pigtail monkeys (Macaca nemestrina) resulted in transient narcosis, after which they appeared normal but then worsened and became comatose (Clay and Murphy, 1977).

Intravenous injection of 1 ml/kg (1.1 g/kg) to one rhesus monkey resulted in no behavioral changes or other signs; in another rhesus 2 ml/kg caused ataxia, then vomiting, with complete recovery after two hours. However, in 4 of 5 chimpanzees given 1, 2, or 6 ml/kg, (1.1, 2.2, or 6.6 g/kg), death occurred after 9.75-37.5 hours. One chimpanzee given 1 ml/kg, became ataxia and vomited, but recovered. Oxalate crystals were found in the kidneys of all treated rhesus monkeys and chimpanzees at autopsy (Felts, 1969).

c) Urine Formation

Wills et al. (1969; meeting abstract) studied the effect of ethylene glycol on the formation of urine by the cat. In one experiment, 1.5 ml/kg (1.7 g/kg) i.v. were administered during the study. Ethylene glycol resulted in an increased production of urine, variable changes in the clearance of creatinine and transtubular transport of

glucose, and decreased clearance of p-aminohippuric acid (PAH). In a second study, 0.5 ml/kg (0.6 g/kg) i.p. ethylene glycol was administered. In this experiment urine production was normal and the clearances of creatine and PAH were reduced; transtubular transport of glucose and sodium, but not PAH, were decreased. The results suggest that ethylene glycol interferes with blood flow through the nephron, possibly by partial blockage of the peritubular network of capillaries.

d) Metabolic Acidosis

Metabolic acidosis occurred in female pigtail monkeys (Macaca nemestrina) given an intraperitoneal injection of 3 or 4 g/kg ethylene glycol. This effect was also noted for oral doses to dogs (section 2-c-1)-d) and was caused by the accumulation of blood glycolate (Clay and Murphy, 1977).

e) Hematology

Albino rats (150-200 g) were given s.c. injections of 4 ml/kg (4.4 g/kg) ethylene glycol every other day for 30-65 days (Paterni et al., 1956). Progressive hemolytic and myelotoxic anemia were noted. The reticulocyte count and hemoglobin index were normal but there was a tendency to macrocytosis and granulocytopenia during the later stages of intoxication.

MacCannell (1969) studied the effect of ethylene glycol and 1,2-propanediol on hemolysis or hemodynamic changes in 43 dogs (species not given; 13.2-21.5 kg weight). Either glycol was infused intravenously at 2% in saline (rate of 20 mg/kg/minute) for 2-5 minutes or

at 50% in saline (150-250 mg/kg/min) for 2-5 minutes. At either concentration, both glycols caused an increase in superior mesenteric blood flow and in cardiac output without any change in the cardiac contractile force. At the higher level, renal blood flow was decreased to a greater extent than it was at the lower level; this decrease occurred before the superior mesenteric flow increased. Direct injection of 25-50% glycol into the renal artery produced a decreased blood flow through this vessel while direct injection into the superior mesenteric artery resulted in increased flow.

These hemodynamic changes are partly a result of hemolysis which occurred at levels of 20-50% glycols. However, hemolysis did not occur at the lower level tested (2%) but changes in blood flow were still detected in the superior mesenteric blood flow.

d. Subacute Toxicity

Subacute administration of ethylene glycol, orally or by injection, has been used as a model to study renal hyperoxaluria or to induce oxalate lithiasis (Fonck-Cussac et al., 1971; Kirschbaum and Bosmann, 1974; Lyon et al., 1966; Vaille et al., 1963; Tanret et al., 1962; Gershoff and Andrus, 1962; Hammarsten, 1956). A recent representative study (Kirschbaum and Bosmann, 1974) is discussed in the next section. Other subacute studies are available in which ethylene glycol was administered by inhalation.

1) Oral Administration

a) Renal Changes

Kirschbaum and Bosmann (1974) induced hyperoxaluria in male

Sprague-Dawley rats (200-250 g) by adding 1% ethylene glycol to the drinking water for up to 45 days. After 15 days, kidneys from experimental rats were significantly heavier than controls (1.42 g vs 1.30 g, dry weight) and had a significantly lower protein content (69.2 mg/g vs 77.5 mg/g, wet weight). However, by day 45, kidney weights and protein content were not significantly different from controls. Oxalate was identified in the urine of treated rats, indicating hyperoxaluria. Ethylene glycol administration resulted in increased urine activity of β-mannosidase, β-galactosidase, acid phosphatase, N-acetylglucosaminidase, and N-acetylgalactosaminidase at weeks 3 and 6; these effects were more pronounced at week 3. Also, cytidine monophosphate-sialic acid synthetase activity was reduced on day 15 (but not day 30). Urine neuraminidase activity was elevated on day 15 but depressed on day 45.

Crystallization of calcium oxalate in the proximal tubules was observed in 5 of 7 macaque monkeys (Macaca mulatta, M. irus, M. radiata) receiving a total dose of 15-132 ml/kg (16.6-146.4 g/kg) over 6 to 13 days in the drinking water (Roberts and Seibold, 1969). Of these five monkeys, four were male and one female; the two not showing crystallization were female, which is suggestive of a sex-related difference. In these five monkeys, the tubular epithelium adjacent to the crystals was necrotic. In the glomerulus, focal adhesions and protein precipitate were noted. Some distal tubules contained protein precipitate, desquamated epithelial cells and leukocytes. Epithelial giant cells formed around the crystals in some cases. There was no evidence of renal calcification. Blood urea nitrogen

determinations revealed azotemia in treated monkeys.

b) Calcium and Phosphorus Metabolism

Rajagopal et al. (1977) investigated the effects of ethylene glycol on calcium and phosphorus metabolism. Male albino rats (100-110 g) were given 2 ml/kg/day (2.2 g/kg/day) for six days by gastric intubation; this daily dosage is approximately one-fifth the LD_{50}. The level of bone and serum calcium was decreased, while urinary calcium excretion was increased in treated rats. In addition, serum phosphorus levels were increased while urinary phosphorus excretion decreased. Serum alkaline phosphatase activity was increased. Urinary hydroxyproline was elevated and urinary citric acid was decreased. These results indicate that bone demineralization may be an attempt to maintain serum calcium concentrations during ethylene glycol intoxication.

c) Blood Clotting

Allen et al. (1962) administered 0.5 ml of ethylene glycol (10^{-2} to 10^{-4} dilutions) by stomach tube to SWR/J mice daily for 4 weeks. Every week, blood from treated and untreated mice was assayed for blood clotting defects (prothrombin time and thromboplastin generation time). Clotting abnormalities occurred in 84.3% of ethylene glycol treated mice but in only 12.5% of untreated mice. This study was prompted by the appearance of hemorrhage and death in mice whose bedding (pine shavings) was sterilized with ethylene oxide. Ethylene glycol is a breakdown product of ethylene oxide. Allen et al. (1962) found a 62.3% incidence of clotting defects in mice given oral doses of extracts from ethylene oxide-treated shavings. Reyniers et al.(1964)

reported on tumors in mice exposed to ethylene oxide-treated bedding; this is discussed in section III-A-2-f.

2) Inhalation Exposure

Slight narcosis developed in rats exposed to 500 mg/m^3 ethylene glycol aerosol for 28 hours over five days (Flury and Worth, 1934). No adverse effects were noted in mice or rats exposed to 350-400 mg/m^3 eight hours/day for 16 weeks (Wiley et al., 1936).

There were no signs of toxicity in rats, guinea pigs, rabbits, dogs, or monkeys exposed to 10 or 57 mg/m^3 ethylene glycol for eight hours/day, five days/week for 90 days (Table 31) (Coon et al., 1970). Continuous exposure of these species to 12 mg/m^3 for 90 days resulted in moderate to severe eye irritation in guinea pigs and rats; there was apparent blindness in two of 15 rats after eight days. Five animals died during continuous exposure (Table 31). For all three exposure situations, results of hematological and histopathological examinations were comparable in treated and experimental animals (Coon et al., 1970).

Two chimpanzees (sex and age not given) were exposed continuously to an atmosphere saturated with ethylene glycol aerosol (256 mg/m^3) for 28 days (Felts, 1969). Exposure was in a performance evaluation chamber, in which the animals had been previously trained in two tasks: auditory discrimination, involving locating a source of sound, and visual discrimination, involving adjusting the length of one line to equal another.

Table 31
Mortality in Animals Inhaling Ethylene Glycol Aerosol (Coon et al., 1970)

Exposure, mg/m^3 (Type):	Ethylene glycol			Control
	10 (Repeated)[b]	57 (Repeated)[b]	12 (Continuous)[c]	
Sprague Dawley and Long Evans rats	0/15	0/15	1/15	4/123
Princeton-derived guinea pig	0/15	0/15	3/15	0/73
New Zealand rabbit	0/3	0/3	1/3	0/12
Beagle dog	0/2	0/2	0/2	0/12
Squirrel monkey	0/2	0/2	0/3	0/8

[a]Exposed in modified Rochester-type inhalation chamber.

[b]30 repeated exposures, 8 hours/day, 5 days/week.

[c]Continuous exposure.

For the first test, reaction time was slower during the second and third weeks of exposure, compared to pre-exposure times. During week four, latency was decreased, but not to that of pre-exposure response time. For the visual discrimination task, one chimpanzee maintained pre-exposure performance levels. Performance in the other monkey was impaired during weeks three and four of exposure.

Compared to pre-exposure levels, no major changes were detected in serum chemistry or hematology tests, except for an increase in hemoglobin and mean cell volume of red cells after exposure. Urine concentrating ability, measured as serum and urine osmolality, was impaired in both animals following exposure. This condition is often associated with dysfunction of the renal distal tubules. Other renal tests were within normal units (insulin clearance, PAH clearance; PAH tubular maximum excretion). The kidneys of only one chimpanzee contained oxalate crystals.

Four chimpanzees of unreported age or sex were exposed to an atmosphere of 256 mg/m^3 ethylene glycol vapor for 28 days in a chamber simulating a spacecabin atmosphere and altitude (27,000 ft; 68% oxygen, 32% nitrogen; 5 psi) (Felts, 1969). These tests were designed to evaluate the effects of a possible leak of ethylene glycol from the heat exchanger system in spacecraft. Few effects related to ethylene glycol were detected: total white counts cell were depressed two weeks after exposure was terminated; the uric acid level was slightly elevated in one animal. No effects on other blood parameters were detected. There was no evidence of corneal erosion.

e. Chronic Toxicity

1) Oral Administration

Seven groups of five white rats (50 g) were given water containing ethylene glycol at 0, 0.5, 1, 2, 3, 5, or 10% (Hanzlik et al., 1931). Most rats receiving 2-10% died within 14 days. Rats whose water contained the lower percentages were maintained on this regime for 120-130 days. No renal changes were noted in rats drinking 0.5% ethylene glycol but 4 of 5 rats receiving 1% ethylene glycol had oxalate crystals in the urine.

Three week old albino rats (12 males, 8 females) received 1 or 2% ethylene glycol in the feed for two years (Morris et al., 1942). In six males, large urinary calculi were grossly observed. Most test animals examined developed marked kidney damage and slight liver damage. Changes in other organs were within the control range.

The addition of ethylene glycol to the diet of two male rhesus monkeys at a level of 0.2% and of one female at 0.5% for three years produced no toxic effects (Blood et al., 1962). Every three months, x-rays were taken to detect possible calcification. At the end of three years, animals were sacrificed and necropsied. No abnormal calcium deposits were detected. In the kidney of one male, the glomeruli had thickened Bowman's capsules and were sclerotic; many tubules contained granular eosinophilic material. No significant changes were detected in the other two monkeys. One male and the female were obese.

In three macaque monkeys (Macaca mulatta and irus) given 33-137 ml/kg (36.6-151.9 g/kg) in the drinking water over 13 to 157 days, renal changes were proportional to the dose (Roberts and Seibold, 1969).

There was marked to extreme deposition of calcium oxalate crystals in the proximal tubules; contiguous epithelial cells were necrotic. Occasional focal granulomas were observed in areas where tubular damage was extreme. In two monkeys, calcium oxalate crystals were also present in the walls of cerebral vessels and adjacent tissues.

In three monkeys receiving 17-28 ml/kg (18.8-31.0 g/kg), no renal changes could be attributed to calcium oxalate deposition; however, these monkeys showed mild glomerular damage and azotemia, suggesting a toxic effect of ethylene glycol apart from its conversion to oxalic acid.

2) Inhalation Exposure

Twenty mice and ten rats of unreported strains were exposed to ethylene glycol (350-400 mg/m^3) for eight hours a day, five days a week for 16 weeks (Wiley et al., 1936). Three mice and one rat died during the experimental period. The organs of nine rats and 17 mice were examined histologically; no pathological changes could be attributed to the ethylene glycol exposure. Some mice had a parasitic infection of the liver; isolated cases of myocardial degeneration, testicular degeneration and dermal ulceration were considered as "coincidental findings." Some rats had an intestinal infection; two showed moderate regressive changes in the testes.

3) Parenteral Administration

No excess mortality occurred in 200 Fischer rats of both sexes receiving twice weekly s.c. injections of 0.03-1 g/kg ethylene glycol for one year. Overall mortality was 2% in both treated and control rats (Mason et al., 1971). As discussed further in section "f" on special studies,

tumor incidence was comparable in experimental and control animals.

No growth retardation occurred among 80 male and female Fischer rats given s.c. injections of 1 g/kg twice weekly for one year. At 12 months, the final body weights ranged from 98-105% of the vehicle (saline) and no-treatment controls (Mason et al., 1971).

f. Special Studies

1) Reproduction

Ethylene glycol exhibited an intermediate order of toxicity when injected into the yolk sac of fertile white Leghorn eggs prior to incubation (McLaughlin et al., 1963). Injection of 0.05 or 0.10 ml resulted in 20% or 35% mortality, respectively.

Clegg (1964) reported 17-20% mortality in five day old Light Sussex embryos injected in the yolk sac with 0.1 or 0.05 ml ethylene glycol. A ten second immersion of a five-day incubated egg resulted in 60% mortality (50% in water controls), while similar immersion of a five-day unincubated egg resulted in 20% mortality (25% in water controls). Based on results from this and other compounds, Clegg (1964) concluded that such tests are not reliable indicators of toxicity because of variable results. Also, a clear-cut dose relationship could not be established; such a relationship was only suggested in the immersion test, but even water caused an unusually high incidence of abnormalities.

Walker (1967) reported no mortality in three day incubated eggs injected with 0.1 or 0.05 ml ethylene glycol into the yolk.

Gebhardt (1968) tested the effect of a number of glycols on the White Leghorn chick embryo. Injection of 0.05 ml of ethylene glycol

into the air chamber resulted in 6% mortality on day 0 of incubation and 37% mortality on day 4. When this amount was injected into the yolk sac, mortality was 5.6% by day 4. In neither experiment were malformations noted in surviving embryos.

2) Carcinogenicity

Ethylene glycol was not carcinogenic when administered subcutaneously in day-old mice (WARF, 1969). Groups of 50 male and 50 female Texas-Yale mice were given a single dose of either 1 or 10 mg ethylene glycol; the higher dose is approximately the LD_{50}. Groups of 200 male and 200 females received saline (control). Animals were observed daily and weights were recorded every 1-2 weeks. At 15 weeks of age, a respiratory condition resulted in a moderate level of mortality in the population. Animals were sacrificed at 15 months. Mice which were sacrificed, or which had died, were examined grossly and histologically. There were no changes attributable to ethylene glycol injection. Neoplastic and non-neoplastic pathology were comparable among treated and control animals. Tumor incidence is summarized in Table 32.

The tumor incidence, in rats receiving s.c. injections of 30-1,000 mg/kg ethylene glycol twice weekly for one year was comparable to that found in controls, as shown in Table 33 (Mason et al., 1971).

Homburger (1968; unpublished studies cited in Johnson,1978) investigated the tumorigenic effect of ethylene glycol. Male C57BL/6 mice were injected s.c. in the groin with 26 mg ethylene glycol in tricaprylin. The number and schedule of doses were not reported; negative controls received tricaprylin. Five weeks after the injection, the

Table 32
Evaluation of Carcinogenicity in Texas-Yale Mice
(WARF, 1969) [a]

	Ethylene glycol				Saline	
	1 mg		10 mg			
	M	F	M	F	M	F
I Animals Dying During Test:	19	14	23	17	94	50
1) benign neoplasms						
lung adenoma	0	0	0	0	0	1
adenoma or fibroma	0	0	0	0	0	0
skin papilloma	0	0	0	0	0	0
hemangioma	0	0	0	1	0	0
2) malignant neoplasms						
sarcoma	0	0	0	1	0	2
carcinoma	0	0	0	1	0	1
II Animals Sacrificed at 15 mo.	22	21	22	23	33	43
1) benign neoplasms						
lung adenoma	0	0	1	0	1	9
adenoma or fibroma	0	0	0	0	1	1
skin papilloma	0	0	0	0	1	0
hemangioma	0	0	0	0	0	1
2) malignant neoplasms						
sarcoma	0	6	1	4	1	8
carcinoma	0	1	0	0	0	0

[a] one-day mice given s.c. injection of 1 or 10 mg ethylene glycol; surviving animals sacrificed at 15 months.

Table 33
Tumor Incidence in Fischer Rats Given Twice Weekly S.C. Injections of Ethylene Glycol for One Year (Mason et al., 1971)

	Ethylene glycol	Saline (vehicle control)	No treatment (negative control)
% tumor bearing rats			
male	5	6	10
female	12	14	12
tumor location			
male			
injection site	2/100	0/50	1/50
other	4/100	3/50	6/50
female			
injection site	0/100	0/50	0/50
mammary	5/100	3/50	1/50
uterine	11/100	5/50	5/50
other	6/100	8/50	7/50

[a]Doses used: 30, 100, 300, or 1,000 mg/kg; rats initially four weeks old and weighed 60 g.

injection sites were excised, minced and injected into a mouse of the same strain and age; these mice were sacrificed eighteen weeks after the transfer and no tumors were detected. In another study, females CF1 and A/He mice were given single or repeated (1/month for 7 months) i.v.

injections of 26 mg ethylene glycol; negative controls received Ringer's solution. Mice were sacrificed after 28 weeks and examined for lung tumors. Compared to controls, there was no significant increase in lung tumor incidence in ethylene glycol-treated mice.

Reyniers et al. (1964) reported on hemorrhage in males and tumors in female germfree albino mice exposed accidently to bedding sterilized with ethylene oxide. Ethylene glycol was identified in the bedding and was implicated as a possible causative agent; however, this was not a controlled study and other breakdown products of ethylene oxide or ethylene oxide itself were not assayed for in the bedding. As such, it is not possible to identify this tumor-causing agent(s). As discussed in section III-A-d-1), Allen et al. (1962) found clotting abnormalities in mice fed ethylene glycol. Reyniers et al. (1964) reported that all males exposed to the ethylene oxide-treated bedding died of massive hemorrhages, failure to clot blood and jaundice. Ninety percent of surviving exposed females developed tumors.

Berenblum and Haran (1955) evaluated the carcinogenic effect of urethane in ethylene glycol by skin painting in female Swiss mice. Urethane controls received a primary treatment with ethylene glycol (1,12 or 86 applications); some also received a secondary treatment with croton oil or liquid paraffin (70 applications). No papillomas developed in mice treated with ethylene glycol alone or with liquid paraffin. One mouse in each group receiving ethylene glycol with croton oil (out of 18-19/group which survived) developed a papilloma; none of the mice receiving croton oil alone developed papillomas.

Deringer (1962) also evaluated the carcinogenicity of urethane in ethylene glycol by skin painting. Strain HR/De mice were painted with

ethylene glycol as a control, twice a week for lifetime. Tumor incidence in ethylene glycol treated mice was comparable to that in untreated mice.

3) Mutagenicity

Embree (unpublished thesis cited in Johnson, 1978) tested a "small amount" of ethylene glycol on Salmonella typhimurium strains TA 1535, TA 1537, and TA 1538 in a point mutation study without activation; no revertants were found.

3. Aquatic Organisms

Price et al. (1974) determined that the 24 hour median tolerance limit (Tl_m) of brine shrimp (Artemia salina) to ethylene glycol exceeds 20,000 mg/l.

Portmann and Wilson (1971) determined the LC_{50} of ethylene glycol to be >100 mg/l for Brown shrimp (Crangon crangon). An unspecified number of between 8-25 shrimp were tested in sea water; the LC_{50} was determined after 48 or 96 hours.

Based on the data of Portmann and Wilson, Hann and Jensen (1974) assigned ethylene glycol an aquatic toxicity rating of 1, a rating corresponding to "practically non-toxic" (TL_m 96 ranges from 100-1,000 mg/l). According to Hann and Jensen, ethylene glycol could pose a BOD problem at sub-toxic concentrations.

The 96 hour LC_{50} for rainbow trout (Salmo gairdneri) was more than 18,500 mg/l of reagent grade ethylene glycol (Jank et al., 1974).

4. Plants

Ethylene glycol inhibited elongation of oat (Avena sativa) coleoptile segments over the range of 0.5-3% in aqueous solutions or in indoleacetic acid (Farr and Norris, 1971).

Treatment of maize microsporocytes with ethylene glycol produced aberrant chromosome behavior such that meiotic centromere-spindle interactions were disrupted (Maguire, 1974).

D'amato(1948) found that exposing Allium cepa to 1-2 molar ethylene glycol for 12-24 hours resulted in a lengthening of metaphase and a vacuolization of meristematic cells.

5. In Vitro Studies

Preparations of rabbit intestine and rat uterus were exposed in vitro to ethylene glycol (Hanzlik et al., 1931). At dilutions of 1:250 and 1:100, there was a gradual depression of contraction which recovered upon washing.

In vitro, ethylene glycol at molar equivalents of 5% glycerol, increased total cell lipid content in mouse fibroblast and human liver cultures (Mackenzie et al., 1968).

Bachmann and Golberg (1971) studied the effects of ethylene glycol and its metabolites, primarily glyoxalic acid, on mitochondria isolated from the liver, kidney, and brain of Sprague-Dawley rats (40-50 g), beagle dogs (9 kg) and rhesus monkeys (Macaca mulatta, 9 kg); the compounds were tested at concentrations up to 10 mM in vitro. Ethylene glycol itself had few adverse effects on mitochondria; respiration, oxidative phosphorylation and citric-acid cycle activities were not

affected at any concentration tested while substrate-level phosphorylation was inhibited at 10 mM. In contrast, 1 mM glyoxylic acid inhibited mitochondrial respiration from liver, brain, and kidney of rats (using succinate, α-ketoglutarate or β-hydroxybutyrate as substrate) and also inhibited oxidative phosphorylation from these tissues (only when α-ketoglutarate was used as substrate). In addition, 10 mM glyoxylic acid strongly inhibited two enzyme systems of the citric-acid cycle (isocitrate dehydrogenase and α-ketoglutarate dehydrogenase. In dogs, glyoxylic acid inhibited liver and brain mitochondria using α-ketoglutarate as a substrate. In monkeys, glyoxylic acid inhibited respiration of brain mitochondria with all substrates and oxidative phosphorylation with succinate and α-ketoglutarate as substrates; only a slight effect was noted with liver mitochondria exposed to glyoxylic acid. These data give further evidence that the toxic effects of ethylene glycol are attributable to the formation of glyoxylate.

B. Propylene Glycols

The biological effects of 1,2- and 1,3-propylene glycols are discussed in separate sections which follow.

1. 1,2-Propanediol

a. Humans

1) Acute Toxicity

a) Oral Ingestion

1,2-Propanediol is classed as a generally recognized as safe (GRAS) food additive in the Code of Federal Regulations (see section IV). It is used in food as an emulsifying and plasticizing agent, humectant, surfactant, and solvent (Griffin and Lynch, 1972). The amount of 1,2-propanediol that is added to certain foods is listed in Table 34, and ranges from about 15% in seasonings and flavors to less than 0.001% in egg products and soups.

The Federation of American Societies for Experimental Biology (FASEB, 1973) has estimated the possible daily intake of 1,2-propanediol to be as follows:

Age group	Daily average		Daily maximum	
	mg	mg/kg	mg	mg/kg
0-5 months	11	21	81	20
6-11 months	10	13	333	42
12-23 months	183	17	594	54
2-65+ years	349	6	1,380	23

Table 34
Level of 1,2-Propanediol Used in Food
(FASEB, 1973)

Food category	Propylene glycol	
	usual use	maximum use
	percent	percent
seasonings and flavors	14.900	15.199
sugar, confections	5.073	5.086
processed vegetables, juice	--	0.500
sweet sauce, toppings, syrups	0.310	0.421
frozen dairy desserts, mixes	0.138	0.213
soft candy	0.089	0.144
baked goods, baking mixes	0.079	0.244
hard candy	0.072	0.135
chewing gum	0.068	0.300
alcoholic beverages	0.066	0.588
gravies, sauces	0.049	0.098
processed fruit, juices, drinks	0.049	0.082
non-alcoholic beverages	0.038	0.124
gelatins, puddings, fillings	0.036	0.068
meat products	0.023	0.053
milk, milk products	0.023	0.038
fats and oils	0.014	0.032
cheese	0.007	0.062
reconstituted vegetable proteins	0.006	0.006
snack foods	0.002	0.092

Table 34 (Continued)

Food category	Propylene glycol	
	usual use	maximum use
poultry products	0.001	0.010
other grain products	0.001	0.001
eggs, egg products	<0.001	<0.001
soups, soup mixes	<0.001	<0.001
dairy product analogs	--	--

Few reports of adverse effects of 1,2-propanediol ingestion have appeared in the literature.

Martin and Finberg (1970) reported a case of suspected 1,2-propanediol intoxication in a 15-month old boy receiving large doses of vitamin C suspended in propanediol. The patient received 250 mg vitamin C three times a day (the dose of the glycol was not estimated). By the eighth day of this treatment, the child had an irregular apical heart rate (sinus arrhythmia) and by days 10-13 had three episodes of unresponsiveness and tachypnea. Blood glucose concentration during these episodes was 70, 41, and 42 mg/100 ml. Symptomatology disappeared when vitamin C treatment was withdrawn. The authors also reported on personal communication with two physicians who each noted stupor in a patient receiving about 60 ml 1,2-propanediol in a vitamin D preparation. Recovery was complete in a few hours.

Cate and McGlothlin (1976) described a case of 1,2-propanediol overdose associated with lactic acidosis. A patient of unreported age and sex ingested an unknown quantity of the glycol. The patient initially was comatose with metabolic acidosis and the following measurements were made: blood pH, 7.24; CO_2, 11 meq/l; anion gap, 29; blood lactic acid level, 18 meq/l; blood level of 1,2-propanediol 70 mg/dl. The patient responded to bicarbonate therapy. It is known that 1,2-propanediol is converted to lactic acid in the liver and then metabolized to pyruvic acid. The authors suggest that the lactic acid in this patient was rapidly metabolized to pyruvic acid with disappearance of the metabolic acidosis.

b) Dermal Exposure

Seidenfeld and Hanzlik (1932) reported that 1,2-propanediol resulted in a burning sensation when applied to the tongue. Other investigators have reported on the potential for allergic reaction after skin application.

Warshaw and Herrmann (1952) patch tested the skin of 866 volunteers for allergic reactions to undiluted 1,2-propanediol. These volunteers were patients at a clinic treating dermatologic conditions. Sixteen percent (138) of the patients showed a positive occlusive patch test; positive reactions ranged from simple erythema to erythema with induration and vesiculation. However, when an "open" test (i.e., no patch) was used in 16 patients showing a positive reaction in the "closed" test, no reaction was noted. The authors suggest that excessive dehydration of the skin might predispose subjects to the reactions. They further

suggest that skin-sensitivity to propanediol has not been widely reported because most uses of the glycol are without an occlusive dressing.

Using a modified Draize test, Phillips et al. (1972) applied undiluted USP 1,2-propanediol to an occluded area on the forearm of four male volunteers. Examination at 24 and 72 hours revealed no irritation. Furthermore, no irritation was observed in a 21-day continuous patch test using 1-80% propanediol (in water), and a 21-day open testing system using 50 or 100% propanediol.

1,2-Propanediol failed to produce contact sensitization or skin irritation in the Draize test using 204 male volunteers (Marzulli and Maibach, 1973). One half gram of a 12% preparation in a creme vehicle was applied to the arm with an occlusive patch and removed after 48-72 hours. Two weeks later, the test material was applied again in the same manner. No adverse effects were recorded.

Pevny and Uhlich (1975) calculated a "sensitivity index" for 1,2-propanediol based on the percentage of subjects showing a positive skin test reaction. In three studies, 40 of 778 patients tested (5.1%) showed a positive reaction.

Shanahan (1977) evaluated the dermatopharmacologic activity of 1,2-propanediol in humans. This compound was a mild skin irritant following patch test exposure. A synergistically enhanced irritation potential was observed with triethanolamine-stearate, a cosmetic emulsifier. This combination resulted in progressive desquamation of the stratum corneum. Detection of irritation was influenced by the use of a semi-occlusive rather than a fully occlusive patch. Shanahan (1977) suggests that the conflicting evidence for the allergy/irritation potential of propanediol alone and in cosmetic preparations is due to several

factors. 1) The degree of occlusivity of the patch test used; 2) the concentration of propanediol used; 3) presence of surface active agents in preparations tested; and 4) the influence of environmental temperature and humidity.

2) Controlled Studies

In three subjects given oral doses of 1 ml/kg (1 g/kg) 1,2-propanediol, the maximum concentration of blood glycol was measured after 0.5 hour (Hanzlik et al., 1939a). This level persisted for about four hours, but individual variation occurred (Table 35). After ten hours, about 20-25% of the dose had been eliminated in the urine. 1,2-Propanediol was also detected in the saliva.

b. Nonhuman Vertebrates

1) Absorption, Distribution and Excretion

In a study on 48 cats, 72 rats, and 16 rabbits, Van Winkle and Newman (1941) demonstrated that absorption of 1,2-propanediol was particularly rapid from the jejunum. Ten ml/kg (10.4 g/kg) were injected directly into the jejunum, duodenum, colon, or stomach. Data were presented for cats and were as follows:

Table 35

Amount of 1,2-Propanediol in the Blood, Saliva, and Urine of Three Subjects[a] Following an Oral Dose of 1 ml/kg.
(Hanzlik et al., 1939a)

Hours	Blood, mg%			Saliva, mg%			Urine, g		
	A	B	C	A	B	C	A	B	C
0	0	0	0	0	0	0	0	0	0
0.5	174	79	47.4			142.2			
1	158	95	31.6			126.4			
2	95	111	47.4			142.2	1.86		
3	79	111	63.2			142.2			
4	111	79	63.2			94.8	7.56		5.16
6	47		15.8			94.8			
7.5				95	63		6.20		6.60
8	79	16	15.8			47.4		13.10	
10							1.64		

[a]Sex not reported.

	% Absorbed After		
	30 min	60 min	120 min
stomach	20	20	30
colon	40	50	75
duodenum	60	65	95
jejunum	90	90	98

Following i.v. injection of 1.0 g/kg 1,2-propanediol, the blood level of the glycol in rabbits (strain and sex unreported) was 80 mg% at 0.5 hour, 40 mg% at 2 hour, 16 mg% at 5 hour, and 8 mg% at 7 hour (Strack et al., 1960). The elimination of propanediol was calculated to be 0.366 mg/cm^3 per hour.

Lehman and Newman (1937) measured the level of 1,2-propanediol in the blood for several hours after oral and intravenous administration to intact and nephrectomized dogs. As shown in Table 36, urinary excretion is quite important in the elimination of 1,2-propanediol; a large fraction of the dose remained in the blood of nephrectomized animals. In another experiment, Lehman and Newman (1937) estimated that up to 45% of the total dose was excreted within 24 hours.

According to Lehman and Newman (1937) 1,2-propanediol was rapidly absorbed from the gastrointestinal tract. A 50% solution was given by stomach tube to four dogs at 2, 8, or 12 ml/kg (2.1, 8.3, 12.4 g/kg). The maximum concentration of propanediol in the blood was reached in

Table 36
Rate of Disappearance of 1,2-Propanediol in Dogs
(Lehman and Newman, 1937)

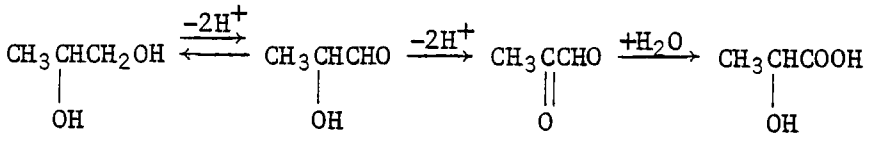
Hours after dose	mg Propylene glycol/ml blood			
	Oral (12 ml)		Intravenous (4 ml)	
	Intact dog	Nephrectomized dog	Intact dog	Nephrectomized dog
2	14.5	17	5	6
4	12	--	3	5.5
6	11.5	16.5	--	5
8	10	15.5	--	4
10	--	--	2	--
12	--	--	--	--
14	8	15	--	--

0.5 hours with a 2 ml/kg dose. However, with the 8 and 12 ml/kg doses, 4-8 hours were required for complete absorption. The authors speculate that absorption through the stomach is slight, as 124 mg% 1,2-propanediol introduced into an isolated stomach was only slightly absorbed. Also, absorption of the glycol was delayed in anesthetized dogs which, according to the authors, was likely a result of depressed gastric motility.

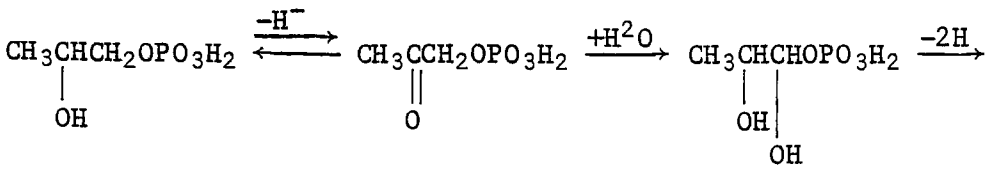
Weil et al. (1971) administered a single dose of 5 g/kg 1,2-propanediol to female beagle dogs previously treated with 2 or 5 g/kg daily for up to two years. Peak levels (0.56%) of plasma propanediol were reached after 6-8 hours. Levels were halved by 12 hours. In dogs receiving daily doses of 5 or 2 g 1,2-propanediol, a maximum blood value of 0.2% (V/V) was recorded, but all other individual values were below 0.1% (V/V).

2) Metabolism

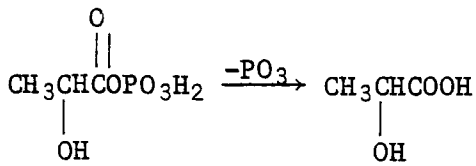
Ruddick (1972) reviewed the biochemistry of 1,2-propanediol and suggested that the oxidation of this compound to lactic acid or pyruvic acid follows one of two pathways depending on whether the substrate is the free glycol or the phosphorylated glycol (data primarily from Rudney, 1954 and Miller and Bazzano, 1965). Free 1,2-propanediol is metabolized through lactaldehyde, methylglyoxal, and lactic acid as shown below:



Phosphorylated glycol (1,2-propanediol phosphate) takes the following route: acetol phosphate, lactaldehyde phosphate, lactyl phosphate, and lactic acid, as follows:



1,2-propanediol phosphate | acetol phosphate | lactaldehyde phosphate



lactyl phosphate | lactic acid

According to Rudney (1954), 1,2-propanediol phosphate occurs in rat liver at 1-2% of the total acid-soluble phosphorus in liver.

Once 1,2-propanediol is oxidized to lactate or pyruvate, it can provide energy by further oxidation through the tricarboxylic acid cycle or through the glycolytic pathway, the latter contributing to glycogen formation (Ruddick, 1972). Hanzlik et al. (1939a and b) were the first to report on the glycogenic action of 1,2-propanediol. In starved rats given oral doses of 0.5-15.0 ml/kg (0.5-15.5 g/kg), the amount of liver glycol was increased compared to controls, as shown on the next page. Total body glycogen was also increased following 1,2-propanediol ingestion.

Giri et al. (1970) reported a significant increase in blood glucose 15 minutes after i.p. injection of a near fatal dose of 1,2-propanediol (10 ml/kg or 10.4 g/kg) to male Sprague Dawley rats. Blood

Dose, ml/kg[a]	Liver glycogen, mg%					Maximum increase, mg/g liver
	controls	1 hr	2 hr	3 hr	4 hr	
0.5	148	211	156	208	135	0.63
1.0	123	333	336	330	294	2.13
2.0	113	241	371	465	720	6.07
5.0	241	331	425	570	852	6.11
10.0	75	72	224	673	726	6.51
15.0	212	359	581	699	627	4.87

[a]Rats weighed 80-150 g; strain and sex not reported; five rats/group; data from Hanzlik et al. (1939a & b).

glucose reached a maximum by 90 minutes, but remained significantly elevated ($p < 0.01$) by hour 6. During this period, liver glycogen remained unchanged, suggesting that the increase in blood glucose may have been due to conversion of the glycol to blood glucose, rather than to the mobilization of liver glycogen. Twelve hours after propylene glycol administration, there was a severe depletion of liver glycogen.

Whittman and Bawin (1974) presented data showing that glucose formation from 1,2-propanediol proceeds via phosphoenolpyruvate carboxykinase. Fasted female Charles River CD rats (110-198 g) were injected i.m. with 200-2,000 mg/kg 1,2-propanediol during pentobarbital-induced

amnesia. After 90 minutes, the concentrations of blood glucose and liver glycogen were determined. Propanediol caused a dose dependent increase in liver glycogen, blood glucose, and the rate of glycogen synthesis. In a time course study using 500 mg/kg propanediol injected i.m., the rate of synthesis of liver glycogen reached a maximum 90 minutes after the injection, returning to control values after three hours. Stimulation of gluconeogenesis was also demonstrated in another experiment using intraperitoneal injection of propanediol. Quinolinic acid, a weak inhibitor of phosphoenolpyruvatecarboxykinase (the first enzymatic step of gluconeogenesis from citric acid cycle intermediates), markedly inhibited gluconeogenesis resulting from propanediol administration. According to the authors, this is consistent with the sequence of glucose formation from 1,2-propanediol via phosphoenolpyruvatecarboxykinase.

The glucogenic effect of 1,2-propanediol has also been confirmed in fasted cows given 150-500 g intraruminally (Voigt and Piatkowski, 1973; Giesecke et al., 1975).

These data show that glycogen formation is enhanced by 1,2-propanediol. Thus, this diol can be used as a synthetic nutrient source.

3) Acute Toxicity

a) Oral Administration

i) Lethal Dose Values

For 1,2-propanediol, the LD_{50} averages 14.3-24.8 g/kg for mice, 21.8-29.0 g/kg for rats and 18.35-19.6 g/kg for guinea pigs; these data appear in Table 37. For rabbits, the minimum lethal dose was 20 g/kg (Braun and Cartland, 1936).

Table 37
Oral Lethal Dose Values for 1,2-Propanediol

Species/Strain	Sex/No.	LD_{50}			Reference
		Reported value	Deviation	Converted value (g/kg)	
mouse/White	NR/4 per dose	22.0 cm^3/kg	--	22.8	Latven and Molitor, 1939
mouse/NR	M&F/10-20 per dose	23.9 ml/kg[a]	range: 22.8-25.1	24.8	Laug et al., 1939
mouse/NR	NR	13.79 cm^3/kg[b]		14.3	Fischer et al., 1949
rat/Wistar	M/10 per dose	26.38 g/kg	95% C.L. = 24.50-28.39	26.38	Smyth et al., 1941
rat/NR	NR/25	28 ml/kg[b]	--	29.0	Thomas et al., 1949
rat/NR	M&F 19-10 per dose	21.0 ml/kg[a]	range: 19.2-23.0	21.8	Laug et al., 1939
guinea pig/NR	M&F/10 per dose	18.9 ml/kg[a]	range: 17.2-20.7	19.6	Laug et al., 1939
guinea pig/NR	M&F/10 per dose	18.35 g/kg	95% C.L. = 16.94-19.87	18.35	Smyth et al., 1941

NR = not reported.

[a]Animals fasted overnight; observed for five days.

[b]LD_{50} after 24 hours.

ii) Signs

In white mice, the minimum symptomatic dose for 1,2-propanediol was 8.3 g/kg (Latven and Molitor, 1939). In Wistar rats, a dose of 10 g/kg was without effect (Litton Bionetics, 1974). Large oral doses of the glycol to mice, rats, and guinea pigs resulted in loss of equilibrium, marked depression, analgesia, coma, and finally, death after a prolonged moribund period (Laug et al., 1939). Gross observation revealed hemorrhagic areas in the small intestine. In the kidney, microscopic changes included vacuolar degeneration of the cytoplasm and nuclear pyknosis. The liver showed slight congestion and hyperemia with no fatty changes.

Gastric administration of 1.5, 2.0, or 10.0 ml/kg (1.6, 2.1, or 10.4 g/kg) 1,2-propanediol to three dogs of unreported breed and sex in divided doses (6, 4, or 2 doses, respectively) was without effect (Hanzlik et al., 1939a).

Three horses (sex and weight not reported) given 0.5-1 gallon of 1,2-propanediol via a stomach tube developed ataxia and depression within 15-30 minutes (Myers and Usenik, 1969). Recovery occurred within three days without treatment. A 454 kg gelding was fed two gallons of the glycol. Within 15 minutes it became ataxic. It became recumbent within three hours and remained so until death three days later. Initially, diarrhea and abnormal peristalsis were noted. At necropsy, the following was observed: moderate sloughing of the gastric mucosa; full and dilated stomach, although the gelding had not eaten in three days; moderate to severe inflammation of the intestinal tract; congestion of large colon with ecchymotic hemorrhages on the

serosa of small intestine. Also, the kidney was congested and the brain edematous. Degenerative changes of the liver cells were seen microscopically.

iii) Behavioral Effects

Isgrig and Ayres (1968) evaluated the behavioral effects of 1,2-propanediol using voluntary activity and equilibrium measures in male Sprague-Dawley rats. A hunger-activity cycle was imposed seven days before testing, and continued for the duration of the experiment; rats were given access to food for only three hours a day. Four rats were given 11.43 ml/kg (11.84 g/kg) 1,2-propanediol by stomach intubation and the percentage of voluntary activity during the next three hours was recorded. Activity in those receiving 1,2-propanediol was during the second and third hour compared to those given an isocaloric, isovolumetric dose of sucrose.

b) Dermal, Ocular, and Ear Application

USP 1,2-propanediol was a mild irritant to the skin of New Zealand white rabbits (2.5-3.9 kg). In three replicate modified Draize tests, the glycol was applied to an occluded area of shaved dorsal skin of four rabbits. After 24 hours, an average score of 0.39 was obtained, corresponding to barely perceptible erythema or edema (Phillips et al., 1972).

Instillation of 0.5 ml 1,2-propanediol into rabbits' eyes caused moderate edema and hyperemia after 24 hours (Latven and Molitar, 1939).

1,2-Propanediol adversely affected hearing in guinea pigs

(250-400 g) (Morizono and Johnstone, 1975). Two pinholes were made in the tympanic bullae and propylene glycol at concentrations ranging from 10-100% was instilled into the middle ear cavity; controls were similarly treated with Ringer's solution. The duration of exposure was 1, 2, or 6 days. Hearing was monitored by cochlear microphonic responses. Effects on hearing loss were variable at concentrations of 10 or 20%, (i.e., hearing loss occurred in one animal when the middle ear was exposed to 10% for six days, but not in another animal similarly exposed to 20%). Concentrations of 50 or 100% 1,2-propanediol caused deafness in all six animals tested after one day's exposure. 1,2-Propanediol is used as a vehicle in some ear drop preparations; the authors caution against its use in preparations instilled in the middle ear cavity.

c) Inhalation Exposure

Inhalation of 10% 1,2-propanediol aerosol for 20 or 120 minutes produced ultrastructural changes in the tracheal epithelium of six rabbits (2,000-3,000 g) (Konradova et al., 1978). In particular, mucous secretion by goblet cells was increased; degeneration and sloughing off of these cells was also observed. Two hours after inhalation, no differentiation of new goblet cells was noted. The method used to generate the aerosol was not specified; it is not clear what the level of 10% propanediol aerosol corresponds to.

d) Parenteral Administration

i) Lethal Dose Values

The lethal dose for 1,2-propanediol administered by injection is listed in Table 38. 1,2-Propanediol is more toxic via this route than by oral administration. The LD_{50} for mice averages 6.6-8.3 g/kg i.v., 9.7-17.48 g/kg i.p. and 19.2 g/kg s.c. In rats, the LD_{50} averages 6.4-6.8 g/kg i.v., 13.5 g/kg i.p., 22.5-29.0 g/kg s.c., and 14-20.7 g/kg i.m. In rabbits, the LD_{50} was 6.5 g/kg.

Brown and Conine (1971) found no difference in toxicity to mice of the optical isomers of propylene glycol. For 1,2-propanediol (dl-propylene glycol), the LD_{50} was 17.48 g/kg; for d-propylene glycol, the LD_{50} was 17.41 g/kg and for l-propylene glycol, 16.61 g/kg.

ii) Signs

Giri et al. (1970) reported a maximum nonlethal dose of 10 ml/kg (10.4 g/kg) i.p. in male 50-60 g Sprague-Dawley rats. This dose of 1,2-propanediol caused mild central nervous system depression lasting for two or three hours. The minimum lethal dose was 15 ml/kg (15.5 g/kg) and the LD_{100} was between 25-30 ml/kg (25.9-31.0 g/kg). Death resulted from severe CNS depression and respiratory failure.

Vasquez et al. (1977) reported that 1,2-propanediol produces amnesia in mice when administered prior to a training experience. Fifty day old HA/ICR male mice were injected i.v. with 20, 40, or 60% aqueous propanediol (2.08, 4.16, or 6.24 g/kg); controls received saline. Treatment was given either 30 minutes before or up to three hours after training in a 1-trial inhibitory (passive) avoidance task. Although

Table 38
Parenteral Lethal Dose Values for 1,2-Propanediol

Species/Strain	Sex/No.	Route	LD_{50}			Reference
			Reported value	Deviation	Converted value (g/kg)	
mouse/White	NR/4 per dose	i.v.	8.0 cm^3/kg		8.3	Latven and Molitor, 1939
mouse/SPF NMR I	M&F/10 per dose	i.v.	6.4 ml/kg[a]	95% C.L. = 6.1-6.9 ml/kg	6.6	Bartsch et al., 1976
mouse/NR	NR/10 per dose	i.p.	10.96 ml/kg[b]	95% C.L. = 9,715-13,380 mg/kg	11.4	Davis & Jenner, 1959
mouse/Carworth Farm	F/NR	i.p.	127.87 milli-moles/kg	--	9.7	Karel et al., 1947
mouse/NR	NR/NR	i.p.	17.48 g/kg	--	17.48	Brown and Conine, 1971
mouse/NR	F/60	i.p.	9.36 ml/kg	S.E. = 1.20	9.7	Karel et al., 1947
mouse/White	NR/4 per dose	s.c.	18.5 cm^3/kg	--	19.2	Latven and Molitor, 1939
rat/White	NR/40	i.v.	6.8 g/kg	--	6.8	Weatherby and Haag, 1938

Table 38 (Continued)

Species/Strain	Sex/No.	Route	LD_{50}			Reference
			Reported value	Deviation	Converted value (g/kg)	
rat/Sprague Dawley	M&F/10 per dose	i.v.	6.2 ml/kg[a]	95% C.L. = 5.2-7.4	6.4	Bartsch et al., 1976
rat/Sprague Dawley	M&F/10 per dose	i.p.	13.0 ml/kg[a]	95% C.L. = 10.2-16.5	13.5	Bartsch et al., 1976
rat/NR	NR/25	i.p.	13 ml/kg[c]		13.5	Thomas et al., 1949
rat/NR	NR/25	s.c.	28 ml/kg[c]		29.0	Thomas et al., 1949
rat/White	NR/15	s.c.	22.5 g/kg		22.5	Weatherby and Haag, 1938
rat/White	NR/12	i.m.	14 g/kg		14	Weatherby and Haag, 1938
rat/NR	NR/25	i.m.	20 ml/kg[c]		20.7	Thomas et al., 1949
rabbit/NR	NR/18	i.v.	6.5 g/kg		6.5	Weatherby and Haag, 1938

NR = Not reported

[a] LD_{50} determined after 7 days.

[b] Based on cumulative mortality during a 28-day post-injection period.

[c] LD_{50} determined after 24 hours.

more pronounced at 60%, treatment at all levels prior to training significantly impaired retention performance. In general, post-trial treatments were ineffective. According to the authors, the amnestic effect is likely due to central nervous system depression.

Intraperitoneal injection of up to 4 ml/kg (4.1 g/kg) of 1,2-porpanediol had no narcotic effect in four Wistar rats, two Mongrel dogs, or two rabbits (Eichbaum and Yasaka, 1976). The anesthetic dose was 21.2 ml/kg (22.0 g/kg) in dogs (Hanzlik et al., 1939a).

Intramuscular injection of doses greater than 7.4 g/kg to white rats resulted in increased respiratory rate, loss of equilibrium, depression, coma, and death (Seidenfeld and Hanzlik, 1932).

Injection of 0.3 ml of undiluted 1,2-propanediol into the sciatic nerve of 44 anesthetized adult albino rats caused complete paralysis in 28 and moderate paralysis in 28 rats (Chino et al., 1974). Histological changes included diffuse necrotic lesions four days after injection. Regeneration was noted two weeks following injection when small axons, and an increased amount of perineural connective tissue were observed. Intramuscular injection of 0.1 ml of undiluted propanediol produced localized necrotic lesions. The authors suggest from these findings that 1,2-propanediol might be useful for chemical neurolysis as a means for control of spasticity in patients with central nervous system disease.

Eichbaum and Yasaka (1976) reported that 0.2-0.3 ml/kg (0.2-0.3 g/kg) 1,2-propanediol (70% solution) had antiarrhythmic-antifibrillatory effects on the heart when injected intravenously into mongrel dogs (8-15 kg) and male Wistar rats (400-480 g) with spontaneous or drug-induced arrhythmias.

iii) Hematology and Hemodynamics

Intravenous injection of 4 ml/kg (4.1 g/kg) of USP 1,2-propanediol (12.5, 25, or 50% in saline) to 2-3 kg Himalayan rabbits had no effect on red blood cell count, white blood cell count, hemoglobin concentration, or packed cell volume (Brittain and D'Arcy, 1962). However, there was a dose-dependent increase in the number of circulating polymorphs and a dose-dependent decrease in the number of lymphocytes. The number of circulating monocytes, eosinophiles, and basophiles remained unchanged. At the highest concentration of the glycol administered, there was a marked decrease in blood clotting time and an increase in platlet count.

Hemolysis was observed following i.v. administration of sublethal doses of 1,2-propanediol to rats (molar concentrations 0.278-0.167) (Weatherby and Haag, 1938). Lehman and Newman (1937) reported that if propanediol dilutions (up to 30% propylene glycol) were prepared with 0.9% NaCl, no hemolysis occurred.

Two of seven cats given 2 ml/kg (2.1 g/kg) 1,2-propanediol by intramuscular injection showed very low serum calcium levels within 24 hours. Four of the cats showed crystals in the convoluted tubules. However, in six cats given 5 ml/kg (5.2 g/kg) by i.m. injection, no changes in serum calcium levels were detected (Van Winkle and Newman, 1941).

MacCannell (1969) investigated the effect of 1,2-propanediol and ethylene glycol on hemolysis or hemodynamic changes in 43 dogs; this study is discussed in more detail in section II-A-2-c-3). Both compounds were infused i.v. for 2-5 minutes at a rate of 20 mg/kg/min

or 150-250 mg/kg/min. At either rate, cardiac output and superior mesenteric blood flow were increased. Renal blood flow was markedly decreased at the higher rate. Direct injection of 25-50% glycol into the renal artery resulted in decreased blood flow through this artery; injection into the superior mesenteric artery increased flow through this vessel.

4) Subacute Toxicity

a) Oral Administration

Groups of 15 male and 15 female Charles River rats were fed diets containing 0 (control) or 50,000 ppm (5%) 1,2-propanediol for 15 weeks (Gaunt et al., 1972). There were no significant differences between the control and treated rats for the following: analyses of serum and urine; hematological indices; organ weights; and gross examination of organs at autopsy. No data are presented for these parameters.

When 1,2-propanediol was fed at levels higher than 30% in the diet, weanling rats lost weight and died in a few days (Whitlock et al., 1944). Older ("half grown") animals were able to tolerate higher levels (exact level not given).

Hyperglycemia resulted in male Wistar rats given 5 or 10% 1,2-propanediol orally for five weeks (Vaille et al., 1971).

Daily doses of 1-8 ml/kg (1.0-8.3 g/kg) were administered by gavage to 11 rabbits (1.6-2.6 kg) over 50 days (Braun and Courtland, 1936). Body weight gain was comparable to that of controls. No gross pathology was attributed to glycol administration.

Dean and Stock (1974) presented evidence that 1,2-propanediol is not an inert solvent. Administration of 2-6 ml/kg (2.1-6.2 g/kg) i.p. twice a day for three days to male Wistar rats (170-230 g) caused a significant elevation of the rate of *in vitro* hepatic microsomal metabolism of aniline and p-nitroanisole; also, there was a significant decrease in the rate of aminopyrine demethylation but no change in p-nitrobenzoic acid metabolic rate. When 1,2-propanediol and phenobarbital were administered concurrently for three days, an additive response was observed in the rate of metabolism of aniline and p-nitroanisole. No changes in cytochrome 450 were observed. *In vivo*, pretreatment with 4 ml/kg i.p. twice daily for three days prior to injection of 125 mg/kg hexobarbital resulted in increased hexobarbital sleeping times compared to rats receiving hexobarbital only; this result suggests inhibition of hexobarbital metabolism by propanediol. Similarly, administration of 120 mg/kg zoxazolamine after propanediol pretreatment resulted in increased paralysis times which was likely due to a reduction in the rate of metabolism of zoxazolamine.

Zaroslinski et al. (1971), however, found no change in hexobarbital sleeping time after administration of 4 ml/kg (4.1 g/kg) 1,2-propanediol daily for four days to CF-1 mice.

5) Chronic Toxicity

a) Oral Administration

i. Rats

i) Weight Gain

Weanling male rats (initially 55 g) were given 1,2-propanediol

in the drinking water in concentrations of 0, 0.1, 0.3, 1.0, or 10.0% for 100 days. The weight gain of rats receiving the highest level was depressed during the first ten days. All rats thereafter showed rate of weight gain comparable to controls. No pathological changes were observed which could be attributed to glycol treatment (Weatherby and Haag, 1938).

Incorporation of 1-10% 1,2-propanediol in the drinking water of 20 white rats (50 g) for 140 days had no effect on body weight or growth compared to no-treatment controls (Seidenfeld and Hanzlik, 1932).

In a paired feeding experiment, six rats (strain and sex not given) received 1,2-propanediol by stomach tube in a volume equal to 12.8% of the food intake of the previous day; six control rats were given an equal quantity of water by stomach tube (Hanzlik et al., 1939a). Experimental rats showed a higher rate of weight gain during the 180 day experiment.

Groups of 30 male and 30 female Charles River CD rats were fed for two years diets which contained 6,250, 12,500, 25,000, or 50,000 ppm 1,2-propanediol (0.625, 1.25, 2.5, or 5%, respectively). At the four dietary levels, the mean daily intake of the glycol was 0.2, 0.4, 0.9, and 1.7 g/kg in males and 0.3, 0.5, 1.0, and 2.1 g/kg in females. There were no statistically significant differences between control and treated rats in survival, food consumption, or body weight gain (Gaunt et al., 1972).

ii) Organ Effects

One of three rats receiving for five months a diet in which 1,2-propanediol replaced half of the carbohydrates, showed moderate degeneration of the liver and of the convoluted tubules of the kidney (Hanzlik et al., 1939a).

Compared to controls, no pathological changes were observed in the kidney, heart, spleen, and liver of 20 white rats which received 1-10% 1,2-propanediol in the drinking water for 140 days (Seidenfeld and Hanzlik, 1932).

Slight liver damage was observed in 20 albino rats receiving 2.45 or 4.9% 1,2-propanediol in the diet for two years. No other pathological changes were attributed to the glycol (Morris et al., 1942).

No differences in absolute or relative organ weights were noted among Charles River rats receiving 0-50,000 ppm (0-5%) 1,2-propanediol in the diet for two years (Gaunt et al., 1972). There was a wide spectrum of histological abnormalities, especially in the kidney, liver, and lung. These occurred with equal frequency among control and treated rats and were consistent with those expected in aging rats. As discussed further in Section B-1-b-6, the incidence of neoplasms was similar among control and propylene glycol treated animals.

iii) Hematology and Urinalyses

No hematological differences were found among Charles River rats fed diets containing 0 to 50,000 ppm (0-5%) 1,2-propanediol for two

years (Gaunt et al., 1972). These parameters were measured at weeks 13, 21, 52, and 80 in eight rats of each sex: hemoglobin content, packed cell volume, erythrocyte, and leucocyte counts, and differential cell counts. Reticulocyte counts were made at week 52, 54, and 80 and hemoglobin counts were made at week 104.

No significant difference was noted in urinary cell excretion or renal concentration tests among Charles River rats receiving dietary 0, 25,000, or 50,000 ppm (0, 2.5, or 5.0%, respectively) 1,2-propanediol for one year (Gaunt et al., 1972). At weeks 13, 30, and 52, the following measurements were taken on 6-10 rats of each sex: specific gravity and volume of urine produced during a six-hour period of water deprivation, during a two-hour period following a water load, and during a four-hour period beginning 16 hours after a water load. In addition, urinary cell counts were taken on the six-hour samples.

ii. Dogs

i) Weight Gain

The general health and weight of four female dogs (breed not given, 6.2-21 kg) were unaffected by oral ingestion of 5% aqueous 1,2-propanediol for 5-9 months; the average daily intake was 5.1 ml/kg (5.3 g/kg).

In a two year feeding study, groups of five male and five female beagle dogs (initially 10-14 months old) received 5.0 or 2.0 g 1,2-propanediol/kg/day (Weil et al., 1971). Isocaloric controls received 6.35 or 2.54 g dextrose/kg; another control group received no treatment. One dog each died in experimental and control groups. Body

weight gain was comparable in dogs receiving either the experimental diet or no treatment. Isocaloric control males showed a significantly greater increase in weight during the first six months compared to no treatment controls. The authors suggest that although the propylene glycol and dextrose diets were isocaloric, the calories in the diet were not necessarily equally available for conversion to adipose tissue. This may explain differences in weight gain.

Water consumption in dogs treated with 1,2-propanediol was reduced during the first year of the study. Accompanying this was a low specific gravity of some urine samples and a discrepancy between water intake and urine volumes. According to Weil et al. (1971), these factors are accounted for by the generation of water during oxidation. One gram of 1,2-propanediol yields 0.95 g water and 1 g dextrose yields 0.60 g water when oxidized in the body.

ii) Organ Effects

Four female dogs (breed not reported; 6.2-21 kg) were given 1,2-propanediol for 5-9 months and received no other fluid; the average daily intake was 5.1 ml/kg (Van Winkle and Newman, 1941). At irregular intervals during the experiment, tests were made of kidney function (phenolsulfonphthalein excretion) and liver function (rose bengal in blood; galactose and uric acid in urine). Compared to pre-exposure levels, no effect on these tests occurred with glycol treatment. Histological examination revealed no pathological changes in the livers or kidneys. In four male dogs drinking about 4.5 ml/kg (4.7 g/kg) daily for 5-6 months, the only change in renal function noted was elevated blood urea levels.

No differences were measured in relative liver or kidney weights in dogs receiving 5 or 2 g 1,2-propanediol/kg/day for two years, compared to dextrose or untreated controls (Weil et al., 1971). Organs were examined grossly and micropathologically. Numerous sporadic lesions were observed in dogs receiving the glycol or dextrose which were comparable to those found in untreated controls. No findings were considered to be the result of treatment.

iii) Hematology and Urinalyses

In dogs fed 5.0 or 2.0 g 1,2-propanediol for two years, Weil et al. (1971) measured no changes in the following parameters compared to dextrose or no treatment controls: differential leucocyte counts, erythrocyte fragility, urinary pH and micro-examination, alkaline phosphatase, bromsulphthalein retention, liver glycogen, blood glucose, total liver lipids, metabolic rate of liver slices using propylene glycol, or activities of serum glutamic-oxalacetic and glutamic-pyruvic transaminases.

In dogs receiving 5 g/kg (but not 2 g/kg) 1,2-propanediol an effect on erythrocytes was apparent when compared to the nutritionally equivalent dextrose group (6.35 g dextrose/kg). Hemoglobin, hematocrit and total erythrocyte count were slightly decreased; also, anisocytosis, poikilocytes, and reticulocytes were increased. The foregoing changes indicate some erythrocyte destruction with replacement from the bone marrow. There was no evidence of damage to the spleen or bone marrow.

Some changes were not dose related and occurred only sporadically.

These included a decreased total leucocyte count in males receiving the lower dose of the glycol, and a decreased level of liver triglyceride in females given the lower dose.

Total bilirubin and urine output were significantly increased in females receiving 5 g of 1,2-propanediol/kg.

b) Inhalation Exposure

i. Rats

A group of 20 seven week old white rats (initially 80-90 g) were exposed to an atmosphere of 1,2-propanediol aerosol (170-350 mg/m^3) for 18 months (Robertson et al., 1947). Weight gain was slightly higher in the experimental group than in controls. Both groups were in good condition and bred regularly. At sacrifice made during various intervals after 3-18 months, no abnormal changes were observed in the kidney, liver, or spleen. In experimental animals, round cells accumulated in the lung after five months' exposure.

ii. Monkeys

Twenty-nine rhesus monkeys (2959 g) were exposed for up to 13 months to an atmosphere of 100-220 mg/m^3 or 230-350 mg/m^3 1,2-propanediol (Robertson et al., 1947). No pathological effects were attributable to the exposure; organs were examined grossly and microscopically after 1-13 months' exposure. Urine concentrating ability, blood cell counts, and hemoglobin determinations in experimental animals were comparable to controls.

6) Special Studies

a) Reproduction

i. Mice

1,2-Propanediol was evaluated for teratogenicity in albino CD-1 outbred mice (Food and Drug Research Laboratories, 1973a). Groups of 25-28 females were given oral doses of 16.0, 74.3, 345.0, or 1,600.0 mg/kg on days 6-15 of gestation. Animals were killed on day 17. 1,2-Propanediol was without effect on the following: the number of implantation sites, resorption sites, live and dead fetuses; pup body weight; presence of abnormalities of fetal soft or skeletal tissues.

ii. Rats

Groups of 25-28 female Wistar rats were given daily oral doses of 16.0, 74.3, 345.0, or 1,600.0 mg/kg of 1,2-propanediol on days 6-15 of gestation (Food and Drug Research Laboratory, 1973a). On day 20, the number of implantation sites, resorption sites, and live and dead fetuses were recorded. Pups were weighed and the soft and skeletal tissue were examined. Propanediol was without effect on these parameters when compared to sham-treated controls.

In rats, addition of 30% 1,2-propanediol to the basal diet resulted in low rates of reproductive success (Whitlock et al., 1944); no additional information was given in the paper.

iii. Hamsters

Groups of 24-27 adult female golden hamsters received oral doses

of 15.5, 72.0, 334.5, or 1,550.0 mg/kg 1,2-propanediol on days 6-10 of gestation (Food and Drug Research Laboratories, 1973a). On day 14, the numbers of implantation sites, resorption sites and live and dead fetuses were determined. Fetuses were weighed and examined for anatomical abnormalities. No adverse effects were attributed to glycol administration.

iv. Rabbits

No teratogenic effect was noted in groups of 15-20 Dutch-belted rabbits given 12.3, 57.1, 267.0, or 1,230.0 mg/kg 1,2-propanediol on days 6-18 of gestation (Food and Drug Research Laboratory, 1973a). Animals were examined on day 29. Propanediol was without effect on the following parameters: numbers of corpora lutea, implantation sites, resorption sites, live and dead fetuses; urogenital tract; fetal weight; visceral or skeletal abnormalities of fetuses.

v. Chickens

McLaughlin et al. (1963) labeled 1,2-propanediol as "nontoxic" when injected into the yolk sac of fertile white Leghorn eggs prior to incubation. Injection of 0.05 ml undiluted propanediol resulted in a 95% hatch rate. Walker (1967) reported no mortality in ten three-day incubated eggs injected with 0.1 or 0.05 ml propanediol into the yolk.

No mortality occurred in five day incubated Light Sussex embryos after injection with 0.1 ml 1,2-propanediol (Clegg, 1964). When five day old incubated eggs were immersed for ten seconds in the

glycol, mortality was 70% compared to 50% in eggs immersed in water.

Gebhardt (1968) injected several glycols, including 1,2-propanediol, into the air chamber or yolk sac of white Leghorn chick embryos. When injected into the air chamber, 0.05 ml 1,2-propanediol resulted in an incidence of up to 27% micromelia, a condition characterized by reduction and torsion of the lower limbs and by parrot beak. No micromelia or other abnormalities occurred following yolk sac injection of 0.05 ml. Injection of a higher dose (0.2 ml) of 1,2-propanediol on day 4 into the yolk sac did not result in micromelia but did cause the formation of a large liquid containing cyst in 40% of the eggs.

Granich and Timiras (1969) reported that when 1,2-propanediol is injected onto the chorioallantoic membrane, toxicity is low. However, injection into the air chamber resulted in high toxicity, possibly due to damage of the vasculature near the site of injection.

Walker (1967) found that when 1,2-propanediol was injected into in vitro preparations of fresh intact and broken yolks, it remains at the site of injection.

1,2-Propanediol had a dose-dependent glycogen-depleting effect on the embryonic myocardium of 8.5 day-old chick embryos (Delphia and Frierdich, 1973). Fertile White Leghorn eggs were exposed for three hours to 0.025, 0.040, 0.050, 0.075, 0.100, or 0.200 ml/egg propanediol or sterile water (controls). The myocardial glycogen level for pooled controls was 10.80 mg/g. Significant ($p < 0.01$) myocardial depletion occurred at all but the lowest dose of propanediol For treated eggs, myocardial glycogen ranged from 8.54 mg/g at 0.040 ml to 2.68 at 0.200 ml.

b) Carcinogenicity

No carcinogenic potential was attributable to 1,2-propanediol in Charles River rats receiving up to 50,000 ppm (5.0%) in the diet for two years (Gaunt et al., 1972). The incidence of neoplasms is shown in Table 39. Among both treated and control rats, there was a high incidence of mammary fibroadenomas, pituitary adenomas, and subcutaneous fibrosarcomas. According to the authors, the random distribution of other tumors and the lack of any dose-response relationship show that the tumors were unrelated to propylene glycol administration.

1,2-Propanediol was not carcinogenic when given by s.c. injection to 18 male mixed strain rats (200 g) (Umeda, 1957). The back of rats was injected with 1 ml once a week for 15 months, after which time the amount was reduced to 0.5 ml. The experiment was terminated at 88 weeks. Eleven rats survived past 43 weeks. No tumor was produced at the site of injection in any rat. In addition, internal organs at autopsy appeared normal. One rat, dying on the 403rd day, had adenoma of the hypophysis, which the author claimed was of spontaneous origin.

Baldwin et al. (1968) used 1,2-propanediol as a vehicle in testing the carcinogenicity of 4-acetamidostilbene and N-hydroxy-4-acetamidostilbene. Twenty control female Wistar rats received three injections of the glycol (dose not given) over four weeks. No tumors were observed for 60 weeks, when the experiment was terminated for all groups.

Dewhurst et al. (1972) evaluated the carcinogenic potential

Table 39
Incidence of Neoplasms in Charles River Rats Fed 1,2-Propanediol in the Diet for Two Years (Gaunt et al., 1972)

Organ and neoplasm	Dietary Levels[a] (%)									
	0		6.25		1.25		2.5		5.0	
No. of rats examined	26	28	27	25	27	27	23	28	24	27
	M	F	M	F	M	F	M	F	M	F
Kidney										
adenocarcinoma	0	0	1	0	0	0	0	1	0	0
lung										
adenoma	1	0	1	2	0	1	0	2	0	0
brain										
malignant astrocytoma	1	0	0	0	0	0	0	0	0	0
pituitary										
adenoma	2	9	2	7	4	13	1	12	1	4
adrenal										
adenoma	1	1	1	0	1	2	2	0	3	1
pancreas										
islet cell adenoma	0	0	1	0	1	0	0	0	1	0
thyroid										
adenoma	1	1	1	0	0	0	0	0	0	0
carcinoma	0	1	0	0	0	0	0	0	0	0
testis										
interstitial cell tumor	0	--	1	--	0	--	0	--	1	--
ovary										
follicular adenoma	--	0	--	0	--	1	--	0	--	0

Table 39 (Continued)

Organ and neoplasm	Dietary Levels[a] (%)									
	0		6.25		1.25		2.5		5.0	
No. of rats examined	26	28	27	25	27	27	23	28	24	27
salivary gland										
malignant tumor	0	0	0	0	0	0	0	1	0	0
subcutaneous tissue										
fibroma	0	0	0	1	0	0	0	0	0	0
fibrosarcoma	1	2	0	0	1	0	2	0	3	3
rhabdomyosarcoma	0	0	1	0	0	0	0	0	0	0
mammary gland										
fibroadenoma	2	17	3	16	2	15	1	18	1	13
adenocarcinoma	1	0	0	3	0	0	0	0	0	0
skin										
squamous cell carcinoma	0	0	0	0	1	0	0	0	0	0
lymph tissue										
lymphoma	0	0	1	0	0	0	1	0	1	0
abdomen										
fibrosarcoma	1	0	0	0	0	0	0	0	0	0

[a]Figures represent the numbers of rats with tumors out of the total.

of several six-substituted benzo(a)pyrene derivatives using 1,2-propanediol

as the vehicle. A group of 20 young female Balb/c control mice received 1 mg propanediol by injection. No control animals developed tumors over a two year period.

1,2-Propanediol was not found to be carcinogenic when applied to the dorsal skin of female Swiss mice (Stenbäck and Shubik, 1974). Groups of fifty mice were treated with 10, 50, or 100% propanediol (in acetone) every day for life. As shown in Table 40, the overall tumor incidence in treated mice was 40-52%; in untreated and acetone controls, the incidence was 42 and 44%, respectively. These differences are not significant. The distribution of tumor types was similar among glycol-treated and control mice (Table 40).

Fujino et al. (1965) evaluated the carcinogenicity of 4-nitroquinoline N-oxide in 1,2-propanediol by daily lifetime skin application to the labial mucosa of male ddN mice. Neither the 36 glycol controls nor the 30 untreated mice developed carcinoma of the oral mucosa.

Application of 1,2-propanediol to the soft palate of six female Sprague-Dawley rats (150 g) three times a week for up to eight months did not result in any evidence of oral cancer. Propanediol was used as a control to evaluate 4-nitrochinoline N-oxide in (Wallenius and Lekholm, 1973).

c) Mutagenicity

i. Host Mediated Assay

1,2-Propanediol was tested for mutagenic response in a host-mediated assay using male ICR mice as hosts and using Salmonella

Table 40
Number and Type of Tumors in Swiss Mice Treated with 1,2-Propanediol (Stenbäck and Shubik, 1974)

	1,2-Propanediol (in acetone)			Acetone	Untreated
	10%	50%	100%	100%	
No. animals	50	50	50	50	150
% tumor-bearing animals	52	52	40	44	42
No. tumors:					
lumphomas	15	13	9	12	26
lung adenomas	7	13	7	9	17
liver hemangiomas	1	2	4	2	4
thymomas	1	2	1	-	6
skin tumors	-	-	-	2	3
ovarian cystadeno-carcinoma	1	-	-	-	-
ovarian fibroma	1	-	-	-	2
ovarian hemangioma	1	-	-	2	2
subcutaneous fibromas	2	-	-	-	1
forestomach papilloma	1	1	-	1	2
mammary adeno-carcinomas	-	-	2	1	2
others	-	-	-	2	8

typhimurium (strains G 46 and TA 1530) and Saccharomyces cerevisiae (strain D3) as indicator organisms (Litton Bionetics, 1974). In an acute study, groups of ten mice received 30, 2,500, or 5,000 mg/kg propanediol by intubation, followed by an i.p. dose of an indicator organism. In a subacute study, mice received five daily doses of propanediol (30, 2,500, or 5,000 mg/kg) and then were inoculated with the indicator organism. The mice were killed three hours after dosing with the test organism. The induction of reverse mutation was determined with Salmonella and mitotic recombination was determined with Saccharomyces. 1,2-Propanediol caused no significant increases in mutant frequencies with Salmonella TA 1530. At the high dose only, propanediol produced a "weak or questionable positive" result with Salmonella G 46. According to Litton Bionetics (1974) results from Saccharomyces D3 were difficult to interpret. The yeast showed increased recombinant frequencies at all levels of the glycol except the acute high dose. The high dose resulted in a low recombinant frequency, which may have been due to selective killing of the mutants.

ii. Cytogenetic Assay

To assess possible chromosomal damage in somatic cells, 1,2-propanediol was tested in an in vivo cytogenetic assay (Litton Bionetics, 1974). Groups of 15 male albino rats (random-bred; 10-12 weeks old) received an acute dose of propanediol at 30, 2,500, or 5,000 mg/kg; they were killed after 6, 24, or 48 hours and bone marrow metaphase chromosomes were examined. In a subacute study

groups of five rats were given five daily doses at each of the levels before sacrifice. There were no significant aberrations of the bone marrow metaphase chromosomes in glycol-treated animals.

Human embryonic lung cultures (WI-38) were exposed to 1,2-propanediol at 0.001, 0.01, or 0.1 mcg/ml. There was no significant aberration in anaphase chromosomes (Litton Bionetics, 1974).

iii. Dominant Lethal Assay

Litton Bionetics (1974) evaluated 1,2-propanediol for mutagenicity using the dominant lethal test in 10-12 week old random bred rats. Groups of ten males were given 30, 2,500, or 5,000 mg/kg orally in an acute study (one dose) or in a subacute study (one dose per day for five days). After treatment, males were mated to two females per week for 7-8 weeks. Females were killed 14 days after exposure to males and examined for deciduomata (early deaths), late fetal deaths and total implantations. Propanediol exhibited no significant adverse effects in the dominant lethal test and was considered non-mutagenic at the dosages employed.

c. Aquatic Organisms

In rainbow trout, the lethal concentration range for 1,2-propanediol is between 50,000-100,000 mg/ℓ. At the lower range, the trout survived while at the upper range, all succumbed (Lennon, 1968 in Hann and Jensen 1974). Based on this information Hann and Jensen (1974) rate the aquatic toxicity of this glycol to be "0" (an insignificant hazard). They suggest, based on sewage decay rates, that a BOD problem could exist at sub-toxic concentrations.

The 24-hour median tolerance limit (TL_m) of 1,2-propanediol to brine shrimp (Artemia salina) is greater than 10,000 mg/ℓ; a precise value was not determined (Price et al., 1974).

Tanaka et al. (1975) tested the effect of several solvents in a brine shrimp (Artemia salina) assay. Propylene glycol at concentrations of 1-5% had no effect on viability of the brine shrimp.

d. Plants

1,2-Propanediol inhibited elongation of oat (Avena sativa) segments at concentrations of 0.5-3% in indoleacetic acid (but not in water) (Farr and Norris, 1971).

e. In Vitro Studies

Newman et al. (1940) examined the effect of 1,2-propanediol on isolated cat liver. Five livers were perfused with 500-600 mg% propylene glycol, and three with 100-200 mg%; three control livers were perfused. 1,2-Propanediol decreased the oxygen consumption and carbon dioxide production of the liver, but increased the glycogen content of the liver, and the lactic acid content of the blood; the utilization of dextrose by the liver was also depressed. The authors were unclear whether these effects showed an impaired or beneficial function of this glycol.

1,2-Propanediol depressed the amplitude and frequency of contractions of in vitro smooth muscle preparations (Bonnardeaux, 1971). Duodenal, rectal, and uterine muscles were obtained from adult female rats of unspecified strain and exposed to concentrations of the glycol

at 2.5-25 µg/ml. Amplitude and frequency of contractions were measured. The amplitude of contractions was decreased at levels greater than 2.5 µg/ml for uterine muscle and at 2.5 µg/ml or greater for duodenal and rectal muscle. The frequency of contraction was reduced to a lesser extent at higher concentrations (maximally at about 10 µg/ml). The authors suggest that propanediol may be directly affecting cellular metabolism.

2. 1,3-Propanediol

a. Humans

No studies were located on the toxic effects of 1,3-propanediol to humans.

b. Nonhuman Vertebrates

1) Metabolism

According to Van Winkle (1941), the toxicity of 1,3-propanediol is attributable to the metabolite malonic acid which forms insoluble calcium salts and is an enzyme inhibitor. However, Williams (1959) stated that its metabolic fate is not known. Gessner et al. (1960) were not able to identify any metabolites in the urine of four Chinchilla rabbits given 4 g of 1,3-propanediol orally; they found no unchanged diol or malonic acid and suggested that 1,3-propanediol is oxidized completely to carbon dioxide.

2) Acute Toxicity

a) Oral Administration

i. Lethal Doses

Fischer et al. (1949) reported an LD_{50} of 6.0 ml/kg (6.4 g/kg) for mice given oral doses of 1,3-propanediol.

Van Winkle (1941) administered 1-19 ml/kg (1.1-20.1 g/kg) of 1,3-propanediol to 132 rats of unidentified strain by gastric intubation. A dose of 18-19 ml/kg was fatal to all ten rats tested. Mortality was as follows at other doses:

Dose (ml/kg)	No. Tested	% Mortality
16	6	50
15	11	64
17	5	40
11-14	6-11	10-18
10	15	47
1-9	51	0

In three cats of unreported strain given 3 ml/kg (3.2 g/kg) of 1,3-propanediol orally, no signs were observed within 48 hours; on day three, however, the cats refused to eat and vomited after drinking water, and by day seven, all three cats had died (Van Winkle, 1941). Other cats receiving 3-15 ml/kg (3.2-15.9 g/kg) died within 16 days. Starvation was suggested as the cause of the delayed deaths.

ii. Glycogenic Action

1,3-Propanediol showed no glycogenic action in rats, in contrast to 1,2-propanediol (see section III-B-1) (Van Winkle, 1941). Forty fasted rats were given oral doses of 3, 5, 10, or 15 ml/kg (3.2-15.9 g/kg) 1,3-propanediol and killed after three hours. Liver glycogen content was comparable in treated and control animals.

Opitz (1958) confirmed that 1,3-propanediol is without a glycogenic effect. Male rats (150-250 g) were given an oral dose of 50 mmol (3.8 g/kg) of 1,3 or 1,2-propanediol. After three hours, the liver glycogen was 116 mg% in rats receiving the 1,3-propanediol but was 779 mg% in those receiving the 1,2-isomer. The liver glycogen content in untreated controls was 138 mg%.

b) Parenteral Administration

Intravenous administration of 3 ml/kg (3.2 g/kg) 1,3-propanediol was not fatal to cats. In contrast, this dose given orally was fatal to all cats tested (Van Winkle, 1941).

Van Winkle (1941) administered 3-7 ml/kg (3.2-7.4 g/kg) 1,3-propanediol by i.v. injection to 19 rabbits. Mortality was as follows:

Dose (ml/kg)	No. Rabbits	% Mortality
6-7	6	100
5	5	60
4	5	40
3	3	0

Based on these data, the 50% fatal dose would be between 4 and 5 ml/kg

(4.2-5.2 g/kg), comparable to 1,2-propanediol.

I.M. injection of 3-9 ml/kg (3.2-9.5 g/kg) 1,3-propanediol in 42 white rats resulted in the following mortality (Van Winkle, 1941):

Dose ml/kg	No. Rats	% Mortality
8-9	9	100
7	5	80
6	5	40
3-5	15	0

The 50% mortality would be between 6-7 ml/kg (6.3-7.4 g/kg) which is about twice that for 1,2-propanediol.

3) Chronic Toxicity

Van Winkle (1941) conducted a 15 week feeding study in rats of unreported strain. Groups of five rats received 0, 5, or 12% 1,3-propanediol in the diet or 5 or 10 ml/kg daily (5.3-10.6 g/kg) by stomach tube. Most rats receiving 1,3-propanediol showed reduced food intake compared to controls (10-11 g food/day compared to 15 g/day in controls) and, consequently, a reduced rate of growth. The slowest growth rate occurred in the groups given 5 or 12% in the diet. All rats receiving 10 ml/kg by stomach tube died at the end of five weeks. Based on a similar study by Van Winkle (1941), twice as much 1,2-propanediol is required to produce the same effect.

4) Reproductive Studies

Gebhardt (1968) evaluated the toxicity of several glycols to

White Leghorn chick embryos. Injection of 0.05 ml 1,3-propanediol into the air chamber resulted in 5% mortality when administered on day 0 of incubation and 95% mortality when administered on day 4. For day 0 embryos, 81% of those surviving developed micromelia and for day 4 embryos, all survivors developed micromelia. Micromelia was characterized by reduction and torsion of the lower limbs and frequently parrot beak. No saline controls developed micromelia, and mortality was 10% when administered on day 0 and 0% on day 4. When 0.05 ml 1,3-propanediol was injected on various days of incubation into the yold sac, the following mortality and malformations were noted:

Day of incubation[a]	% Mortality	% Survivors with micromelia
1	11	88
2	5	63
3	5	53
4	11	65
5	16	69
6	0	79
7	16	56
8	20	38
9	20	19

[a]19-20 embryos tested/day.

Again, no saline controls developed micromelia; mortality in controls was 10.5% on day 4.

Van Oostrom and Van Limborgh (1976) further described the effect of 0.05 ml 1,3-propanediol injected in White Leghorn chicken eggs. Seven experiments each using 31-34 embryos were designed to test the influence of the injection-site and of the egg-position on mortality and abnormalities in 1,3-propanediol or saline-treated embryos. Mortality data for these seven experiments appear in Table 41. No embryos survived treatment of 1,3-propanediol in the air chamber when eggs were incubated in a vertical position.

Gross examination of embryos surviving 1,3-propanediol treatment (experiments 6 & 7, Table 41) revealed a 60% incidence of a chondrodystrophy-like condition (micromelia): the legs and wings were shortened, the lower leg and metatarsal area were bent dorsally, and the beak often was parrot-like. Untreated or saline-treated control embryos did not show any abnormalities. Histological examination of the tibia of treated embryos revealed an underdevelopment of the periosteal bone collar, which was replaced posteriorly by endochondral bone trabeculae. The abnormalities induced by 1,3-propanediol were unlike hereditary congenital chondrodystrophy or chondrodystrophy following insulin or sulfonamide treatment. The authors concluded, therefore, that the micromelia induced by 1,3-propanediol represents a highly specific type of artificial micromelia.

Table 41
Effect of 1,3-Propanediol on Mortality of White Leghorn Chicken Embryos
(Van Oostrom and Van Limborgh, 1976)

Experiment No. and Treatment	Dose	Injection site	Position of egg during incubation	No. of eggs	Mortality (%)
1. none	--	--	vertical	31	3
2. isotonic saline	0.05 ml	air chamber	vertical	32	6
3. 1,3-propanediol	0.05 ml	air chamber	vertical	31	100
4. none	--	--	horizontal	32	6
5. isotonic saline	0.05 ml	air chamber	horizontal	33	9
6. 1,3-propanediol	0.05 ml	air chamber	horizontal	31	3
7. 1,3-propanediol	0.05 ml	yolk sac	horizontal	34	12

b) Rabbits

In rabbits continuous infusion for more than ten hours of 0.1-0.3 g/kg/hr of 1,2-butanediol resulted in a dimunition of muscle tone. Convulsions were not observed. In addition, no histological abnormalities were noted in the liver or kidney following this continuous infusion (Strack et al., 1960).

1,2-Butanediol was not irritating to the skin of rabbits when applied repeatedly nor was there evidence of absorption of toxic amounts. When applied to the eyes of rabbits, undiluted 1,2-butanediol was painful, irritating, and injurious but a 10% aqueous solution was without effect (unpublished data, Dow Chemical Co. in Rowe, 1963).

c) Dogs

In anesthetized dogs, i.v. injection of up to 1 g/kg 1,2-butanediol had no effect on blood pressure, heart rate, or respiration (unpublished data, Dow Chemical Co. in Rowe, 1963).

3) Subacute Toxicity

All female albino rats given 5-30% 1,2-butanediol in the diet for eight weeks survived (Schlüssel, 1954). At 40%, however, death occurred within 11-29 days.

c. Aquatic Organisms

No studies were found on the aquatic toxicity of 1,2-butanediol. Hann and Jensen (1974) hypothesized that the four butanediols would be "practically nontoxic" to aquatic life. They suggest,

however, that a BOD problem could exist at sub-toxic concentrations.

2. 2,3-Butanediol

a. Humans

No studies on the biological effects of 2,3-butanediol were located in the literature.

b. Nonhuman Vertebrates

1) Metabolism

According to Neuberg and Gottschalk (1925), 2,3-butanediol is excreted partly with glucuronic acid in the urine of rabbits. Gessner et al. (1960) identified a glucuronide of 2,3-butanediol in the urine of four Chinchilla rabbits after oral dosing (2 g). Neither diacetyl nor acetoin was detected in the expired air or the urine of rabbits given 1.2-1.5 g 2,3-butanediol.

2) Acute Toxicity

The acute oral lethal dose value (LD_{50}) of 2,3-butanediol averaged 8.9 g/kg in mice of unreported strain (Fischer et al., 1949).

Based on the following evidence 2,3-butanediol does not appear to produce narcotic effects. Marcus et al. (1976) administered 6.7 mmol/kg (0.6 g/kg), i.v. and 16 mmol/kg (1.4 g/kg), i.p. to Sprague-Dawley rats; no changes in EEG tracings or a loss of righting reflex were noted. Similarly, Menon et al. (1973) found no central nervous effects, akensia or rigidity in albino mice given i.p. injections of 500 mg/kg 2,3-butanediol.

or urea resulted in a less negative nitrogen balance, 1,3-butanediol plus urea had an additive effect. In subjects receiving 1,3-butanediol alone, blood glucose levels were significantly lower. Taken together, these data indicate that 1,3-butanediol provided calories that substituted for calories which would otherwise have been obtained from protein sources in the diet. 1,3-Butanediol did not result in any change in serum proteins, white blood count, hematocrit, hemoglobin, transaminase enzymes, ketoacids, electrolytes, cations, cholesterol, triglycerides, or fatty acids.

To study possible effects of 1,3-butanediol on endocrine function and glucose homeostasis, Tobin et al. (1975) gave 27 adult women a diet containing 40 g butanediol or 40 g sucrose for ten days. The experimental procedure is described in Table 42. Levels of various serum parameters were determined (Table 42). There were no significant differences in blood glucose, cholesterol or triglycerides between women fed sucrose of butanediol. Levels of serum insulin and growth hormone were slightly elevated in subjects receiving 1,3-butanediol, but the differences were not significant. No evidence of toxic reactions to 1,3-butanediol were detected.

Tobin et al. (1975) then examined the effects of 1,3-butanediol during glucose loading. Ten adult male and female volunteers ingested diets containing sucrose or 1,3-butanediol, accounting for 10% of the total caloric intake for five days; from days 6-10, the diets were reversed. Glucose tolerance tests were performed on days 6 and 12, following a 10-14 hour fast. In both groups, there was a normal rise and fall of blood glucose during the four-hour test. Serum insulin,

Table 42
Various Parameters Measured in the Blood of Volunteers Fed 1,3-Butanediol[a] (Tobin et al., 1975)

	Diet Adjustment Period[b]	Diet Plus 40 g Sucrose[c]	Diet Plus 40 g Butanediol[c]
cholesterol (mg/100 ml)	194 ± 7[d]	161 ± 7	167 ± 8
triglycerides (mg/100 ml)	87.7 ± 8	115 ± 13	107 ± 8
glucose (mg/100 ml)	80.3 ± 1.0	77.4 ± 0.8	77.6 ± 1.1
insulin (μU/ml)	15.8 ± 1.1	14.5 ± 0.9	15.2 ± 1.0
HGH (μg/ml)[e]	7.54 ± 1.91	2.03 ± 0.58	2.84 ± 0.76

[a]Total of 27 volunteers.

[b]Five-day adjustment period to a diet with wheat protein as a nitrogen source.

[c]After five-day adjustment period, half of volunteers were fed a sucrose diet and half fed a 1,3-butanediol diet for five days; five days later, the diets were reversed.

[d]Mean ± standard error of the mean.

[e]HGH: human growth hormone.

lactate, pyruvate, free fatty acids, triglycerides, β-hydroxybutyrate, acetoacetate, and growth hormone were not significantly different between the 1,3-butanediol and sucrose groups during the course of the glucose tolerance test. The authors concluded that the mechanism of 1,3-butanediol-related lowered blood glucose in humans and rats

(refer to section C-3-b) is not explained by differences in the circulating levels of insulin or growth hormone.

2) Dermal Toxicity

Fischer et al. (1949) reported no irritation to the skin of the arm of human subjects after repeated application of 5 g 1,3-butanediol over 16 days.

Schwartz (1962; unpublished data in Dymsza, 1968) patch tested 200 subjects with 1,3-butanediol. Patches remained on for 72 hours; tests were repeated 14 days later on the same area. There were a total of eight adverse reactions to the compound among the 200 subjects.

Shelanski (1974) evaluated the dermal effects of 1,3-butanediol in 200 human volunteers using a repeated insult patch test. A pad was moistened with a 50% solution in water (about 0.9 ml) then applied to the upper arm; the pad remained in place for a 24 hour period. This procedure was repeated 15 times over several weeks on each volunteer. No adverse reactions occurred in any person after the first three applications. After four or more applications, only 2 individuals showed visible skin injury, which was described as mild. Thus, the author was unable to sensitize most volunteers to 1,3-butanediol.

b. Nonhuman Vertebrates

1) Metabolism

In 1960, Gessner et al. suggested that 1,3-butanediol was metabolized through β-hydroxybutyric acid, although they were not able to

detect metabolites in Chinchilla rabbit urine after oral dosing. Miller and Dymsza (1967) disagreed with Gessner et al.; they found no change in serum and urine ketone bodies in rats fed 20 or 30% 1,3-butanediol in the diet for 30 weeks and because of this, concluded that 1,3-butanediol is not metabolized via β-hydroxybutyrate. However, evidence from other investigators, notably Mehlman and his colleagues, strongly suggests that in rats, 1,3-butanediol is metabolized via β-hydroxybutyrate. Rosmos et al. (1975) confirmed this metabolic pathway for 1,3-butanediol fed to pigs and chickens. Evidence for this pathway includes: i) formation of blood ketone bodies in vivo; ii) formation of urine ketone bodies in vivo; iii) formation of ketone bodies by liver slices after prefeeding animals with 1,3-butanediol; and iv) metabolism of 1,3-butanediol added to rat liver extract. This evidence, reviewed in Mehlman et al. (1975) is considered in the subsections which follow for studies in rats.

i) Formation of Blood Ketone Bodies

Mehlman et al. (1971a) measured the levels of blood acetoacetate, p-hydroxybutyrate, lactate, and pyruvate in male Sprague-Dawley rats (240-260 g) fed a diet containing 25% 1,3-butanediol and 30% fat for three and seven weeks; controls received a 30% fat diet but no 1,3-butanediol. As shown in Table 43, there were high significant increases in acetoacetate and β-hydroxybutyrate concentrations. Also, total blood ketone bodies increased about threefold, which would indicate either an increased metabolism of fatty acids or conversion of 1,3-butanediol to ketone bodies. Blood lactate levels were increased significantly at seven weeks.

Table 43
Blood Levels of Acetoacetate, β-Hydroxybutyrate, Pyruvate, Lactate, and Total Ketones in Rats Fed 1,3-Butanediol[a] (Mehlman et al., 1971a)

μmoles/ml	Butanediol Diet[b]		Control Diet[b]	
	3 wk	7 wk	3 wk	7 wk
acetoacetate	0.19**	0.12**	0.07	0.05
β-hydroxybutyrate	0.42*	0.45**	0.16	0.18
pyruvate	0.17	0.12*	0.22	0.23
lactate	3.8	5.9	2.4	6.0
total ketones	0.58*	0.63**	0.18	0.22

[a]Male Sprague-Dawley rats fed diet of 25% 1,3-butanediol for three and seven weeks.

[b]Values are estimated from figures in original text; each value, data from six rats.

*$p < 0.05$ compared to corresponding control.

**$p < 0.001$ compared to corresponding control.

Mehlman et al. (1971a) also calculated the ratios of the parameters listed in Table 43. The ratio of β-hydroxybutyrate to acetate (an indicator of the oxidation-reduction potential of liver mitochondria) was significantly increased in rats fed 1,3-butanediol for seven weeks. This increase reflects an increase in the NADH/NAD+ ratio in mitochondria.

The ratio of blood lactate to pyruvate was increased in rats fed 1,3-butanediol, showing that the cystolic NADH/NAD+ ratio was increased. The increase in both ratios indicate that the metabolism takes place in both cytosol and mitochondria.

ii) Formation of Urine Ketone Bodies

Tobin, Mehlman, and Parker (1972) measured the urine ketone body concentration in Sprague Dawley rats fed a diet containing 20% 1,3-butanediol and 30% fat for 34 hours. The total amount of ketone bodies excreted by treated rats was almost ten times that of control rats fed a 30% fat diet. 1,3-Butanediol feeding induced a large increase in β-hydroxybutyrate concentration (2.57 μmoles/ml in treated vs. 0.132 in control), a slight increase in acetoacetate concentration (0.067 μmoles/ml in treated vs. 0.044 in controls) and an increase in the β-hydroxybutyrate to acetoacetate ratio.

iii) Formation of Ketone Bodies by Liver Slices in Animals Prefed Butanediol

Mehlman et al. (1971a) investigated the formation of ketone bodies by rat liver tissue from rats who were fed a diet containing 30% fat, with or without 25% 1,3-butanediol for three and seven weeks. Liver slices from both treatment groups were exposed *in vitro* to glucose, 1,3-butanediol or both glucose and butanediol. Liver slices from both controls or rats prefed 1,3-butanediol converted 1,3-butanediol to ketone bodies. When 1,3-butanediol was the substrate, no metabolites other than ketone bodies were detected. In rats prefed with 1,3-butanediol, the rate of metabolism of glucose to lactate and pyruvate was decreased;

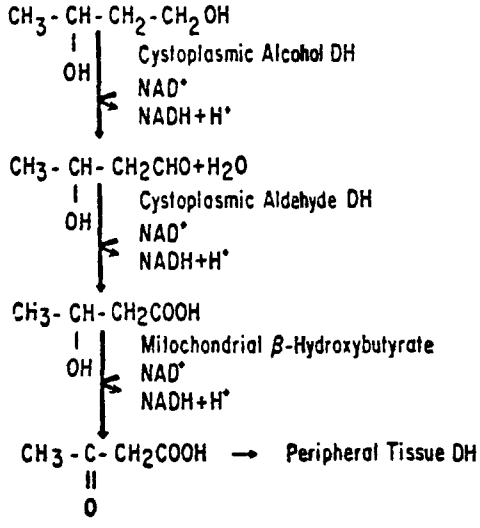
also, the level of β-hydroxybutyrate and β-hydroxybutyrate/acetoacetate ratio was decreased.

iv) Metabolism of Butanediol Added to Rat Liver Extract

When 1,3-butanediol was added in vitro to rat liver perfusate, the tissue lactate: pyruvate ratio was increased when lactate was used as substrate, an indication of increased cytosolic NADH/NAD ratio (Mehlman et al., 1971b). According to Mehlman et al.(1975) this suggests that the cytosol is the site of one or more cofactor-dependent oxidations of 1,3-butanediol.

Further studies by Tate, Mehlman, and Tobin (1971) strongly suggest that liver alcohol dehydrogenase is the major (or only) enzyme responsible for the initial oxidation of 1,3-butanediol to β-hydroxybutyrate. Briefly, rat liver extracts in vitro showed an NAD+-dependent oxidation of both 1,3-butanediol and ethanol similar to that shown by horse liver alcohol dehydrogenase. Furthermore, known liver alcohol dehydrogenase inhibitors (pyrazole and n-butyraldoxime) resulted in a decrease in β-hydroxybutyrate and, therefore, total ketone body levels. The authors suggested that the initial step in the ADH-catalyzed oxidation of 1,3-butanediol is the formation of 3-hydroxybutanal (aldol) which is then further oxidized to β-hydroxybutyrate.

Based on a review of the foregoing literature and other papers, Mehlman, Tobin, and Mackerer (1975) suggested the following metabolic pathway for the oxidation of 1,3-butanediol:



2) Acute Toxicity

a) Lethal Dose Values

As shown in Table 44, the oral LD_{50} value for 1,3-butanediol averages 23.4 g/kg in mice, 22.8-29.6 g/kg in rats, and 11.5 g/kg in guinea pigs. By injection, the LD_{50} is 16.6 g/kg, s.c. in mice and 20.2 g/kg, s.c., in rats. Inhalation of 1,3-butanediol "vapors" (exposure, however, must have been to the aerosol) for eight hours did not result in mortality to Wistar rats (Smyth et al., 1951).

b) Signs

1,3-Butanediol had a low acute toxicity to adult rats in a series of studies by Bornmann (1954a, b, and 1955). A definite diuretic effect in males was noted, however (Bornmann, 1954b). The amount of urine in eight rats given an oral dose of 10.0 ml/kg (10.1 g/kg) 1,3-butanediol averaged 22-39 ml after 24 hours while in control rats

Table 44
Lethal Dose Values for 1,3-Butanediol

Species/Strain	Sex/No.	Route	LD_{50}		Reference
			Reported value	Converted value (g/kg)	
mouse/NR	NR	oral[a]	23.31 cm^3/kg	23.4	Fischer et al., 1949
mouse/NR	NR	s.c.[a]	16.51 cm^3/kg	16.6	Fischer et al., 1949
rat/NR	NR	oral[a]	29.42 cm^3/kg	29.6	Fischer et al., 1949
rat/Wistar	M/5 per group	oral[b]	22.8 g/kg	22.8	Smyth et al., 1951
rat/Wistar	M/10 per group	oral[b,c]	18.61 g/kg	18.61	Smyth et al., 1941
rat/NR	NR	s.c.[a]	20.06 cm^3/kg	20.2	Fischer et al., 1949
guinea pig/NR	NR	oral[b,d]	11.46 g/kg	11.46	Smyth et al., 1941

[a]24 hours observation period.

[b]14 days observation period.

[c]Standard deviation of LD_{50} = 21.8-23.9 g/kg.

[c]95% C.L. = 17.43-19.88 g/kg.

[d]95% C.L. = 10.29-12.77 g/kg.

given 0.9% sodium chloride the amount of urine was 8-10 ml. No adverse effects were noted in the organs of treated animals 24 hours after dosing.

1,3-Butanediol is capable of causing intoxication in male Sprague Dawley rats at acute oral doses higher than 4 g/kg (Majchrowicz et al., 1976). At 6 g/kg ataxia was observed, at 8 g/kg, loss of righting reflex occurred, and at 10 g/kg, coma was induced. No signs of intoxication were observed at 4 g/kg; this dose actually ameliorated withdrawal signs in mice physically dependent on ethanol.

At large acute doses, 1,3-butanediol acts as a muscle relaxant (Sprince et al., 1966). In Sprague Dawley or Holtzmann rats, a dose of 500 mg 1,3-butanediol/kg i.p. (which dose of 1,4-butanediol resulted in anesthesia) produced no anesthetic or behavioral effects. At 7,000 mg/kg, anesthesia was induced. The response was different from that occurring with an anesthetic dose of 1,4-butanediol. There was extreme flaccidity and loss of limb and body tone; myoclonic jerking was not observed. Recovery from anesthesia was slower than than observed after 1,4-butanediol administration. In the EEG tracing, there were no periods of spiking, polyphasic bursting, or electrical silence.

Infusion of 6 ml/kg (6.03 g/kg) 1,3-butanediol i.v. into dogs resulted in central nervous system depression, measured by electroencephalography (Stoewsand and Dymsza, 1967).

Application of 0.01 ml undiluted 1,3-butanediol to the clipped belly of an albino rabbit resulted in slight necrosis within 24 hours (Smyth et al., 1951). Fischer et al. (1949) reported no irritation

after dermal application of 1,3-butanediol to guinea pigs or rats.

One half ml of a 1% solution of 1,3-butanediol applied to the eye of rabbits caused no reaction within 24 hours (Smyth et al., 1951).

c) Gluconeogenesis and Lipogenesis

The effect of 1,3-butanediol on blood glucose levels depends on the length of treatment. In acute experiments, injection of 800 mg (Romsos et al., 1974) or feeding 7.5 g/kg 1,3-butanediol (Parker, 1972) resulted in elevated blood glucose levels in Sprague Dawley rats. However, in chronic studies, blood glucose levels were depressed. Mackerer et al. (1975) correlated decreased blood glucose levels with increased pancreatic insulin content in Charles River rats given up to 27% butanediol for 30-31 days. In another study, lowered blood glucose levels in Sprague Dawley rats given 18% 1,3-butanediol for 14 days were attributed to a block of gluconeogenesis in the kidney at the conversion of 3-phosphoglycerate to glyceraldehyde-3-phosphate (Mehlman et al., 1970).

Mehlman et al. (1970) also investigated an enzyme involved in gluconeogenesis (phosphoenolpyruvate carboxykinase, PEPcK) and an enzyme involved in lipogenesis (malic enzyme). In treated animals, hepatic PEPcK activity increased 43%. Malic enzyme activity was the same in liver and epididymal fat in treated and control rats indicating that 1,3-butanediol did not affect lipogenesis. Mitochondrial synthesis of glucose from pyruvate and bicarbonate by hepatic pyruvate carboxylase was increased in treated rats. However, other liver and kidney metabolites were unchanged.

Mehlman et al. (1970) also reported a decrease in the weight

of epididymal fat pads (as a measure of epididymal lipid content) in treated rats. This had been reported on earlier by Mehlman et al. (1966) who related higher free fatty acid levels in the plasma to a mobilization of lipid from epididymal and adipose tissue. Parker (1972) suggested that the mobilization of fat would result in increased blood levels of ketone bodies.

Romsos et al. (1974) reported a depressed level of fatty acid synthesis in Sprague Dawley rats given 18 or 36% 1,3-butanediol in the diet for 23 days.

Romsos et al. (1974) suggested that a shift in cytoplasmic redox state and an increase in hepatic long-chain acyl CoA levels are involved in the decrease in hepatic fatty acid synthesis after feeding 1,3-butanediol. They postulate that the conversion of 1,3-butanediol to β-hydroxybutyrate in the liver shifts the cytoplasmic redox potential toward a more reduced state, thus reducing the rate of glycolysis and substrate availability for fatty acid synthesis. The shift in redox potential would spare fatty acid oxidation, causing long-chain acyl CoA levels to increase. The latter are inhibitory to hepatic fatty acid synthesis. Thus, the overall effect is a decrease in the rate of hepatic fatty acid synthesis.

d) Behavioral Effects

1,3-Butanediol affects voluntary activity in Sprague-Dawley rats (Isgrig and Ayres, 1968). A hunger-activity cycle was imposed prior to and during testing, in which rats had free access to food for only three hours a day. Rats were given 11.43 ml/kg (11.49 g/kg) by gavage

in replicate experiments. Voluntary activity in a wheel was recorded over the next three hours. In treated rats, activity was significantly depressed during hours 2-3 compared to controls receiving an isocaloric, isovolumetric dose of sucrose. Similar results were obtained for 1,2-propanediol (section III-B-1). Effects on equilibrium were measured in another experiment using rats previously trained to balance on a rotating bar. A dose of 11.43 ml/kg significantly disturbed equilibrium compared to propanediol or sucrose treated rats; however, the difference was small. These findings were confirmed in replicate experiments by Isgrig and Ayres (1968). They suggested that 1,3-butanediol acts as a CNS depressant or strong muscle relaxant.

3) Subacute Toxicity

a) Rats

Bornmann (1954b) added 1, 2, 5, 10, or 20% 1,3-butanediol in the drinking water of male rats for 13.5 weeks. The weight of the kidney of rats receiving the two highest doses (0.216 g/100 g body weight [bw] at 10%; 0.330 g/100 g bw at 20%) was greater than in controls (0.188 g/100 g bw); no statistical analysis was performed.

The incorporation of 1,3-butanediol into the diet often results in a decrease in body weight gain and food consumption. Typical findings were reported by Mehlman et al. (1970) for Sprague Dawley rats fed a ration containing 18% 1,3-butanediol for two weeks; the decreased body weight gain after two weeks in treated rats was attributed to a decrease in food consumption. Fischer et al. (1949), however, found no effect on weight gain in rats given orally 10 ml/kg bw from 1-20% solutions of 1,3-butanediol for 44 days.

Feeding 1,3-butanediol also results in a decrease in the weight of epididymal adipose tissue in rats (Mehlman et al., 1971). Stoewsand et al. (1966) reported this effect when it was added to the diet at 20% for four weeks, and related this decrease to the reduced resistance of rats to severe cold stress (−20°C).

In a series of subacute feeding experiments, Miller and Dymsza (1967) evaluated the ability of rats to use 1,3-butanediol as a synthetic source of energy. Rats were fed high fat diets (25%) in which carbohydrate was replaced by 1,3-butanediol. In all experiments, a one week period of adaptation was required for maximum utilization of 1,3-butanediol. After one week, butanediol had a caloric value of about 6 kcal/g. In an ad libitum study (experiment 1), rats fed 20% 1,3-butanediol for four weeks gained significantly less weight than those with 5 or 10% 1,3-butanediol in their ration; rats fed 10 or 20% 1,3-butanediol consumed less food than animals on the other diets. In all groups receiving 1,3-butanediol (5, 10, and 20%), a high level of food, protein, and caloric efficiency was maintained. In a paired feeding experiment (experiment 2), total food consumption and body weight gain were reduced in all animals receiving 20% butanediol for three weeks. However, compared to animals receiving no 1,3-butanediol, animals pair fed diets containing 5 or 20% 1,3-butanediol had "essentially similar" body weight gains and food and protein efficiencies; in the paired feeding, the amount of the diet fed was controlled by the group with the lowest food intake. In rats force fed 20% 1,3-butanediol, weight gains were comparable to controls after a one week adaptation period.

b) Cattle

Bonner et al. (1974) suggested that small amounts of 1,3-butanediol can be used as an energy source in cattle rations. Feeding a diet containing 4% butanediol to Holstein cows for up to six weeks was without effect on rumen pH, volatile fatty acid ratios, blood glucose, blood ketones, body weight, or feed efficiency. At 6-8%, however, blood ketones were elevated, the animals were hyperactive, gained less weight and had a lower feed efficiency.

Young (1975) reported on studies in which 4% 1,3-butanediol was fed to lactating fat-depressed Holsteins; treated cows had a greater milk fat production than controls.

c) Chickens

In broiler chickens receiving 5% 1,3-butanediol in feed for four weeks, no effect on weight gain was noted compared to controls (Davenport and Griffith, 1969). However, weight gain was reduced when levels exceeded 5% (10, 15, and 21% tested). Feed conversions were poorer when 10% or more was introduced in the diet. The authors suggested feed consumption to have been the major factor in reduced weight gain.

Davenport and Griffith (1969) found that at dietary levels less than 5%, 1,3-butanediol can be substituted for part of the fat in broiler ration. No adverse effects were detected in weight or feed conversion.

4) Chronic Toxicity

a) Rats

Kopf et al. (1950) administered to male and female rats (85-216 g) an oral dose of 10 ml/kg (10.6 mg/kg) of a 50% solution of 1,3-butanediol every 3-4 days for 45 to 185 days. No adverse effects on growth were noted. Monthly blood counts revealed no differences in control or treated rats. After 185 days, rats were sacrificed and examined; no abnormalities in endocrine organs, kidney, bladder, or liver were found.

Bornmann (1954a and b; 1955) administered 1-20% 1,3-butanediol in the drinking water of rats twice a week for 96 days; no toxic effects were observed except for diuresis.

Miller and Dymsza (1967) incorporated 20 or 30% 1,3-butanediol in the diets of rats for 30 weeks to replace carbohydrates. The levels of protein, fat, and carbohydrates were varied. Treated rats received one of the following diets:

Protein %	Fat %	Butanediol %	Carbohydrate %
18	30	20	22
36	30	20	0
18	30	30	12
36	30	30	0

Ten other diet schedules consisted of no 1,3-butanediol, but varying combinations of protein, fat, and carbohydrate.

At 30% butanediol, but not at 20%, there was a significant impairment in utilization of butanediol; for example, weight gains were lower and food and calorie efficiencies were reduced.

After 30 weeks, urine, blood, and liver were assayed in tests which included: urine and serum ketone bodies, liver glycogen, and phosphohexose isomerase, and serum glucose. When the level of fat was increased in a diet not containing butanediol, serum and urinary ketone bodies and also the liver glycogen content were increased. When 1,3-butanediol was added to the diet, these changes did not occur. Liver, phosphohexose isomerase (PHI) activity and the serum glucose level generally decreased with increasing fat in the diet, but when butanediol was added, PHI activity decreased, and no change occurred in serum glucose.

In a 476-day feeding study, 20 rats were given 20% 1,3-butanediol in a 22% casein and 30% fat semi-synthetic diet; 20 controls received the same diet without the diol. Lower body weights were noted in treated rats. Survival to 476 days was 65% in treated and 100% in control rats. Upon histologic examination, no lesions were detected which could be attributed to treatment (Dymsza and Stoewsand, 1965 in Dymsza, 1968).

In a two-year feeding study, groups of 30 male and 30 female weanling Sprague-Dawley rats received diets containing 1.0, 3.0, or 10% (by weight) 1,3-butanediol (Scala and Paynter, 1967). No differences were recorded in any parameter in treated animals compared to controls. Parameters examined included body weight gain, food consumption, survival hematology (erythrocyte and leucocyte counts,

hematocrit, hemoglobin) and urinalysis (specific gravity, pH, protein, sugar, acetone, urobilinogen, bilirubin, occult blood, and sediment). Also, organs were weighed and examined histologically in animals sacrificed after one or two years. Experimental findings were not attributed to 1,3-butanediol ingestion. Findings, which included chronic inflammatory disease of the lungs, spleen, and kidneys and spontaneous neoplasms, occurred in control and experimental rats and were consistent with changes common for rats of this strain and age.

b) Dogs

Kopf et al. (1950) orally administered 2.0 ml/kg (2.01 g/kg) of an aqueous 50% solution of 1,3-butanediol to two dogs twice a week for 5-6 months. Histological examination revealed no adverse effects on the liver, kidney, bladder, or small intestine in the treated dogs compared to two control dogs.

In a chronic feeding study, three adult male beagle dogs were given a diet containing 20% 1,3-butanediol and 30% fat and three controls received a basal diet containing 30% fat (Stoewsand and Dymsza, 1967; Dymsza and Stoewsand, 1966 in Dymsza, 1968). Endurance capacity on treadmills was measured four times over five weeks and was comparable in control and treated dogs. Plasma free fatty acids were significantly lower in treated dogs during weeks three and five. When the level of 1,3-butanediol in the feed was raised from 20 to 30% for a short time, incoordination was observed 1-4 hours later. After 343 days on the test, the dogs were sacrificed. No gross or histologic changes of significance were found in any treated dogs, except for one case of heart worm.

Groups of four male and four female beagle dogs each received 0, 0.5, 1.0, or 3.0% 1,3-butanediol (dry weight basis) in the basal diet for two years (Scala and Paynter, 1967). No toxic effects were observed at any treatment level. Daily or weekly measurements were made of weight, food consumption, and signs. At eight intervals, samples of blood were taken for determinations of erythrocyte and leukocyte counts, sedimentation rate, hematocrit, hemoglobin, blood urea nitrogen, and bromosulphalein retention. Urine was analyzed for specific gravity, pH, protein, sugar, acetone, urobilinogen, bilirubin, and occult blood. Autopsies and histological examinations were performed on animals sacrificed at 12 or 24 months. Both control and test animals showed chronic nephritis.

5) Special Studies

a) Reproduction

i. Rats

In a meeting abstract Dymsza and Adams (1969) reported on reproductive studies in parents and two generations of rats given diets containing 20% 1,3-butanediol. Fertility, litter size, and number of pups born alive were not affected by dietary treatment. The

three-generation litter survival to three weeks was 77% compared to 51% in controls. Body weight gain on 1,3-butanediol was slower than that of controls; adult weights decreased with each generation.

The Food and Drug Research Laboratories, Inc. (FDRL, 1973b) carried out a series of reproductive and genetic studies on 1,3-butanediol. In a four-generation feeding study, groups of 25 male and 25 female Wistar rats received 1,3-butanediol in a semi-purified diet to provide 50, 25, 12.5, or 0% of the calories based on the metabolizable energy value for the diol of 6.0 calories per gram; 1,3-butanediol accounted for 24, 10, 5, and 0% of these diets, respectively. The butanediol partially replaced the starch-dextrose component of the diet. The parent generation (F_0) rats were mated after four weeks on the 1,3-butanediol diet and then continued on this diet; rats were subjected to two successive mating cycles. Reproductive performance for the two litters is summarized in Tables 45 and 46; there was a decrease, particularly in the second litter, in the fertility index of 1,3-butanediol-treated rats. Longevity studies were conducted on rats in the first litter (F_1); weight gain was decreased in animals receiving 1,3-butanediol. Hematologic, biochemical, and urinary tests were within the normal range in treated rats. F_1 females were subjected to five successive mating cycles; in treated females, fertility decreased progressively with each cycle. Survival of F_1 rats to 77 weeks was somewhat lower in treated rats, but this difference was not significant (survival: control, 66%; 5% diol, 54%; 10% diol, 54%; 24% diol, 52%). No gross pathological changes noted at autopsy were attributed to treatment.

Table 45
Summary of Reproduction and Lactation Responses in Reproductive Study in Rats: Data on F_0 Generation, $Litter_1$ Fed 1,3-Butanediol (FDRL, 1973b)

1,3-Butanediol Level	Percent			
	0	5	10	24
number of matings:	25	25	25	25
number of dams surviving:	25	25	25	25
number of pregnancies:	23	21	19	20
number of litters:				
cast alive	23	21	19	20
alive at four days	22	20	19	16
alive at 21 days	22	20	19	16
number of pups:				
cast alive	229	219	196	185
cast dead	18	6	6	6
number of pups:				
alive at four days	225	198	188	155
culled to at four days	164	149	126	117
alive at 21 days	160	147	121	112
number of pups per litter:				
cast alive	10.0	10.1	10.3	9.3
alive at four days	10.2	9.7	9.9	9.7
culled to at four days	7.5	7.5	6.6	7.3
alive at 21 days	7.3	7.4	6.4	7.0

Table 45 (Continued)

1,3-Butanediol Level	Percent			
	0	5	10	24
mean body weight per pup, g				
at four days:	9.9	10.0	10.0	10.2
at 21 days:	85.0	83.0	87.0	74.0
indexes*				
fertility	92	84	76	80
gestation	100	100	100	100
viability	98	91	96	84
lactation	98	99	96	96

*Fertility = percent of matings resulting in pregnancies.

Gestation = percent of pregnancies resulting in litters cast alive.

Viability = percent of pups cast alive that survived at four days.

Lactation = percent of pups alive at four days that survived to weaning at 21 days.

F_2 females were mated twice; no decrease in the fertility index was noted. Pups of the second litter were subjected to teratologic studies. 1,3-Butanediol had no effect on maternal or fetal survival, on rate of nidation and/or resorption, or on fetal soft or skeletal abnormalities. Offspring from the first litter of the F_2 generation

Table 46
Summary of Reproduction and Lactation Responses in Reproductive Study in Rats: Data on F_0 Generation, $Litter_2$ Fed 1,3-Butanediol (FDRL, 1973b)

1,3-Butanediol Level	Percent			
	0	5	10	24
number of matings:	25	25	25	25
number of dams surviving:	25	25	25	25
number of pregnancies:	20	17	13	16
number of litters:				
cast alive	20	17	13	16
alive at 4 days	19	15	12	15
alive at 21 days	19	15	12	13
number of pups:				
cast alive	175	149	125	130
cast dead	10	14	6	5
number of pups:				
alive at 4 days	164	127	119	114
culled to at 4 days	131	98	91	87
alive at 21 days	131	93	87	79
number of pups per litter:				
cast alive	8.75	8.76	9.61	8.13
alive at 4 days	8.63	8.47	9.92	7.60
culled to at 4 days	6.89	6.53	7.58	5.80
alive at 21 days	6.89	6.20	7.25	6.08

Table 46 (Continued)

1,3-Butanediol Level	Percent			
	0	5	10	24
mean body weight per pup, g				
at 4 days:	10.7	10.9	9.75	10.4
at 21 days:	63.2	57.4	55.6	53.4
indexes*				
fertility	80.0	68.0	52.0	64.0
gestation	100.0	100.0	100.0	100.0
viability	93.7	85.2	95.2	87.7
lactation	94.7	94.9	95.6	90.8

*Fertility = percent of matings resulting in pregnancies.

Gestation = percent of pregnancies resulting in litters cast alive.

Viability = percent of pups cast alive that survived at 4 days.

Lactation = percent of pups alive at 4 days that survived to weaning at 21 days.

were reared and later mated two times. No treatment related effects on reproduction or clinical tests were detected.

ii. Dogs

Female beagles received 20% 1,3-butanediol in the feed for at

least 60 days (dose about 30-50 g/kg/day) then mated and continued on the treated diet through parturition (FDRL, 1973b). Five-day-old pups were examined for soft and skeletal abnormalities; no differences were found compared to control pups. Treatment was without effect on maternal health or reproduction.

iii. Rabbits

On days 6-18 of gestation, Dutch-belted does received oral doses of 1.3, 2.7, or 5.4 g/kg of 1,3-butanediol in the drinking water (FDRL, 1973b). On day 29 of gestation, the uterine contents were examined for evidence of abnormal fetal development compared to controls, no significant adverse effects were found among treated rabbits.

iv. Chickens

Injection of 0.05 ml 1,3-butanediol into the yolk sac of White Leghorn chick embryos resulted in 12% mortality in 0 day-old embryos (0% in controls) and 89% mortality in 4 day-old embryos (10% in controls) (Gebhardt, 1968). No surviving 0 day-old embryos developed any malformations, while 10% of the 4 day-old embryos developed asymmetric micromelia (reduction and torsion of lower limbs; also, parrot beak). When 0.05 ml was injected into the yolk sac of 4 day-old embryos, mortality was 22.1% (10.5% mortality in controls); no malformations were detected.

Partial immersion of five-day incubated Light Sussex chicken eggs for ten seconds in 1,3-butanediol resulted in 40% mortality and no abnormalities; for water controls, a 50% mortality was recorded (Clegg, 1964).

b) Mutagenicity

i. Dominant Lethal Test

Male Wistar rats, receiving 0, 5, 10, or 24% 1,3-butanediol in the diet for about 80 days, were mated with virgin untreated females over an eight week period; parents of these males had received the same level of the diol (FDRL, 1973b). An average mutagenic index (resorptions/implant sites) was calculated for the mated females:

%	mutagenic index
0	5.49
5	6.05
10	4.34
24	3.13

ii. Cytogenetic Studies

Bone marrow samples were taken from weanling Wistar rats whose parents had received 0, 5, 10, or 24% 1,3-butanediol in the diet (FDRL, 1973b). Metaphase cells were examined. The occurrence of abnormal cells was not higher among treated than control rats (0.7-3.6% of cells abnormal in all groups).

c. Aquatic Organisms

No data were located on the aquatic toxicity of 1,3-butanediol. Hann and Jensen (1974) suggested that the aquatic toxicity of this compound might be rated as a "1," "practically nontoxic." They suggest a BOD problem could exist at sub-toxic concentrations.

4. 1,4-Butanediol

a. Humans

Reports of adverse effects of 1,4-butanediol to humans are not available.

b. Nonhuman Vertebrates

1) Metabolism

1,4-Butanediol appears to be metabolized via succinic acid. Four Chinchilla rabbits (2-3 kg) were given a total oral dose of 9 g 1,4-butanediol. Seven percent of the dose was recovered in the urine as succinic acid. No unchanged diol was identified in the urine (Gessner et al., 1960).

The central nervous system depression induced by 1,4-butanediol, discussed in section b-2) is mediated through a metabolite, gamma-hydroxybutyrate. Roth and Giarman (1968) identified this metabolite in blood and brain tissue of rats 1.5 hours after intravenous injection of 5.8 meq/kg.

Maxwell and Roth (1972) showed that brain, liver, kidney, and heart can convert 1,4-butanediol to gamma-hydroxybutyrate. Tissue slices or minces from male Sprague-Dawley rats were incubated for 30 minutes in a medium containing 0.94 μc of radio-labeled 1,4-butanediol. In other experiments, 5.8 meq of 1,4-butanediol was injected intracisternally or intravenously. In all experiments, levels of gamma-hydroxybutyrate were higher in the liver than the brain, kidney, or heart. That the liver is the primary site for conversion to gamma-hydroxybutyrate was confirmed in an experiment on partially hepatectomized rats; these rats showed a reduced rate of formation of the metabolite and also a resistance to 1,4-butanediol-induced anesthesia.

In mice, as in rats, 1,4-butanediol is probably converted to

gamma-hydroxybutyric acid. Menon et al. (1973) compared the effects of equimolar doses (ip) of these two compounds in male Swiss mice. Both compounds caused marked akinesia and rigidity, marked hypothermia and similar changes in brain monoamine levels (Section 2-b). Menon et al. (1973) suggested that quantitative differences between the compounds might possibly be due to differences in rate of transport.

2) Acute Toxicity

a) Lethal Dose Values

1,4-Butanediol is the most acutely toxic of the butanediol isomers.

The acute median oral LD_{50} value for 1,4-butanediol is 2.1-2.2 g/kg in mice, 1.5-1.78 g/kg in rats, 1.2 g/kg in guinea pigs, and 2.5 g/kg in rabbits. By i.p. injection, the median LD_{50} is 1.3-1.4 g/kg in rats (Table 47).

b) Signs

Signs of toxicity elicited by 1,4-butanediol are different from those of the other isomers. For example, while acute doses of 1,3- or 2,3-butanediol (0.6 g/kg i.v. and 1.4 g/kg i.p.) did not cause changes in EEG tracings or a loss of righting reflex in Sprague-Dawley rats, 1,4-butanediol (0.3 g/kg i.v. and 0.4 g/kg i.p.) resulted in high amplitude slow wave EEG tracings within five minutes of administration and a loss of the righting reflex within 20 minutes, at which time the EEG showed spiking and periods of electrical silence (Marcus et al., 1976). According to Marcus et al. (1976) 1,3- and 2,3-butanediols may fail to produce a central nervous system effect because they are too hydrophilic to easily pass the blood-brain barrier.

Menon et al. (1973) also found no central nervous system effects

Table 47
Lethal Dose Values for 1,4-Butanediol

Species/Strain	Sex/No.	Route	LD_{50}		Reference
			Reported value	converted value (g/kg)	
mouse/NR	NR	oral	2,062 mg/kg	2.1	Knyshova, 1968
mouse/NR	NR	oral[a]	2.14 cm^3/kg	2.2	Fischer et al., 1949
rat/Wistar	NR	oral	1,525 mg/kg	1.5	Knyshova, 1968
rat/NR	NR	oral	1.78 g/kg	1.78	Dow Chemical Co., in Rowe, 1963
rat/Wistar	M&F/36	i.p.[b]	11.87-11.90 mmol/kg	1.1	Taberner and Pearce, 1973
rat/Sprague-Dawley	M/NR	i.p.	1,328 mg/kg	1.3	Zabik et al., 1974
guinea pig/NR	NR	oral	1,200 mg/kg	1.2	Knyshova, 1968
rabbit/NR	NR	oral	2,531 mg/kg	2.5	Knyshova, 1968

[a] LD_{50} after 24 hours.

[b] LD_{50} after 18 hours.

after 1,3- or 2,3-butanediol administration but did after 1,4-butanediol. I.P. injection of 143 or 250 mg/kg of 1,4-butanediol to male Swiss albino mice resulted initially in reduction in locomotor activity and exophthalmos. Within 10-15 minutes, the animals assumed a spread-eagle position; some muscular movement was observed. This akinesia and rigidity did not occur when 1,3- or 2,3-butanediol was administered.

Rats appear to be more susceptible to the central nervous system effects of 1,4-butanediol than mice. Anesthesia, measured as loss of righting reflex, could not be induced by i.p. injection of up to 1 g 1,4-butanediol/kg to Swiss albino mice. In contrast, a dose of 350 mg/kg to rats Sprague-Dawley rats caused a loss of the righting reflex within 24 minutes (Menon et al., 1973). A dose of 250 mg/kg i.p. to Sprague-Dawley rats had no effect on righting reflex although at 50-200 mg/kg, spontaneous motor activity was reduced; at 200 mg/kg, rotorod performance was significantly affected (Zabik et al., 1974). Sprince et al. (1966) reported an optimal anesthetic dose of 500 mg/kg i.p. for Sprague-Dawley rats. In Wistar rats injection of sub-lethal doses (<10 mmol/kg) produced an hypnotic state within 20 minutes, accompanied by a loss of the righting reflex; muscle tone was maintained. A dose of 500 mg/kg, i.p. resulted in a significant lowering of body temperature. Higher doses produced a deeper hypnosis with a marked bradycardia, analgesia, and labored respiration. Death was due to respiratory failure (Taberner and Pearce, 1973).

The narcotic effect of 1,4-butanediol in rats has been confirmed by Hinricks et al. (1948) for oral administration. Oral doses of

0.12 and 1.92 ml were fatal within 313 and 137 minutes, respectively, to 50-100 g rats of unreported sex and strain. Signs included rapid narcosis, constriction of the pupils and loss of reflexes; death was attributed to central nervous system paralysis.

The central nervous system effects of 1,4-butanediol are probably mediated through a metabolite, gamma-hydroxybutyrate, as previously discussed.

In male Swiss mice, i.p. injection of 250 mg/kg 1,4-butanediol resulted in an increased level of brain dopamine (170% of control at 20 minutes) and a decreased level of brain norepinephrine (60% of control at 20 minutes). Brain serotonin remained unaltered (Menon et al., 1973).

c) Dermal Effects

1,4-Butanediol elicited slight irritation when applied to the eyes of rabbits; very slight conjunctival irritation and no corneal injury were noted. No irritation or absorption of toxic amounts were induced with repeated application to abraded or intact rabbit skin (unpublished data from Dow Chemical in Rowe, 1963).

3) Subacute Toxicity

Fourteen daily doses of 500 or 1,000 mg 1,4-butanediol per kg, i.p., were without effect on liver triglycerides in male Sprague-Dawley rats (300-350 g) (Zabik et al., 1974).

4) Reproduction Studies

Injection of 0.05 ml 1,4-butanediol into the air sac of White Leghorn chick embryos resulted in 35% mortality in 0 day-old embryos (10% in control) and 89% in 4 day-old embryos (0% in controls) (Gebhardt, 1968). Injection of 0.05 ml into the yolk sac of 4 day-old embryos resulted in 5.6% mortality, which is less than for the control (10%). No malformations were detected in surviving control or treated embryos.

A ten-second immersion of five day incubated Light Sussex eggs in 1,4-butanediol resulted in 40% mortality, compared to 50% in water controls (Clegg, 1964). No abnormalities were detected.

c. Aquatic Organisms

No information was located on the aquatic toxicity of 1,4-butanediol. Hann and Jensen (1974) speculated that the four butylene glycol isomers would be "practically nontoxic" to aquatic life but that a BOD problem could exist at sub-toxic concentrations.

IV. REGULATIONS, STANDARDS, AND HANDLING

A. Federal Regulations

1. Food and Drug Administration

The Food and Drug Administration regulates 1,2-propanediol and 1,3-butanediol as both direct and indirect food additives and ethylene glycol, 1,4-butanediol and butylene glycol (isomer unspecified) as indirect food additives. A description of these approved food additive uses appears in Table 48. 1,2-Propanediol is classed as a generally recognized as safe (GRAS) food additive and is approved as an emulsifying agent, as a general-purpose food additive or as a component in food packaging; indirect additive uses include applications in adhesives, resins, solvents, and coatings. Ethylene glycol is approved for some uses in adhesives intended for packing, transporting, or holding food, as a component of resins, in defoaming agents and in resins. 1,3-Butanediol can be added directly to food as a solvent for natural and synthetic flavoring substances and indirectly as a component of adhesives, cellophane, and sealing gaskets. 1,4-Butanediol is approved as a component of adhesives.

On June 23, 1978, the FDA proposed to set exposure limits for the sterilant ethylene oxide and its two major reaction products, ethylene glycol and ethylene chlorohydrin in certain drug products and medical devices (Gardner, 1978). Proposed residue limits for ethylene glycol are as follows:

Table 48
FDA Status of the Glycols Used as Food Additives
(21 CFR; Union Carbide, 1978)

Section in 21 CFR	Description of Approved Uses	Ethylene glycol	1,2-Propanediol	1,3-Butanediol	1,4-Butanediol	Butylene glycol (isomer unspecified)
A. Direct	Food Additive					
172.850	adjuvant for production of lactylated fatty acid esters intended for use as emulsifiers, plasticizers, or surface-active agents in food		X			
173.220	solvent for natural and synthetic flavoring substances			X		
182.1666	emulsifying agent or as general-purpose food additive, or as a component in food packaging		X			
B. Indirect	Food Additive					
175.105	component of adhesives used in articles intended for packaging, transporting, or holding food	X	X	X	X	
175.300	component of various resinous and polymeric coatings. Applied as continuous films or enamels over a metal or other suitable substrates. Coatings serve as functional barriers between food and substrates and are intended for repeated contact with food	X	X			X

Table 48 (Continued)

Section in 21 CFR	Description of Approved Uses	Ethylene glycol	1,2-Propane-diol	1,3-Butane-diol	1,4-Butane-diol	Butylene glycol (isomer unspecified)
175.320	component of resinous and polymeric coatings for polyolefin films intended for producing, manufacturing, processing, preparing, treating, packaging, transporting, or holding food	X	X	X		
175.380	component of xylene formaldehyde resins condensed with 4,4-isopropylidene diphenolepichlorohydrin epoxy resins		X			
175.390	solvent (removed by water washing) use in the preparation of zinc-silicon dioxide matrix coatings that have contact with food surfaces in bulk re-usable containers intended for storing, handling, and transportation of food.	X	X			
176.170	component of coated or uncoated paper and paperboard intended for use in contact with fatty, aqueous, and dry foods		X			
176.180	component of coated or uncoated paper and paperboard intended for use in contact with dry food		X			

Table 48 (Continued)

Section in 21 CFR	Description of Approved Uses	Ethylene glycol	1,2-Propanediol	1,3-Butanediol	1,4-Butanediol	Butylene glycol (isomer unspecified)
176.200	component of defoaming agents used in preparation and application of coatings for paper and paperboard		X			
176.210	used in preparation of esters from fatty acids and alcohols derived from fatty tryglycerides and marine oils. Used in formulation of defoaming agents employed in the manufacture of paperboard and paper prior to and during sheet forming operations	X	X			X
177.1200	component of base sheet cellophane of coatings applied to cellophane to impart desired properties		X	X		
177.1210	component of closure sealing gaskets and overall discs for food containers		X	X		
177.1240	component of 1,4-cyclohexylene dimethylene terephthalate and 1,4-cyclohexylene dimethylene isophthalate copolymers		X			
177.1400	component in base sheet or of coatings applied to water-insoluble hydroxyethyl cellulose film used for packaging food		X			

Table 48 (Continued)

Section in 21 CFR	Description of Approved Uses	Ethylene glycol	1,2-Propane-diol	1,3-Butane-diol	1,4-Butane-diol	Butylene glycol (isomer unspecified)
177.1630	component of polyethylene terephthalate film used for packaging, transporting, or holding alcoholic beverages that do not exceed 50 per cent alcohol by volume		X			
177.1680	component of polyurethane resins used as the food contact surface for dry bulk food	X	X			
177.2420	component of crosslinked polyester resins used in articles intended for repeated use in contact with food	X	X			X
177.2600	plasticizer in rubber articles intended for repeated use. Limit of 30 per cent by weight of the rubber product		X			
177.2800	adjuvant in the production of textiles and textile fibers intended for contact with dry food		X			
178.3300	adjuvant employed in use of corrosion inhibitors used for steel or tinplate		X			
178.3740	plasticizer in polymeric food packaging materials		X			

Table 48 (Continued)

Section in 21 CFR	Description of Approved Uses	Ethylene glycol	1,2-Propanediol	1,3-Butanediol	1,4-Butanediol	Butylene glycol (isomer unspecified)
178.3910	component of surface lubricants used in drawing, stamping, and forming of metallic articles from rolled foil or sheet by further processing		X			

	ppm Ethylene glycol
Drug Product	
ophthalmics (for topical use	60
injectables (including veterinary intramammary infusions	20
intrauterine device (containing a drug)	10
surgical scrub sponges (containing a drug)	500
hard gelatin capsule shells	35
Medical Device	
implant:	
small (<10 grams)	5,000
medium (10-100 grams)	2,000
large (>100 grams)	500
intrauterine device	10
intraocular lenses	500
devices contacting mucosa	5,000
devices contacting blood (ex vivo)	250
devices contacting skin	5,000
surgical scrub sponges	500

2. Environmental Protection Agency

There are no specific EPA regulations governing water or air quality

with respect to the glycols. In 40 CFR section 180.1001(c), the EPA lists propylene glycol as one of many inert (or occasionally active) materials exempt from tolerances for pesticide formulations applied to growing crops or to raw agricultural commodities after harvest. Propylene glycol is also exempt from the requirement of a tolerance when used in formulations applied to animals (40 CFR 180.1001-e). In both applications, propylene glycol is used as a solvent or cosolvent. Recently, EPA has proposed that pesticide applications of ethylene glycol (involving use as an inert ingredient) be exempt from tolerances for pesticide chemicals when used in foliar application to peanut plants (43 FR 29809, July 11, 1978).

3. Occupational Safety and Health Administration

None of the glycols considered in this report are specifically regulated by the Occupational Safety and Health Administration.

4. Department of Transportation

The glycols are not regulated by the Department of Transportation so therefore do not have DOT shipping names, hazard classifications, or warning labels.

B. State Regulations

Agencies in 15 states were contacted about state-level regulations of the glycols; their responses are listed in Tables 49 to 51.

1. Workplace Standards

State agencies responding indicated that they rely on the standards

Table 49

Regulations for Glycols Food Contact and Workplace Standards in Selected States in Response to Queries

	Food Contact	Workplace Standards
California	*	*
Connecticut	*	*
Delaware	*	*
Kentucky	-	-
Louisiana	-	-
Missouri	-	-
New Jersey	*	*
New York	*	-
Ohio	-	-
Pennsylvania	-	*
South Carolina	*	*
Tennessee	-	*
Texas	-	-

*Federal standards followed; dashes indicate no response.

Table 50
Water Standards for the Glycols in Selected States
in Response to Queries

State	Standard
California	not specifically controlled
Connecticut	no specific water quality standards or regulations; subject to case-by-case technical permit review by Water Compliance and Hazardous Substance Unit
Delaware	not specifically controlled
Kentucky	no response
Louisiana	case-by-case permit review for discharge
Missouri	general water quality standards apply
New Jersey	comply with federal discharge requirements under FWPCA
New York	no specific water quality standards
Ohio	general water quality standards apply
Pennsylvania	general water quality standards apply
South Carolina	indirectly limited by general water quality criteria
Tennessee	general standards for toxic substances and organics apply
Texas	measured indirectly as BOD_5 or COD in individual discharge permits issued to manufacturers

Table 51
Air Standards for the Glycols in Selected States in Response to Queries

State	Standard
California	controlled as "reactive organics" in California basins in which federal oxidant standards are exceeded
Connecticut	emission of organic material restricted to 160 lb/hr, 800 lbs/day; State law: Section 19-508-20f(4)
Delaware	general air quality standards apply; State law: Reg. 1-XXIII of Dept. Nat. Res. & Env. Control (for air pollution)
Kentucky	no response
Louisiana	no specific regulations
Missouri	no specific regulations
New Jersey	general ambient air quality standards apply; State law: NJEPA N.J. Adm. Code Title 7, Chp. 27
New York	processes, exhaust and/or ventilation systems are regulated under State law: Industrial Process Air Pollution Control Rule, part 212
Ohio	The glycols are considered not photochemically reactive (NPR) by the Ohio Environmental Protection Agency. There are no specific regulations for NPR compounds. State law: OAC 3745-21-01(C)
Pennsylvania	no weight rate emission limitations standards for organic compounds apply if storage, loading, water separation or the operation of pumps and compressors would be involved in their handling. State law: Pa. Air Pollution control Act
South Carolina	no specific regulations
Tennessee	general process emission standards; State law: 1200-3-7-.07
Texas	regulated as volatile carbon compounds, State law: Reg. V rule 505.2

set by the Occupational Safety and Health Administration (OSHA), (Table 49). As discussed in the previous section, OSHA does not regulate the title glycols.

2. Food Contact

States queried enforce the regulations of the FDA and the USDA (Table 49).

3. Water Quality

No specific water quality regulations exist in the states questioned. Rather, the glycols are indirectly limited by general water quality standards (Table 50).

4. Air Emissions

The title glycols are not specifically regulated in the states queried (Table 51).

C. Foreign Countries

Agencies in several foreign countries were contacted about regulations concerning the glycols.

1. United Kingdom

In the United Kingdom, occupational standards exist only for ethylene glycol, which are the following:

particulate:

threshold limit value (TLV) -- 10 mg/m^3

short-term exposure limit (STEL) -- 20 mg/m^3

vapor:

TLV -- 100 ppm (260 mg/m^3)

STEL -- 125 ppm (325 mg/m^3)

1,2-Propanediol is permitted as a solvent in food under the Solvents in Food Regulations (1967) to the extent set out in the British Pharmacopoeia (1963).

Air pollution control for industrial processes is regulated by HM Alkali and Clean Air Inspectorate in England and Wales and by HM Industrial Pollution Inspectorate in Scotland. There are currently no specific air or water standards for the glycols.

Ethylene glycol, 1,2-propanediol and 1,3-butanediol are permitted as humectants in tobacco according to the Ordinance on Tobacco. Ethylene glycol and 1,3-butanediol are also permitted as solvents in the production of cigarettes, cigars, smoking tobacco, and snuff. 1,2-Propanediol is permitted as a solvent for flavorings and as a solvent for anti-oxidants; in food, 1,2-propanediol may not exceed 500 mg/kg.

2. West Germany

No workplace standards exist for the glycols under consideration.

Air emission standards for ethylene glycol appear in the Air Purity Regulations (6 MBI, 1974). In waste gas, ethylene glycol cannot exceed 300 mg/m^3 when the flow rate is 6 kg/hour or higher.

3. Japan

The glycols do not appear in a list of toxic substances which are controlled under the Air Pollution Control Law (Law No. 97; 1968).

The Water Pollution Control Law (Law No. 138; 1970) regulates a number of industries including the textile industry, synthetic plastic industry, and organic chemicals industry. Specific levels of glycols do not appear to be regulated under this law.

4. Canada

In Canada, occupational health is under provincial rather than federal jurisdiction. In general, provincial standards follow ACGIH and/or OSHA recommendations.

The Environmental Protection Service (EPS) in Canada is currently developing regulations and guidelines to reduce air and water pollution. Effluent guidelines are being written for the organic chemicals industry (Anon, 1978b); these might possibly regulate the glycols.

Ethylene glycol is not permitted as a food additive. Use of 1,2-propanediol and 1,3-butanediol is allowed as a food additive; good manufacturing practice must be followed. Glycol esters may be used in certain pesticide formulations as solvents.

D. Other Standards -- Threshold Limit Value

The American Conference of Governmental Industrial Hugenists (ACGIH) recommended a threshold limit value (TLV) for ethylene glycol of 100 ppm (250 mg/m^3) for vapor exposure and a TLV of 10 mg/m^3 for particulate exposure. In 1977, the ACGIH recommended that the Short Term Exposure

Limit (STEL) maximum for ethylene glycol be 125 ppm (325 mg/m^3) for vapor exposure and 20 mg/m^3 for particulate exposure. The ACGIH has not recommended exposure limits for the other glycols.

E. Handling and Storage Practices

1. Handling, Storage and Transport

The glycols are considered stable, noncorrosive chemicals with high flash points. They can be stored in mild steel vessels under ordinary storage conditions. Vessels lined with a baked-phenolic resin, epoxy-phenolic resin, or vinyl resin may be used for long-term storage or if trace iron contamination and the development of color would be objectionable; alternatively, stainless steel or aluminum tanks can be used for storage, but these are more costly. For above ground outside storage, tanks and lines may be heated because glycols become relatively viscous at low temperatures. Excessive temperatures can result in product degradation (Union Carbide, 1978).

Ethylene glycol is shipped in one gallon polyethylene jugs, five gallon DOT 17E steel pails and 55-gallon DOT 17E steel drums. 1,2-Propanediol is shipped in one-gallon glass jugs, and 5- and 55-gallon DOT 17E UCC #2 phenolic-lined steel pails and drums. 1,4-Butanediol is available in 50, 100, and 400 pound lined steel drums and in ten pound packages (GAF, n.d.).

2. Personnel Exposure

Respiratory protective equipment would not be needed unless workers are exposed to heated glycols. When handling ethylene glycol, Dow (1978a) suggests workers wear clean, body-covering protective clothing. For

1,2-propanediol, no protective clothing is usually necessary (Dow, 1978b). For neither glycol is eye protection normally necessary.

3. Accident Procedures

Union Carbide (1976) suggests that small spills of ethylene glycol should be flushed with large quantities of water. Larger spills should be collected for disposal. To dispose, they suggest mixing the waste glycol with a flammable solvent and incinerating in a furnace where permitted under Federal, State, and Local regulations. Dow (1978a&b) suggests flushing spills of ethylene glycol or 1,2-propanediol with water and soaking up with absorbent material; large spills should be diked and pumped into suitable containers. As an alternate to incinerating, Dow suggests recovering the spilled glycol with a vacuum truck and returning it to the plant for reprocessing.

V. EXPOSURE AND EFFECTS POTENTIAL

The most likely source of direct human contact with the glycols is by ingestion. 1,2-Propanediol is a GRAS (generally recognized as safe) food additive; the estimated daily intake by persons 2-65 years old is 349 mg or 6 mg/kg (FASEB, 1973). 1,2-Propanediol is also used in some oral drug preparations. 1,3-Butanediol is approved as a direct food additive for flavoring substances; daily intake has not been estimated. For the other glycols, which are not approved as direct food additives, ingestion occurs only during accident or suicidal attempts. Ingestion of ethylene glycol, usually as antifreeze, has accounted for about 40-60 deaths per year (Haggerty, 1959).

Dermal contact is another source of human exposure to the glycols. 1,2-Propanediol and 1,3-butanediol are used in some cosmetic formulations, such as hand creams. Occupationally, exposure to the skin is possible during production and handling, but few reports of adverse effects by this route were found in the literature. Eczematous dermatitis developed in a worker exposed to aqueous ethylene glycol solutions during eyeglass manufacture (Dawson, 1976).

Inhalation is not a significant route of human exposure to the glycols. Their vapor pressures are low at ambient temperatures (Tables 2-4), so only at elevated temperatures will a potential inhalation hazard exist. Only one industrially-related report involving adverse effects of inhalation was located in the literature. This involved the heating of ethylene glycol in an electrolytic condenser factory where 14 of 38 workers suffered loss of consciousness, nystagmus, and/or lymphocytosis (Troisi, 1950; see section III-A-1-b).

Major sources of environmental contamination by ethylene glycol and 1,2-propanediol are from the disposal of spent antifreeze and from the runoff of de-icing fluids. Demand for antifreeze was about 195-215 million gallons in 1977 (Anon, 1977h; Anon, 1977d) but estimates are unavailable on the percentage of annual demand which eventually is disposed of directly into the environment. Limited monitoring data indicate that entry of ethylene glycol and 1,2-propanediol into the environment during production is a minor source (section II-D-1). No environmental monitoring data are available for the butanediol isomers. The 2,3-isomer occurs in the environment as an endproduct of fermentation by several strains of enteric bacteria, such as Aerobacter, Klebsiella, and Serratia (section II-D-5). Another source of environmental exposure by the glycols is during transportation accidents.

The glycols present from any source are not likely to persist. As discussed in section II-F, they are subject to moderately rapid breakdown by soil, water, and sewage microorganisms. In the case of an accidental spill into surface waters, a BOD problem could exist. For example, Price et al. (1974) found that in freshwater, the bio-oxidation on day five was 34% complete for ethylene glycol and 62% for 1,2-propanediol and on day 20, 79% of the 1,2-propanediol had been biologically oxidized and all of the ethylene glycol had disappeared. Evans and David (1974) reported complete degradation of ethylene glycol within three days in river waters at 20°C. It is possible that this relatively rapid rate of degradation, imposing a high oxygen demand, might possibly kill aquatic organisms through dissolved oxygen (DO) depletion. Lower rates of degradation were reported by Lamb and Jenkins (1952) (on day five,

12.5% of theoretical oxygen demand was satisfied for ethylene glycol and 2.2% for 1,2-propanediol) which would not likely result in DO depletion.

Fuller et al. (1976) evaluated the potential of several hundred organic chemicals, including ethylene glycol and 1,2-propanediol to enter the atmosphere and pose a toxicological threat. They used a scoring system based on production, volatility, and toxicity; a maximum score of 125 was possible. The higher the score, the more likely a toxicological threat. A final score of 11 was assigned to ethylene glycol and 5 was assigned to 1,2-propanediol. The scoring system is most useful when comparing chemicals. Examples of other final scores are as follows: acetonitrile, 23; acrotein, 21; acrylonitrile, 20; n-butyl alcohol, butane, 7; ethylene, 9; and propylene, 4.

TECHNICAL SUMMARY

Production and Use

The subject compounds contain two hydroxyl groups attached to carbon atoms in an aliphatic carbon chain. The following glycols are discussed in this report: ethylene glycol, 1,2-propanediol (propylene glycol), 1,3-propanediol, 1,3-butanediol, 1,4-butanediol, 2,3-butanediol, and 1,2-butanediol. Of these, the most important commercially is ethylene glycol. About 3.7 billion pounds of this glycol were produced in the U.S. during 1977 by the hydration of ethylene oxide or by the acetoxylation of ethylene. It was produced at 16 sites by 12 manufacturers. Ethylene glycol is used in antifreeze (45% of production), polyester fiber (35%), alkyd and polyester resins (4%), latex paints, and other emulsions (1%) as well as for export (8%) and in a variety of miscellaneous uses (7%) (MCP, 1977).

Domestic production of 1,2-propanediol was about 0.5 billion pounds during 1977. This glycol is produced by five manufacturers at six sites by the hydration of propylene oxide. It has applications in polyester resins (45%), pet food (12%), exports (12%), food and pharmaceuticals (11%), cellophane (7%), tobacco (7%), as well as other uses (6%) (Anon, 1977f). 1,2-Propanediol is a generally recognized as safe (GRAS) food additive. 1,3-Propanediol is of minor commercial importance, being recovered in commercial glycerol plants when there is sufficient demand (Budke and Banerjee, 1971).

1,4-Butanediol is manufactured in the U.S. by three producers at four sites; total domestic demand is 175 million pounds. It is used in the production of tetrahydrofuran (57%), acetylenic chemicals (26%),

polyurethanes (9%), and polybutylene terephthalate (7%) (Brownstein and List, 1977). 1,2- and 1,3-Butanediols are produced by two manufacturers and 2,3-butanediol is produced by another manufacturer; figures for plant capacity or total demand are unavailable. The 1,2- and 1,3-isomers are used primarily in the production of polymeric plasticizers while the 2,3-isomer is used as a solvent, a humectant and a coupling agent.

Environmental Exposure

Only limited data are available on sources of entry of the glycols into the environment. Ethylene glycol and 1,2-propanediol were identified as components of the wastewater from production facilities (Zeitoun and McIlhenny, 1971); environmental entry from this source will depend on the extent of waste stream treatment and on whether spent glycol recycling is practiced. The major source of environmental contamination by ethylene glycol and 1,2-propanediol is likely from the disposal of spent antifreeze, but no estimates are available which assess the magnitude of this problem. Runoff of de-icing fluids which are sprayed, for example, on runways and airplanes, is another source of environmental contamination. 2,3-Butanediol occurs in the environment as an endproduct of fermentation by several strains of enteric bacteria.

The glycols are capable of being degraded by a variety of microorganisms. Ethylene glycol (2 or 10 mg/ℓ) was biodegraded completely in three days when tested in four types of river water at 20°C (Evans and David, 1974). When added to adapted activated sludge, most (97%) of a sample of ethylene glycol was degraded over 120 hours (Pitter, 1976). Price et al. (1974) found that the bio-oxidation of ethylene glycol (up to 10 mg/ℓ) was 34%, 86%, 92%, and 100% complete after 5, 10, 15, and 20

days, respectively, when settled domestic wastewater was used as seed; using synthetic seawater as seed, bio-oxidation was 20, 60, 65, and 77% complete after 5, 10, 15, and 20 days, respectively. Price et al. (1974) obtained similar results with 1,2-propanediol. Bedard (1976) labeled both ethylene glycol and 1,2-propanediol as readily degradable based on BOD measurements using raw sewage seed. For 1,4-butanediol, degradation was 98.7% complete in 120 hours using adapted sludge (Pitter, 1976).

The glycols are soluble in water in all proportions; when spilled in a body of water they will sink then dissolve. Since their vapor pressure is low, they will evaporate slowly. Relatively rapid breakdown by microorganisms will preclude environmental persistence.

Biological Effects of Ethylene Glycol

Most cases of ethylene glycol intoxication in humans involved accidental ingestion. Clinical signs may include nausea, hypertension, tachycardia, cardiopulmonary failure, renal impairment, and coma; oxalate crystals, formed by oxidation of ethylene glycol, are usually in the urine. The lethal dose in humans is about 1.4-1.6 g/kg or about 100 ml (Lavelle, 1977).

Ethylene glycol is oxidized to glycolaldehyde, which is further oxidized to glycolate, then to oxalate and CO_2. Glycolate has been identified as the specific toxic agent in acute ethylene glycol poisoning in the rat (Chou and Richardson, 1978) and the monkey (Clay and Murphy, 1977).

In rats given i.v. doses of labeled ethylene glycol, 60% of the dose had been eliminated within 24 hours as $^{14}CO_2$ in expired air and

^{14}C-labeled compounds in the urine; the rest was widely distributed in the tissues. In monkeys, 15% was excreted in urine and expired air within four hours. Unchanged ethylene glycol and glycolic acid were the most important urinary products (McChesney et al., 1971).

The oral lethal dose averages 8.3-15.3 g/kg in mice, 6.1-8.5 g/kg in rats and 6.6-8.1 g/kg in guinea pigs. Comparable values were obtained following parenteral administration. Signs include weakness, loss of muscular coordination, prostration, and coma (Laug et al., 1939). Microscopic findings include deposition of calcium oxalate crystals in the kidney; ethylene glycol has been used as a model to study renal hyperoxaluria or to induce oxalate lithiasis.

Renal changes are frequently noted with chronic ethylene glycol administration. Rats given 1% (but not 0.5%) ethylene glycol in the drinking water for 120-130 days had oxalate crystals in the urine (Hanzlik et al., 1931). In three macaque monkeys given 37-152 g/kg ethylene glycol over 13 to 157 days, renal changes were proportional to the dose (Roberts and Seibold, 1969); these changes included deposition of calcium oxalate in the proximal tubule, necrotic epithelial cells, and occasional focal granulomas. Few chronic effects other than renal changes have been noted. The addition of ethylene glycol to the diet of three rhesus monkeys at 0.2 or 0.5% for three years produced no observable toxic effects (Blood et al., 1962).

Several inhalation studies were carried out to evaluate the effects of a possible leak of ethylene glycol from the heat exchanger system in spacecraft. Inhalation of 10 or 57 mg/m^3 ethylene glycol for eight hours/day, five days a week for 90 days was without effect in rats, guinea pigs, rabbits, dogs, or monkeys; continuous exposure to 12 mg/m^3 for 90

days resulted in eye irritation (Coon et al., 1970). Chimpanzees continuously exposed to 256 mg/m^3 of ethylene glycol aerosol for 28 days showed some impairment of auditory and visual discrimination compared to pre-exposure levels.

A single s.c. dose of 1 or 10 mg (~LD_{50}) ethylene glycol elicited no carcinogenic effect in mice after 15 months (WARF, 1970). In rats receiving 30-1,000 mg/kg ethylene glycol s.c. twice a week for one year, tumor incidence was comparable to that found in controls (Mason et al., 1971). Skin painting of mice with ethylene glycol up to 86 times (Berenblum and Haran, 1955) or twice a week for life (Deringer, 1962) did not result in excess tumor incidence compared to controls.

For aquatic organisms, the TL_m (median tolerance limit) or the LC_{50} was >20,000 mg/ℓ for brine shrimp, >100 mg/ℓ for brown shrimp, and >18,500 mg/ℓ for rainbow trout.

Biological Effects of Propylene Glycols

1,2-Propanediol (propylene glycol) is classed as a Generally Recognized as Safe (GRAS) food additive by the FDA. Few reports of adverse effects to humans have appeared in the literature; four case studies were located on suspected intoxication due to 1,2-propanediol ingestion. Signs included arrhythmia, tachypnea, stupor, and lactic acidosis (Martin and Finberg, 1970; Cate and McGlothlin, 1976). Following an oral dose to three volunteers (1 g/kg), 20-25% of the dose was eliminated in the urine after ten hours (Hanzlik et al., 1939a). The potential for allergic reaction to contact with this chemical has been noted by several investigators.

In laboratory animals, 1,2-propanediol was rapidly absorbed following oral dosing or injection (Van Winkle, 1941b; Lehman and Newman, 1937). Up to 45% of the dose was excreted in the urine within 24 hours.

1,2-Propanediol is metabolized through lactaldehyde, methylglyoxal, and then lactic acid or pyruvic acid (Ruddick, 1972). It is further oxidized through the tricarboxylic acid cycle or through the glycolytic pathway, the latter contributing to glycogen formation. The glycogenic effect of 1,2-propanediol has been noted by many investigators (Hanzlik et al., 1939a and b; Giri et al., 1970; Whittman and Bawin, 1974).

The LD_{50} for orally administered 1,2-propanediol averages 14-25 g/kg in mice, 22-29 g/kg in rats and 18-20 g/kg in guinea pigs. This glycol is more acutely toxic after injection than by oral administration. Large doses of 1,2-propanediol resulted in loss of equilibrium, central nervous system depression, and respiratory failure (Laug et al., 1939; Giri et al., 1970; Seidenfeld and Hanzlik, 1932). Following i.v. injection of 1,2-propanediol to rabbits, there was a dose dependent increase in the number of circulating polymorphs and decrease in the number of lymphocytes (Brittain and D'Arcy, 1962). No hematological or other changes were noted in rats fed diets containing 5% 1,2-propanediol for 15 weeks (Gaunt et al., 1972). Other investigators failed to note consistent chronic effects of 1,2-propanediol treatment. No pathological changes were reported in rats given the glycol at levels up to 10% in the drinking water for up to 140 days (Weatherby and Haag, 1938; Seidenfeld and Hanzlik, 1932). Gaunt et al. (1972) reported that of up to 5% 1,2-propanediol in the diet of Charles River rats for two years was without effect on mortality, body weight gain, hematology, urinary cell

excretion, renal chemistry, organ weights, or pathology. In dogs receiving 8 or 20% 1,2-propanediol in the diet for two years, Weil et al. (1971) found no effects on the following parameters: mortality, body-weight change; diet utilization, or water consumption, micropathology; liver, kidney, and spleen weights; and most values for blood, urine, and biochemical parameters. Some erythrocyte destruction occurred in dogs receiving the higher level of 1,2-propanediol.

1,2-Propanediol was not teratogenic at daily oral doses up to 1,550-1,600 mg/kg administered during days 6-15 of gestation to mice, rats, or hamsters. No teratogenic effect was noted in rabbits similarly treated on days 6-10 of gestation with up to 1,230 mg/kg (FDRL, 1973a). No carcinogenic potential has been attributed to 1,2-propanediol administered orally to mice (5% in the diet for two years), by injection to mice (0.5-1.0 ml weekly for 88 weeks; single injection of 1 mg) or by skin painting to mice (10-100% 1,2-propanediol daily for life).

No positive mutagenic effects were noted in a host-mediated assay using mice receiving 30, 2,500, or 5,000 mg/kg 1,2-propanediol orally followed by an i.p. dose of an indicator organism (Salmonella typhimurium or Saccharomyces cerevisiae) (Litton Bionetics, 1974). Mice receiving the highest dose daily for five days showed a "weak or questionable positive" result with one strain of Salmonella. Cytogenetic assays of somatic cells from rats given up to 5,000 mg/kg of 1,2-propanediol showed no chromosomal aberrations. Negative results were also obtained in in vivo tests with human embryonic lung cultures. A dominant lethal gene test with rats given 1 or 5 doses of up to 5,000 mg/kg 1,2-propanediol showed no evidence of mutagenicity (Litton Bionetics, 1974).

In rainbow trout, the LC_{50} is between 50,000-100,000 mg/ℓ (Hann and Jensen, 1974) and in brine shrimp, the 24 hour TL_m is greater than 10,000 mg/ℓ (Price et al., 1974).

1,3-Propanediol has not been studied as extensively as the 1,2-isomer. The 50% fatal dose to rabbits was 4.2-7.4 g/kg, comparable to 1,2-propanediol. By i.m. injection, the 50% fatal dose was 6.3-7.4 g/kg, which is about twice that for 1,2-propanediol (Van Winkle, 1941). Fischer et al. (1949) reported an LD_{50} of 6.4 g/kg for mice given 1,3-propanediol orally. 1,3-Propanediol has no glycogenic action in rats, in contrast to 1,2-propanediol. In a 15 week study, rats given 5 or 12% 1,3-propanediol in the diet or 5.3 or 10.6 g/kg daily by gavage showed a reduced growth rate, particularly those given the dietary diol. Based on a similar study by Van Winkle (1941), twice as much 1,2-propanediol is required to produce the same effect as 1,3-propanediol.

Biological Effects of Butylene Glycols

For 1,2-butanediol, few studies on biological effects are available. The LD_{50} to rats is about 16 g/kg (Rowe, 1963). In large oral doses to rats 1,2-butanediol caused narcosis, gastrointestinal irritation and peripheral vasodilation. Inhalation of an aerosol of 1,2-butanediol by rats for 7 hours was without effect. I.V. injection of up to 1 g/kg to dogs had no effect. It was not irritating to the skin of rabbits (Dow Chemical Co., in Rowe, 1963). 1,2-Butanediol showed a glycogenic effect in starved rats in contrast to the 2,3- and 1.4- isomers(Opitz, 1958). Continuous infusion of 0.1-0.3 g/kg/hr for more than 10 hours resulted in diminished muscle tone in rabbits (Strack et al., 1960).

Little information is available on the biological effects of 2,3-butanediol. Fischer et al. (1949) reported that the oral LD_{50} to mice was 8.9 g/kg. 2,3-Butanediol was without narcotic effects in rats (up to 1.4 g/kg tested) and mice (0.5 g/kg tested)(Marcus et al., 1976; Menon et al., 1973).

1,3-Butanediol has been extensively studied as a synthetic metabolizable source of energy. Several studies in humans showed that isocaloric substitution of 1,3-butanediol for starch provided an adequate source of dietary calories. No toxic effects have been reported in a series of nutritional and metabolic studies in humans. Volunteers receiving the diol had a decreased negative nitrogen balance and a decreased level of blood glucose. Up to 10% of the caloric intake of 1,3-butanediol appears to be utilized (Kies et al., 1973; Tobin et al., 1975).

Several studies in rats have confirmed that 1,3-butanediol is metabolized via β-hydroxybutyric acid (Gessner et al, 1960; Mehlman et al., 1971 a & b; Tobin et al., 1972; Rosmos et al., 1975). In rats, 1,3-butanediol resulted in an elevation of blood glucose in acute studies, but a lowering in chronic studies.

The oral LD_{50} values for 1,3-butanediol average 23 g/kg in mice, 23-30 g/kg in rats and 11.5 g/kg in guinea pigs. By subcutaneous injection, the LD_{50} is 16.5 g/kg in mice and 20 g/kg in rats. Exposure for 8 hours to saturated vapors was without effect in rats (Smyth et al., 1951). Large parenteral doses of 1,3-butanediol have a narcotic effect; it appears to act as a muscle relaxant rather than as a depressant of brain activity (Sprince et al., 1966). Bornmann (1954 a & b; 1955) reported marked diuresis in rats given an acute dose of 10.1 g/kg orally or up to 20% in the drinking water twice a week for 96 days. Several investigators have reported a decrease in body weight gain when levels of 1,3-butanediol were (in most cases) 20% or

higher in the diet. However, no histological or other changes were attributed to butanediol treatment. Administration of 10.6 mg/kg every 3-4 days to rats for 45-185 days was without effect on blood count or organ histology (Kopf et al., 1950). No adverse effects on weight gain, survival, hematology, urinalyses or histology were noted in rats fed diets containing 1, 3 or 10% 1,3-butanediol for 2 years or in dogs fed diets containing 0.5, 1 or 3% for 2 years (Scala and Paynter, 1967). In a multigeneration feeding study, rats received 5, 10 or 24% 1,3-butanediol in a semi-synthetic diet (FDRL, 1973b). The growth rate of males was slightly depressed in all generations. There was a gradual decrease in the pregnancy rate in 5 successive mating cycles in F_1 females which was attributed in part to the added stress of the semi-synthetic diet. No gross or pathological changes noted at autopsy of F_1 rats were attributed to treatment; no teratogenic effects were noted in litters of F_2 rats. No teratogenic effects were noted in litters from rats and dogs receiving up to 20-24% 1,3-butanediol prior to and during pregnancy or in litters from rabbits receiving 1.3-5.4 g/kg daily on days 6-18 of gestation (FDRL, 1973b). A dominant lethal test and cytogenetic test revealed no adverse effects on the genetic material in rats (FDRL, 1973b).

1,4-Butanediol is more acutely toxic than the other butanediol isomers. Its oral LD_{50} value ranges from 1.2-2.5 g/kg in laboratory animals. 1,4-Butanediol is a central nervous system depressant; this effect is mediated through its metabolite, gamma-hydroxybutyrate. Signs of intoxication include narcosis, bradycardia, analgesia and akinesia (Hinricks et al., 1948; Zabik et al., 1974; Menon et al., 1973).

Regulations and Standards

The Food and Drug Administration regulates 1,3-butanediol and 1,2-propanediol as both direct and indirect food additives and ethylene glycol,

1,4-butanediol and butylene glycol (isomer unspecified) as indirect food additives. The FDA has proposed exposure limits for ethylene glycol, ethylene oxide and ethylene chlorohydrin in certain drug products and medical devices. There are no specific EPA regulations governing water or air quality with respect to the title glycols. Propylene glycol can be used as an inert solvent or cosolvent in pesticide formulations. None of the glycols considered in this report are specifically regulated by the Occupational Safety and Health Administration or by the Department of Transportation.

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CONCLUSIONS AND RECOMMENDATIONS

The environmental impact of the title glycols cannot be adequately assessed because only limited monitoring data are available. Major sources of environmental contamination by ethylene glycol and 1,2-propanediol are likely the disposal of spent antifreeze and the runoff of de-icing fluids. No environmental monitoring data are available for the butanediol isomers. Studies would be desirable to assess the magnitude of antifreeze and de-icer disposal on the environment and to monitor other possible sources of contamination (ex. production and use facilities) by the glycols. There is no evidence to suggest that the glycols will persist or bioaccumulate in the environment. A potential aquatic impact of the glycols is the imposition of a high oxygen demand due to rapid biological oxidation which would have an adverse effect on aquatic organisms through dissolved oxygen depletion. This problem should be addressed in further studies.

As reviewed in section V (Exposure and Effects Potential), the most likely source of human contact with the glycols is by ingestion; inhalation is not a significant source because of the low vapor pressure of the glycols. In most areas, adequate biological data exist for ethylene glycol, 1,2-propanediol, and 1,3-butanediol. There is no evidence to suggest that these compounds are carcinogenic. In one study, ethylene oxide-sterilized bedding resulted in hemorrhage and tumors in mice; ethylene glycol, as a breakdown product of ethylene oxide, was implicated as a causative factor but this question remains to be resolved. Only sparse biological data exist for the less commercially significant glycols: 1,3-propanediol, and 1,2- , 2,3- , and 1,4-butanediols. However, 1,4-butanediol should be considered for further study because of its increasing use in plastics and resins.

APPENDIX

Summary of Sources Employed

References used in this report were selected from searches of automated information retrieval systems, indices, standard references works, journals, books, etc. Manufacturers, researchers, and federal and state agencies, among others, were contacted directly.

The following is a list of on-line systems searched:

Agricola
Biological Abstracts
Cancerline
Chemical Abstracts
Dissertation Abstracts
Food and Science and Technology Abstracts
National Technical Information System
PTS Market Abstracts
Smithsonian Science Information Exchange
Science Citation Index
Toxline
Toxback

Also, the Technical Information Center data base was searched by the National Institute of Occupational Safety and Health.

Manually searched indices included:

Biological Abstracts (1957-1970)
Chemical Abstracts (1957-1971)
Excerpta Media
  Cancer (1953-1978)
  Pharmacology and Toxicology (1965-1978)
  Development Biology and Teratology (1965-1978)
  Environmental Health and Pollution Control (1972-1978)
  Occupational Health and Industrial Medicine (1971-1978)
Index Medicus (1957-1978)

Appropriate books and compendia were examined and current journals screened. The literature search is considered complete through November 1978.

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16. ABSTRACT

This report reviews aspects of production, use, environmental exposure and biological effects of ethylene glycol, two isomers of propylene glycol (1,2- and 1,3-propanediol) and four isomers of butylene glycol (1,3-, 1,4-, 2,3-, and 1,2-butanediol). Annual production of ethylene glycol is about 3.7 billion pounds for use primarily in antifreeze and polyester fiber. About 0.5 billion pounds of 1,2-propanediol are produced per year for use in polyester resins, food, pharmaceuticals, and cellophane. Annual domestic demand for 1,4-butanediol is about 0.2 billion pounds for use in the production of tetrahydrofuran and acetylenic chemicals. The other title glycols are of less importance commercially.

The major source of environmental contamination by ethylene glycol and 1,2-propanediol is likely from the disposal of spent antifreeze and de-icing fluids. However, limited monitoring data make it difficult to adequately assess environmental exposure to the glycols. The glycols are capable of being degraded by a variety of acclimated and unacclimated soil, water, and sewage microorganisms.

In humans, ethylene glycol intoxication, usually as a result of accidental ingestion of antifreeze, may result in nausea, hypertension, tachycardia, cardiopulmonary failure, renal impairment, coma and death. 1,2-Propanediol is a GRAS food additive of low toxicity. 1,3-Butanediol has been studied as a source of dietary energy. Few studies are available on 1,2- , 2,3- and 1,4-butanediol or on 1,3-propanediol.

17. KEY WORDS AND DOCUMENT ANALYSIS

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Ethylene Glycol Propylene Glycol Butylene Glycol Environmental Engineering Regulations Toxicology		Biological and Medical Sciences -biology -clinical medicine -toxicology

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