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SECOND DRAFT

Information Profiles on Potential Occupational Hazards: Glycols

Center for Chemical Hazard Assessment
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16. Abstract (Limit: 200 words) Based on their importance in the industrial community, information profiles were provided for the following glycols: 2-butene-1,4-diol (110645), 1,3-butylene-glycol (107880), 1,4-butylene-glycol (110634), 2-butyne-1,4-diol (110656), 1,4-cyclohexanedimethanol (105088), diethylene-glycol (111466), dipropylene-glycol (108612), ethylene-glycol (107211), 2-ethyl-1,3-hexanediol (94962), 1,6-hexanediol (629118), 2,5-hexanediol (2935446), 2-methyl-2-propyl-1,3-propanediol (78262), neopentyl-glycol (126307), 1,5-pentanediol (111295), propylene-glycol (57556), tetraethylene-glycol (112607), triethylene-glycol (112276), 2,2,4-trimethyl-1,3-pentanediol (144194), and tripropylene-glycol (1638160). The acute toxicity of these compounds was characterized by central nervous system depression. Some of the glycols have caused renal damage of varying degrees. Some of the glycols were readily absorbed through the skin. Administration of diethylene-glycol to animals has caused formation of bladder stones. Investigation of possible carcinogenic, teratogenic, reproductive, or mutagenic potentials for these compounds had been very limited.

17. Document Analysis a. Descriptors

b. Identifiers/Open-Ended Terms NIOSH-Publication, NIOSH-Contract, Contract-210-79-0030, Agricultural-chemicals, Electroplating, Plasticizers, Resins, Corrosion-inhibitors, Explosives, Toxic-effects, Nervous-system-disorders, Kidney-damage

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18. Availability Statement	19. Security Class (This Report)	21. No. of Pages 212
	22. Security Class (This Page)	22. Price

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I. SCOPE OF DOCUMENT AND SUMMARY OF MAJOR FINDINGS

A. CLASS IDENTIFICATION

Glycols, also called diols, are compounds containing two hydroxyl groups attached to separate carbon atoms in an aliphatic chain (Brown et al., 1980). Although glycols may contain heteroatoms, those discussed in these profiles are composed solely of carbon, hydrogen, and oxygen.

Simple glycols are those in which both hydroxyl groups are attached to an otherwise unsubstituted hydrocarbon chain as presented by the general formula, $C_nH_{2n}(OH)_2$. Ethylene glycol, propylene glycol, butylene glycol, pentanediol, and hexanediol are examples of the simple glycols. The aliphatic chain of the simple glycols may contain a double or triple carbon bond identifying glycols such as butenediol or butynediol. Also, the hydrogen atoms attached to the aliphatic chain of the simple glycols may be substituted by methyl, ethyl, propyl, butyl, or phenyl radicals leading to glycols also considered under this class definition. 2,2,4-Trimethyl-1,3-pentanediol is an example of this type of glycol.

Polyglycols are adducts of simple glycols and are distinguished by intervening ether linkages in the hydrocarbon chain, as represented by the general formula $C_nH_{2n}O_x(OH)_2$. Polyglycols that contain up to and including eight carbon atoms are referred to as the lower polyglycols and include diethylene, triethylene, tetraethylene, and dipropylene glycols. These lower polyglycols and tripropylene glycol have been considered as glycols under the class definition. It may be argued that these polyglycols are not true glycols due to their ether linkages, however, they are referred to as glycols commercially and are therefore included in this class profile.

The compounds known commercially as polyethylene glycol, polyproplyene glycol, and polybutylene glycol are not considered as glycols under this class definition. They are a series of polymers which may have average molecular weights as high as 6000 and would best be considered as a separate class.

Hexylene glycol is not included in this class because a separate profile has been previously prepared.

The list of all the glycols considered by this class definition are listed in the Appendix.

B. CHEMICALS TO BE ADDRESSED

The following glycols have been selected for individual profiles:

2-Butene-1,4-diol
1,3-Butylene glycol
1,4-Butylene glycol
2-Butyne-1,4-diol
1,4-Cyclohexanedimethanol
Diethylene glycol
Dipropylene glycol
Ethylene glycol
2-Ethyl-1,3-hexanediol
1,6-Hexanediol
2,5-Hexanediol
2-Methyl-2-propyl-1,3-propanediol
Neopentyl glycol
1,5-Pentanediol
Propylene glycol
Tetraethylene glycol
Triethylene glycol
2,2,4-Trimethyl-1,3-pentanediol
Tripropylene glycol

These glycols were selected for individual treatment as all, except 2,5-hexanediol, were identified as having annual production volumes on the order of one million pounds or more. 2,5-Hexanediol was included due to its notable neurotoxicity.

Glycols of lesser commercial importance, while still being identified as having commercial significance, are listed in Section II with available data.

C. SUMMARY OF BIOLOGICAL ACTIVITY

In experimental animals, the acute toxicity of many of the glycols is characterized by central nervous system (CNS) depression. Renal damage of varying degrees has been reported for some of the glycols (ethylene glycol, di- and triethylene glycols, 1,4-butylene glycol, dipropylene glycol). Similar CNS and renal effects have been observed in humans acutely poisoned by ethylene glycol, diethylene glycol, or 1,4-butylene glycol.

Rat oral LD50 values for many of the glycols (i.e., ethylene, diethylene, triethylene, tetraethylene, propylene, dipropylene, tripropylene, 1,3-butylene, and neopentyl glycols, and 1,5-pentanediol) are in excess of 5 g/kg (5000 mg/kg), indicating a low order of toxicity. Most of the remaining glycols (1,4-butylene glycol, 1,4-cyclohexanedimethanol, 1,6-hexanediol, 2,5-hexanediol, 2-ethyl-1,3-hexanediol, and 2,2,4-trimethyl-1,3-pentanediol) have oral LD50 values in rats of greater than 500 mg/kg. 2-Butyne-1,4-diol, with a rat oral LD50 in the range of 100 to 300 mg/kg, appears to be the most acutely toxic of the glycols. 2-Butene-1,4-diol and 2-methyl-2-propyl-1,3-propanediol have not been tested in this manner.

The vapor pressures and uses of the glycols are such that humans would not usually be exposed to these chemicals by inhalation. A few of the glycols (diethylene glycol, 1,4-butylene glycol, 2-ethyl-1,3-hexanediol) have been reported to be absorbed in toxic amounts through the skin in animals. With the exception of 2-ethyl-1,3-hexanediol, the liquid glycols do not appear to be particularly irritating to the eyes or skin. The irritancy of the solid glycols cannot be readily evaluated because some of the testing employed vehicles that can be irritating and in other instances the vehicle was not reported.

Subchronic or chronic exposures of experimental animals to ethylene, diethylene, or dipropylene glycol caused damage to their kidneys. In addition,

administration of diethylene glycol resulted in the formation of bladder stones. This effect occurred occasionally in animals given ethylene glycol. Histopathologic changes have been reported to occur in the livers of animals treated subchronically with diethylene glycol 1,4-butylene glycol or 2-ethyl-1,3-hexanediol. Some indications of structural or functional impairment of the CNS were observed in animals given long-term exposures to ethylene glycol, 1,4-butylene glycol, 2-butyne-1,4-diol, or 2-ethyl-1,3-hexanediol. 2,5-Hexanediol, administered subchronically to rats, produced striking clinical and histopathologic evidence of neuropathy.

Propylene glycol and 1,3-butylene glycol are approved by the Food and Drug Administration (FDA) as food additives. Both these glycols can be utilized by the body as a source of calories.

Propylene glycol, 1,3-butylene glycol, triethylene glycol, neopentyl glycol, and 2,2,4-trimethyl-1,3-pentanediol have produced little evidence of toxicity in subchronic or chronic animal tests. The first two glycols have been tested more extensively than the latter three. Glycols not specifically mentioned have not been tested for subchronic or chronic toxicity.

Investigation of the potential teratogenic, reproductive, mutagenic, or carcinogenic effects of the glycols has been minimal. What little testing has been published has given primarily negative results. Prolonged oral administration of diethylene glycol to rats, however, produced bladder tumors, a few of which were malignant. The tumors seemed to be a result of chronic irritation from the bladder stones that were also a consequence of diethylene glycol administration. Repeated long-term administration of 2-ethyl-1,4-cyclohexanedimethanol and 2,5-hexanediol in dosages that produced overt toxic effects resulted in testicular atrophy in animals.

II. DATA FOR COMMERCIALLY IMPORTANT CHEMICALS NOT INDIVIDUALLY PROFILED

Other glycol compounds that have or may have some commercial importance are presented in Tables 1, 2, and 3; these compounds were not treated in individual profiles. Table 1 lists synonyms, CAS numbers, RTECS numbers, and chemical structures; Table 2 presents chemical and physical properties; Table 3 lists production volumes and uses, and summarizes manufacturing processes, and Table 4 lists manufacturers of glycol compounds.

All glycol chemicals considered for selection, regardless of their commercial importance, are listed in the Appendix.

Table 1. Glycols

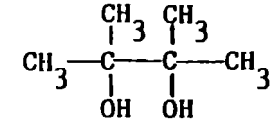
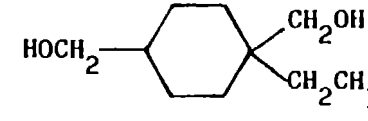
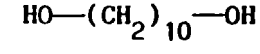
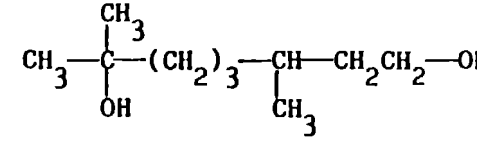
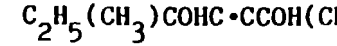
Compound and Synonyms	CAS No.	RTECS No.	Chemical Structure
2,3-Dimethyl-2,3-butanediol Pinacol Pinacone Tetramethylethylene glycol 2,3-Butanediol, 2,3-dimethyl-	76-09-5	---	
1-Ethyl-1,4-cyclohexanedimethanol 1,4-Cyclohexanedimethanol, 1-ethyl-	67663-05-2	---	
1,10-Decanediol	112-47-0	---	
3,7-Dimethyl-1,7-octanediol 1,7-Octanediol, 3,7-dimethyl- Hydroxycitronellol	107-74-4	---	
3,6-Dimethyl-4-octyne-3,6-diol 4-octyne-3,6-diol, 3,6-dimethyl- Dimethyloctynediol	78-66-0	---	

Table 2. Glycols - Physical Properties

Compound	Molecular Weight	Description	Boiling Point	Melting Point	Vapor Pressure	Water Solubility	Specific Gravity
2,3-Dimethyl-2,3-butanediol	118.17	liquid	174.4	41.1	---	soluble	0.9672^{15}
1-Ethyl-1,4-cyclohexanedimethanol	172.27	---	---	---	---	---	---
1,10-Decanediol	174.28	needles	192 at (20 mm Hg)	74	---	slight	---
3,7-Dimethyl-1,7-octanediol	174.28	solid	241-242	44	---	soluble	0.919
3,6-Dimethyl-4-octyne-3,6-diol	170.25	white crystals	222	55-56	---	soluble	0.923^{20}

Table 3. Glycols Production, Use, Manufacturing Methods

Compound	Production	Use	Manufacturing Methods
2,3-Dimethyl-2,3-butanediol	1977 import: >11 thousand lb (U.S. EPA, 1980)	Production of pharmaceuticals and pesticides (Danly, 1979).	Reduction of acetone (The Merck Index, 1976), or by the electroreductive coupling of acetone (Danly, 1979).
1-Ethyl-1,4-cyclohexanedimethanol	1977 import: 1-10 thousand lb (U.S. EPA, 1980).	Not available.	Not available.
1,10-Decanediol	1977: >1 thousand lb 1977 import: 2-20 thousand lb (U.S. EPA, 1980)	Production of its esters and other organic syntheses.	Reduction of dimethyl or diethyl sebacate with sodium and ethyl alcohol (The Merck Index, 1976).
3,7-Dimethyl-1,7-octanediol	1977: >10 thousand lb (U.S. EPA, 1980)	Listed as a flavor and perfume material (USITC, 1980).	Hydration of citronellol in the presence of a strong cationic exchange (Hoffman, 1979).
3,6-Dimethyl-4-octyne-3,6-diol	Not available.	Surface-active agent; intermediate (Hawley, 1977).	Not available.

Table 4. Glycols - Manufacturers
(SRI International, 1980; Danly, 1979; U.S. EPA, 1980; USITC, 1980)

Compound	Manufacturer (Location)
2,3-Dimethyl-2,3-butanediol	Chemical Samples Co. (Franklin, OH) Diamond Shamrok (location not specified) BASF Wyandotte (location not specified)
1-Ethyl-1,4-cyclohexanedimethanol	Roure Bertrand DuPont-importer (Teaneck, NJ)
1,10-Decanediol	Southland Corp. - Fine Chem. (Great Meadows, NJ) Realco Chem. (New Brunswick, NJ) Columbia Organics (Columbia, SC)
3,7-Dimethyl-1,7-octanediol	Elan Chem. (Newark, NJ) SCM Corp. (Jacksonville, FL) Givandan Corp. (Clifton, NJ)
3,6-Dimethyl-4-octyne-3,6-diol	Air Products and Chem. (Middlesex, NJ)

III. INFORMATION PROFILES

A. 2-BUTENE-1,4-DIOL

1. Chemical Name: 2-Butene-1,4-diol

2. Chemical Structure: HO—CH_2CH=$CHCH_2$—OH

3. Synonyms: Butenediol

4. Chemical Abstract Service (CAS) Number: 110-64-5

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

   Not listed

6. Chemical and Physical Properties (cis isomer):

Description:	almost colorless, odorless liquid
Molecular Weight:	88.11
Boiling Point:	234°C
Melting Point:	11.8°C
Vapor Pressure:	---
Solubility:	very soluble in water, ethyl alcohol, and acetone; sparingly soluble in benzene
Specific Gravity:	1.070^{25}_{15}
Stability:	combustible; Flash point: 263°F

7. Production

Annual production of butenediol is judged to be on the order of one million pounds per year (SRC Estimate).

Data available from the U.S. EPA (1980) regarding producers of 2-butene-1,4-diol and production volumes are presented below:

GAF Corp. (Calvert City, KY)
Manufacturer
1977 Production: No report (confidential)

8. Use

Butenediol is used as an intermediate to produce Endosulfan (thiodan), a commercial insecticide (Hort, 1978). In 1975, 1.5 million pounds of Endosulfan were consumed domestically (Ayers and Johnson, 1976); production of

Endosulfan in 1971 was 2 million pounds (Johnson, 1972). The commercial fungicide, germicide, slimicide cis-1,4-bis (bromoacetoxy)-2-butene is made from butendiol for use in paper manufacture (Dalton et al., 1963).

Butendiol is used in the production of pyridoxine hydrochloride vitamin B_6 and small amounts of butendiol are consumed as a diol by the polymer industry (Hort, 1978).

Butenediol is also used in nickel electroplating solutions, as a reducing agent for hexavalent chromium salts in chrome tanning baths, and as a chemical intermediate (Dalton et al., 1963).

9. Manufacturers and Distributors

Butenediol is commercially manufactured by GAF Corp. in Calvert City, KY (SRI International, 1980; USITC, 1980).

Distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Aldrich Chem.	Eastern Chem.
Alfa Products	Frinton Lab.
BASF Wyandotte	MCB Reagents
Bio-Clinical Lab.	Monomer-Polymer and Dajac Lab.
Chem. Procurement Lab.	Pfaltz and Bauer
Chemsampo	Sigma Chem.
Chem Services	SPG International Chem.

10. Manufacturing Process

Butenediol is commercially manufactured by the partial hydrogenation of butynediol (Hort, 1978; Dalton et al., 1963). Suitable hydrogenation conditions can lead to either the cis- or trans-isomer formation, but the commercial product is almost entirely the cis-isomer. The hydrogenation is accomplished by pumping an aqueous butynediol solution into a reactor and pressurizing with hydrogen gas in the presence of an iron, nickel, or cobalt catalyst. The reactor product is dehydrated and distilled to yield the crude butendiol product which contains some butanediol and butynediol.

11. Impurities or Additives

Technical grade butendiol has the following specifications (Hort, 1978):

purity	95% min. (96-98% typical)
trans isomer	2-4%
moisture	0.75% max.
butanediol, butynediol	2.0% max. (<1.0% typically)
4-hydroxybutyraldehyde acetal of butenediol	---

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 2-butene-1,4-diol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 2-butene-1,4-diol were not found in the literature searched.

14. Biological Effects

Very little information concerning the potential biological effects of 2-butene-1,4-diol was available.

a. Animal Studies

(1) Acute Exposures

The LD50 for 2-butene-1,4-diol in rats by the intraperitoneal route was determined to be 0.327 to 0.330 g/kg (95% confidence limits) (Taburner and Pearce, 1974). No oral LD50 values were found in the literature searched. Administration of acutely toxic doses of 2-butene-1,4-diol to rats resulted in depression of the central nervous system (i.e., sedation, loss of motor activity), vasodilation of the extremities, diarrhea, tonic convulsions, and death within about 4 hours (Taberner and Pearce, 1974; Sprince et al., 1966). Body temperature was not depressed significantly (Taberner and Pearce, 1974).

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

Inhibition of alcohol dehydrogenase in vivo by pre-treatment of rats with pyrazole prevented the toxic effects of 2-butene-1,4-diol (Taberner and Pearce, 1974).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of 2-butene-1,4-diol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2-butene-1,4-diol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

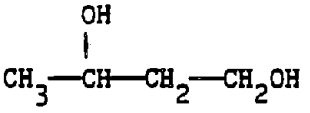
18. Other Pertinent Data

No other information that would aid in the assessment of 2-butene-1,4-diol as an occupational hazard was found in the literature searched.

B. 1,3-BUTYLENE GLYCOL

1. Chemical Name: 1,3-Butylene Glycol

2. Chemical Structure:



3. Synonyms: Butane-1,3-diol
beta-Butylene glycol
1,3-Butanediol
1,3-Dihydroxybutane

4. Chemical Abstract Service (CAS) Number: 107-88-0

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

EK0440000

6. Chemical and Physical Properties:

Description:	colorless, mildly bittersweet, viscous liquid
Molecular Weight:	90.12
Boiling Point:	207.5°C
Melting Point:	-77°C
Vapor Pressure:	0.06 mm Hg (20°C)
Solubility:	soluble in water, lower alcohols, ketones, and esters; not soluble in aliphatic hydrocarbons or most of the common chlorinated solvents
Specific Gravity:	$1.004\text{-}1.006^{20}_{20}$
Stability:	combustible; Flash point: 250°F (COC); Autoignition temp.: 741°F

7. Production

Data available from the U.S. EPA (1980) regarding producers of 1,3-butylene glycol and production volumes are presented in Table 5.

8. Uses

The most important use of 1,3-butylene glycol is in the production of esters for plasticizer use in cellulosics, poly(vinyl chloride) resins, and polyesters (Wagner, 1966, 1980). It is also used as a monomer in producing urethane polymers (Pigott, 1970).

Table 5. Producers of 1,3-Butylene Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Celanese Chemical Co. Bishop, TX	Manufacturer	10-50 million lb.
Haven Chemical Philadelphia, PA	Manufacturer	confidential
Henkel Inc. Teaneck, NJ	Importer	under 1000 lb.
Ashland Chem. Dublin, OH	Importer	none
Mitsui and Co. Houston, TX	Importer	none
Rohm and Haas Co. Philadelphia, PA	Importer	none

1,3-Butylene glycol finds some application in heavy-duty brake-fluid formulations, as a gelling agent for gelatin and similar proteins, as a gelling agent for cellulose nitrate, and as a stabilizer for pharmaceuticals (Wagner, 1966). It is also commercially used as a terminal group in oil-free alkyd resins and for deicing aircraft (Wagner, 1980).

Relatively small amounts of 1,3-butylene glycol are used in other applications. It is used as a humectant for plastic films used on foodstuffs and for tobacco and as an additive to soften and improve the pliability of reconstituted tobacco leaf. It can be used as a solvent for natural and synthetic flavoring substances used in cookies, cakes, pastries, soaps, detergents, and printing inks. Derivatives of 1,3-butylene glycol are used as jet fuel stabilizers, lubricant additives, insecticides, flameproofing agents, ether and ester stabilizers, waterproofing, and specialized solvents (Wagner, 1966, 1980).

9. Manufacturers and Distributors

SRI International (1980) and USITC (1980) list the following commercial producers of 1,3-butylene glycol:

Celanese Chem. Co.	Bishop, TX
DuPont	(location not specified)

Distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Aldrich Chem.	Fisher Sci.
Anachemia Chem.	Gallard-Schelsinger
Atomergic Chemetals	Lachat Chem.
J.T. Baker Chem.	LaPine Sci.
Bio-Clinical Lab.	George Mann and Co.
Chem. Procurement Lab.	MCB Reagents
Chemsampo	Pfaltz and Bauer
Chem Services	Polysciences Inc.
Eastern Chem.	Suburban Chem.
Eastman Kodak	Tayomenka (Amer.)
EM Lab.	Tridom Chem.
	Washine (Mallinckrodt)

10. Manufacturing Processes

1,3-Butylene glycol is commercially manufactured by the hydrogenation of acetaldol which is prepared via self-condensation of acetaldehyde. Figure 1 shows a typical hydrogenation system. The acetaldol is hydrogenated in the presence of Raney nickel or other catalysts. Low boilers are stripped from the hydrogenated product under reduced pressure. After stripping off the low-boiling substance, the residue is filtered to remove precipitated salts and catalyst, and redistilled to low pressure to give 1,3-butylene glycol. The crude diol often contains acetaldehyde, butryaldehyde, crotonaldehyde, various oligomers of the aldehydes, as well as several acetals. Steam stripping or vacuum distillation under carefully regulated conditions can largely free the glycol from them (Wagner 1966, 1980).

11. Impurities or Additives

Commercial 1,3-butylene glycol has the following specifications (Chemical Week: 1981 Buyers' Guide Issue, 1980):

purity	99.5 min. wt. %
water content	0.5 max. wt. %
acidity	0.005 max. wt. %

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 41,354 workers are potentially exposed to 1,3-butylene glycol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 1,3-butylene glycol were not found in the literature searched.

14. Biological Effects

1,3-Butylene glycol has been investigated as a specific source of dietary calories as part of the effort to develop "high nutrient density food" for manned space travel (Dymsza, 1975). (In studies with rats, 1,3-butylene

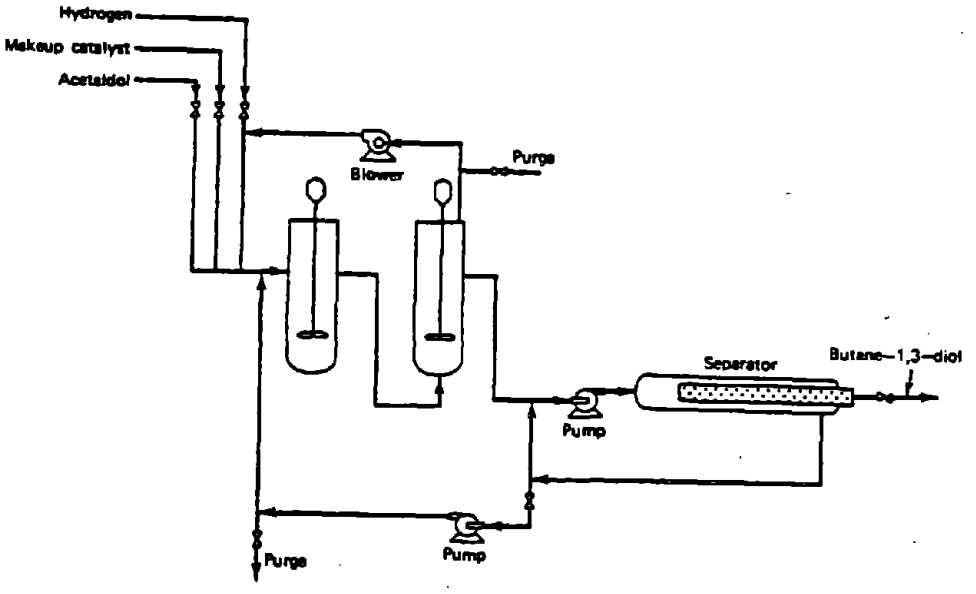


Figure 1. Hydrogenation of acetaldol to yield butane-1,3-diol (Wagner, 1980)

glycol furnished approximately 6 kcal/g of metabolizable energy (Dymsza, 1975)). 1,3-Butylene glycol is approved by the FDA for direct addition to foods as a solvent for flavors and for indirect addition to food from packaging films, adhesives, and gaskets (Miller, 1979). These potential and actual uses of 1,3-butylene glycol have prompted much of the following research on its health effects.

a. Animal Studies

(1) Acute Exposures

Lethal and irritant dose data for 1,3-butylene glycol are summarized in Table 6. The LD50 value calculated from deaths that occurred during the first 24 hours was about the same as the LD50 value calculated from deaths that occurred during the first 6 days after intraperitoneal injection, indicating a lack of significant delayed toxicity (Holman et al., 1979). Administration of sublethal doses of 1,3-butylene glycol to rats or mice resulted in decreased motor activity (Frye et al., 1981; Ayres and Isgrig, 1970), impairment of coordination (Frye et al., 1981) and equilibrium under test conditions (Ayres and Isgrig, 1970), ataxia (Majchrowicz et al., 1976; McCreery and Hunt, 1978), loss of muscle tonus (Fischer et al., 1949), hypotension (Frye et al., 1981), increased respiratory rate (Fischer et al., 1949) and ketosis (Kirsch et al., 1980). Lethal doses caused some irritation of the digestive tract (Smyth et al., 1941) and central depression of respiration and heartbeat (Bornmann, 1955). 1,3-Butylene glycol was not irritating to the eyes and skin of rabbits (Smyth et al., 1951; Carpenter and Smyth, 1946; Husing et al., 1950).

1,3-Butylene glycol, administered orally (method not specified) to male rats three times a day for 2 days and twice on the third day in doses of 5 g/kg, depressed their body weight gain and liver/body weight ratios (Hewitt and Plaa, 1979). The total dosage was 10 g/kg/day during the initial period and 15 g/kg/day during the final period.

Table 6. Acute Effects of 1,3-Butylene Glycol

Route[a]	Species	Dose[b] (g/kg)	Response[b]	Reference
oral	rats	29.57	LD50	Fischer et al., 1949
oral	rats	22.8	LD50, 14 d	Smyth et al., 1951
oral	rats	18.61	LD50, 14 d	Smyth et al., 1941
oral	mice	23.43	LD50	Fischer et al., 1949
oral	guinea pigs	11.46	LD50, 14 d	Smyth et al., 1941
inhalation	rats	saturated vapor, 8 h	No deaths	Smyth et al., 1951
i.p.	mice	11.0	LD50, 24 h	Holman et al., 1979
i.p.	mice	10.3	LD50, 6 d	Holman et al., 1979
s.c.	rats	20.16	LD50	Fishcer et al., 1949
s.c.	mice	16.59	LD50	Fischer et al., 1949
dermal	rabbits	0.01 ml (0.01 g)[c]	No irritation, 24 h	Smyth et al., 1951
ocular	rabbits	0.5 ml (0.5 g)[c]	Little or no irritation, 18-24 h	Smyth et al., 1951; Carpenter and Smyth, 1946

[a] i.p. = intraperitoneal; s.c. = subcutaneous

[b] d = day; h = hour

(2) Subchronic Exposures

Administration of 1,3-butylene glycol in the food to rats at a dosage of 5.6 g/kg/day for 90 days produced no effects on growth, "appetite," and liver or kidney weight. There were no deaths, no overt signs of toxicity, and no microscopic lesions in liver, kidney, spleen, or testis (Smyth et al., 1951).

Miller and Dymsza (1967) investigated the potential value of 1,3-butylene glycol as a source of dietary energy in experiments with rats. The animals were fed high fat diets (25-30% fat) containing 0, 5, 10, 20, or 30% 1,3-butylene glycol. The diets were made isocaloric by adjusting the carbohydrate content. In short-term tests of 3 to 4 weeks, rats fed 10% 1,3-butylene glycol or more consumed significantly less food than did controls; weight gain was significantly decreased by 20% 1,3-butylene glycol. Pair feeding or force pair feeding eliminated differences in body weight gain except during the first week, which appeared to be a period of adaptation. In a long-term test (30 weeks, ad libitum feeding) weight gain was slightly depressed by 20% and statistically significantly depressed by 30% 1,3-butylene glycol. No change in mortality, relative liver or kidney weights, or ketone bodies (concentration in serum, total 18-hour excretion in urine) was associated with either level of treatment.

Similar experiments employing a diet lower in fat content (5% fat) were performed by Romsos et al. (1974). Rats fed a diet in which 18% of the calories were contributed by 1,3-butylene glycol had no statistically significant effects on food consumption, weight gain, the weight and fat content of the liver, and the weight of the epididymal fat pad at the end of 23 days.

Administration of very high levels of 1,3-butylene glycol (16 to 22 g/kg/day based on food consumption) to rats in a "nutritionally

complete liquid diet" for 12 days resulted in signs of hyperexcitably during withdrawal of the chemical that were characteristic of physical dependence, according to Frye et al. (1981). Based on observed food consumption, the rats (N=9) received 180 to 240 mmole/kg/day (16 to 22 g/kg/day) of 1,3-butylene glycol. The glycol replaced dextrose isocalorically. Hyperexcitability was assessed during the first 27.5 hours after the glycol was removed from the diet by monitoring the rats' susceptibility to tremors when lifted vertically by the tail and their susceptibility to audiogenic seizures. During the withdrawal period, the hyperexcitability of glycol-treated rats was similar to that of ethanol-treated rats in the same experiment (Frye et al., 1981).

(3) Chronic Exposures

Scala and Paynter (1967) have performed chronic feeding studies with rats and dogs. Weanling Sprague-Dawley rats (30 males and 30 females/dosage level) were fed diets containing 1.0, 3.0, or 10% 1,3-butanediol for 2 years. Controls (60 males and 60 females) received the same laboratory chow minus the glycol. Observations, made at intervals throughout the experiment, included body weight, food consumption, hematologic measurements, and urinalysis. Autopsies, performed on ten rats from each group at one year and on surviving rats at 2 years, included histopathologic evaluation of brain, endocrine glands, gastrointestinal tract, lung, heart, liver, spleen, kidney, bone, bone marrow, and gonads. No effects attributable to the treatment were observed. Survival (≈10% at 2 years) was unaffected.

Dogs, treated and observed similarly, also had no effects attributable to 1,3-butylene glycol; no deaths occurred (Scala and Paynter, 1967). The dogs (4 males and 4 females/group) received 0, 0.5, 1.0, or 3.0% 1,3-butylene glycol in their diet for 2 years. In addition to the parameters observed for rats, sedimentation rate, blood urea nitrogen, and bromosulphalein retention were measured and found to be unaffected.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

Dominant lethal and cytogenetic testing of 1,3-butylene glycol in rats was apparently negative (Food and Drug Research Laboratories, 1973), but further details of these studies were not available for evaluation.

(6) Teratogenicity

1,3-Butylene glycol was apparently not teratogenic to rats, dogs or rabbits (Food and Drug Research Laboratories, 1973), but further details of these studies were not available for evaluation.

(7) Reproductive Effects

As described in the section on Subchronic Exposures, male rats that received 5.60 g/kg/day of 1,3-butanediol for 90 days had no histological lesions in their testes (Smyth et al., 1951). In the chronic exposure studies of Scala and Paynter (1967), male and female rats and dogs given 1,3-butylene glycol in their food for 2 years had no histopathologic effects on their gonads; these studies were discussed more fully in the Chronic Exposure section.

A gradual decrease in reproductive rate occurred in a multigeneration study with rats fed 5, 10, or 24% 1,3-butanediol in the diet (Food and Drug Research Laboratories, 1973). Results of this study have not been published, but Miller (1979) noted that the data do not show a dose-response and that no indication of statistical significance was given.

Abstracts of two papers from the German literature (Meyer, 1951; Meyer and Shurmeyer, 1951) indicate that long-term oral administration of 1,3-butylene glycol to rats did not affect their fertility or their offspring. The abstracts gave no details and the papers were not readily available.

(8) Other Relevant Information

As reviewed by Miller (1979), 1,3-butylene glycol is thought to be oxidatively metabolized via β-hydroxybutyrate and acetoacetate. The ketone bodies produced by administration of 1,3-butylene glycol (see Acute and Subchronic sections) are, at least in part, metabolities of the glycol. (Ketone bodies can also arise from increase fatty acid metabolism.)

Experiments with rats indicate that 1,3-butylene glycol may potentiate the hepatotoxicity of carbon tetrachloride (Hewitt and Plaa, 1979). Hewitt and Plaa (1979) postulated that the ketone bodies produced from this glycol in the liver were responsible for this effect.

Mehlman and coworkers (Mehlman et al., 1966, 1970; Mehlman and Veech, 1972; Stoewsand et al., 1966) performed a series of experiments investigating the effect of 1,3-butylene glycol on various biochemical parameters associated with lipid and carbohydrate metabolism. The results of these experiments are ambiguous, however, because 1,3-butylene glycol was fed in the diet at a level that significantly decreased the rats' food consumption and weight gain; control rats were not pair fed. The biochemical changes observed in these studies were similar to those resulting from mild starvation (Mehlman and Veech, 1972).

In the experiments of Romsos et al. (1974) described in the Subchronic Exposures section, the feeding of 1,3-butylene glycol to rats as 18% of the caloric content of their food for 23 days had no effect on the concentration of free fatty acids in the plasma. Plasma glucose and triglyceride concentrations were significantly decreased, however, as compared to those of controls fed an isocaloric diet. In the study of Miller and Dymsza (1967), also described in the Subchronic Exposures section, rats fed high fat diets containing 30% butylene glycol for 30 weeks had concentrations of glycogen in their livers than were higher than those of controls fed an isocaloric high fat diet.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

In short-term studies with volunteers maintained in negative nitrogen and energy balance, isocaloric substitution of 1,3-butylene glycol for part of the starch content of the diet had no effect on hemotologic values or blood clinical chemistry values including protein and serum enzyme levels (Tobin et al., 1975). Similar results were obtained when subjects ingested 40 g/day of 1,3-butylene glycol (or sucrose) once a day after breakfast (Tobin et al., 1975). No evidence of toxic reactions was observed in either experiment.

As reviewed by Miller (1979), 1,3-butylene glycol was nonirritating to human skin when applied repeatedly over a period of at least 16 days and had a low potential for sensitization.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of 1,3-butylene glycol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 1,3-butylene glycol were found.

17. Sources of Additional Relevant Information

The Food and Drug Research Laboratories (1973) has performed studies of the potential teratogenic, reproductive, and mutagenic effects of 1,3-butylene glycol in experimental animals. The results of these studies have not been published, but are summarized in a review by Miller (1979). This summary is insufficient to allow an evaluation of the results; the data from this summary are presented in the appropriate sections of this profile.

18. Other Pertinent Data

In short-term studies with human subjects maintained in negative nitrogen and energy balance, isocaloric substitution of 1,3-butylene glycol for part of the starch content of the diet improved the nitrogen balance significantly (i.e., made it less negative) (Tobin et al., 1975). The authors suggested that these results indicate that butylene glycol provided calories that could substitute for those previously obtained from dietary protein. 1,3-Butylene glycol contributed approximately 5% of the caloric intake in this study. No increase in the concentration of ketone bodies in the blood was observed. Blood glucose levels (fasting) were significantly decreased during periods of 1,3-butylene glycol ingestion. Results of a subsequent study, in which human subjects ingested 40 g/day of 1,3-butylene glycol (or sucrose) once a day after breakfast, showed no effect of the glycol on fasting blood glucose levels (Tobin et al., 1975).

C. 1,4-BUTYLENE GLYCOL

1. Chemical Name: 1,4-Butylene Glycol

2. Chemical Structure: $HO-CH_2-CH_2-CH_2-CH_2-OH$

3. Synonyms: Butanediol
1,4-Butanediol
Butane-1,4-diol
1,4-Dihydroxybutane
1,4-Tetramethylene glycol

4. Chemical Abstracts Service (CAS) Number: 110-63-4

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

EK0525000

6. Chemical and Physical Properties:

Description:	viscous, colorless, and odorless liquid
Molecular Weight:	90.12
Boiling Point:	228°C
Melting Point:	20.1°C
Vapor Pressure:	---
Solubility:	completely soluble in water; soluble in alcohol; slightly soluble in ether
Specific Gravity:	1.0154_4^{25}
Stability:	combustible Flash point (closed cup): 385°F

7. Production

The USITC does not list production data for 1,4-butylene glycol. Estimates of plant capacities are discussed in Section 9.

Data available from the U.S. EPA (1980) regarding producers of 1,4-butylene glycol and production volumes are presented in Table 7.

8. Use

The following tabulation presents the percentage of the total amount of 1,4-butylene glycol produced that is used in each of the applications listed (Miller, 1979):

Table 7. Producers of 1,4-Butylene Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Haven Chemical		
Philadelphia, PA	Manufacturer	0.1-1 million lb.
BASF Wyandotte		
Geismar, LA	Manufacturer	10-50 million lb.
Parsippany, NJ	Importer	10-50 million lb.
Morton Chemical		
Ringwood, IL	Manufacturer	1-10 thousand lb.
GAF Corp.		
Calvert City, KY	Manufacturer	confidential
Texas City, TX	Manufacturer	confidential
DuPont		
LaPorte, TX	Manufacturer	100-500 million lb.
Uniroyal Chem.		
Naugatuck, CT	Importer-Not Distributed	10-100 thousand lb.
Thorson Chemical		
New York City, NY	Importer	under 1000 lb.
Steuber Co.		
New York City, NY	Importer	0.1-1 million lb.
Plant Site Not Listed		
	Manufacturer-Not Distributed	1-10 million lb.
	Manufacturer	confidential

	Percentage of Total
Tetrahydrofuran manufacture	57
Acetylenic chemicals	25
Polyurethanes	9
Polybutylene terephthalate	7
Miscellaneous	1

9. Manufacturers and Distributors

The major manufacturers of 1,4-butylene glycol and their estimated annual capacities are shown in the following tabulation (SRI International, 1980):

	Estimated Annual Capacity (Millions of Pounds)
BASF Wyandotte Corp.	
Geismar, LA	55
DuPont	
LaPorte, TX	210
GAF Corp.	
Calvert City, KY	
Texas City, TX	115
TOTAL	380

In addition to the manufacturers, the distributors of 1,4-butylene glycol include (Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Aldrich Chem.	Eastern Chem.
Alfa Prod.	Eastman Kodak
Anachemia Chem.	EM Lab.
Atomergic Chemetals	Fisher Sci.
J.T. Baker Chem.	Gallard-Schelsinger
Bio-Clinical Lab.	ICN/K and K
Chemical Dynamics	Lachat Chem.
Chem. Procurement Lab.	MCB Reagents
Chemsampo	Pfaltz and Bauer
Chem. Services	SPG International Chem.
	Tridom Chem.

10. Manufacturing Processes

1,4-Butylene glycol is manufactured by the condensation of acetylene with formaldehyde via cupric acetylide catalysts. The copper acetylide formed by the reaction of acetylene with copper salts is allowed to react with formaldehyde under a pressure of 5-15 atmospheres and a temperature of

90-100°C. The butynediol formed with 95% yield is hydrogenated as Raney nickel catalyst at 40-120°C and 75-300 psig to give a 85-90% yield of 1,4-butylene glycol. Alternate feedstocks for 1,4-butylene glycol including maleic anhydride, propylene, and butadiene have been proposed but have not been used commercially in the United States.

11. Impurities or Additives

Two grades of 1,4-butylene glycol are available commercially: technical and anhydrous. The typical analyses of technical and anhydrous grades is shown below (Miller, 1966, 1979; Freifeld and Hort, 1966):

1,4-Butylene glycol	97 to 98.5%
Water	< 0.03% (anhydrous)
	< 0.15% (technical)
Butanediol	< 0.05%
Ash	0%
Odor	almost odorless
Carbonyl no., mg KOH/g	1.0

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 21,166 workers are potentially exposed to 1,4-butylene glycol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 1,4-butylene glycol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Lethal and irritant dose data for 1,4-butylene glycol are summarized in Table 8. LD50 values were the same whether calculated for a 24-hour or a 6-day observation period after intraperitoneal injection (i.e., all deaths occurred during the first 24 hours), indicating a lack of delayed toxicity (Holman et al., 1979). Administration of acutely toxic doses of 1,4-butylene

Table 8. Acute Effects of 1,4-Butylene Glycol

Route	Species	Dose (g/kg)	Response[b]	Reference
oral	rats	2	LD50	General Aniline and Film, 1964
oral	rats	1.78	LD50	Dow Chemical, n.d.
oral	rats	1.525	LD50, 2 d	Knyshova, 1968
oral	mice	2.14	LD50	Dow Chemical, n.d.
oral	mice	2.17	LD50	Fischer et al., 1949
oral	mice	2.062	LD50, 2 d	Knyshova, 1968
oral	rabbits	2.531	LD50, 2 d	Knyshova, 1968
oral	guinea pigs	2	LD50	General Aniline and Film, 1964
oral	guinea pigs	1.200	LD50, 2 d	Knyshova, 1968
i.p.[a]	rats	1.370	LD50	Zabik et al., 1973
i.p.	rats	1.07	LD50, 18 h	Taberner and Pearce, 1974
i.p.	mice	1.65	LD50, both 24 h and 6 d	Holman et al., 1979
dermal	rabbits	not stated	No irritation; no evidence of absorption of toxic amounts	Dow Chemical, n.d.
ocular	rabbits	not stated	Mild irritation	Dow Chemical, n.d.

[a] i.p. = intraperitoneal.

[b] d = day; h = hour.

glycol to experimental animals resulted in rapid depression of the central nervous system (General Aniline and Film, 1964; Hinrichs et al., 1948; Holman et al., 1979; Menon et al., 1973; Roth and Giarman, 1968; Sprince et al., 1966; Taberner and Pearce, 1974); akinesia, rigidity, and exophthalmos (Menon et al., 1973); hypothermia (Menon et al., 1973; Taberner and Pearce, 1974); marked bradycardia, analgesia, and dsypnea (Taberner and Pearce, 1974; Hinrichs et al., 1948); and hyperemia of the visible mucosa, internal organs, and brain (Knyshova, 1968). Death was attributed to respiratory failure (Taberner and Pearce, 1974) or "paralysis of the vital centers" (Hinrichs et al., 1948). Hinrichs et al. (1948) reported that administration of 1,4-butylene glycol to animals caused severe nephrosis and degenerative changes in the hepatic parenchymal cells. According to General Aniline and Film (1964), rats and guinea pigs that survived acutely toxic doses of 1,4-butylene glycol recovered completely.

When topically applied, 1,4-butylene glycol was mildly irritating to the eyes and nonirritating to the skin of rabbits (Dow Chemical, n.d.). Application of this glycol to the skin has been variously reported as producing no evidence of systemic toxicity (Dow Chemical, n.d.) and as being highly toxic (Schneider, 1950).

(2) Subchronic Exposures

Zabik et al. (1973) reported that daily intraperitoneal administration of 1000 mg/kg 1,4-butylene glycol to adult male rats for 10 days slightly depressed weight gain; 500 mg/kg did not.

Rats (N=6) that consumed 30 mg/kg 1,4-butylene glycol (per day?) for 6 months were no different from controls in weight gain, behavior, general condition or hemotologic values. The treated animals formed conditioned reflexes more slowly than did controls, however, and had a longer latent period before responding to the stimulus. Histological changes in the cerebrum of treated animals included a reduction in the content of Nissl bodies and the

growth of glial elements. Fatty changes and areas of sclerosis were observed in the livers of treated animals (Knyshova, 1968).

Administration of 0.5% 1,4-butylene glycol in the drinking water to 4 adult Sprague-Dawley rats caused a transient loss in weight during weeks 7 and 8 of treatment, followed by slow growth. At the end of 10 weeks of treatment, tissues from the central and peripheral nervous systems of these treated animals were no different histologically from the corresponding tissues from controls. No other tissues were examined (Spencer et al., 1978).

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

The effects of 1,4-butylene glycol on the central nervous system are thought to be mediated through its metabolite, gamma-hydroxybutyric acid (Taberner and Pearce, 1974).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

According to Hinrichs et al. (1948), oral or rectal administration of 15 to 30 g (0.210 to 0.420 g/kg) of 1,4-butylene glycol as a

purgative rapidly caused unconsciousness, constriction of the pupils, and absence of reflexes in 7 patients, 2 of whom died. Death resulted from "paralysis of the vital centers." The survivors experienced severe headaches after regaining consciousness.

(3) Target Organ Toxicity

Hinrichs et al. (1948) reported that autopsy of 1 of the 2 patients who died from treatment with 1,4-butylene glycol revealed severe edema of the brain, acute tracheobronchitis, bronchopneumonia, acute splenitis, "turbidity" of the parenchymal organs and heart muscle, and hemorrhage of the mucosal lining of the stomach. The dosage and other effects were described in the Health Effects section.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of 1,4-butylene glycol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 1,4-butylene glycol were found.

17. Sources of Additional Relevant Information

The chemistry, environmental aspects, and health effects of 1,4-butylene glycol have been reviewed by Miller (1979).

18. Other Pertinent Data

No other information that would aid in the assessment of 1,4-butylene glycol as an occupational hazard was found in the literature searched.

D. 2-BUTYNE-1,4-DIOL

1. Chemical Name: 2-Butyne-1,4-diol

2. Chemical Structure: $HOCH_2 \equiv CH_2OH$

3. Synonyms: Butynediol
1,4-Butynediol

4. Chemical Abstract Service (CAS) Number: 110-65-6

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

ES0525000

6. Chemical and Physical Properties:

Description:	white orthorhombic crystals
Molecular Weight:	86.09
Boiling Point:	248°C
Melting Point:	58°C
Vapor Pressure:	---
Solubility:	in g/100 ml solvent (25°C): water - 374 ethanol - 83 acetone - 70 ether 2.6 benzene - 0.04
Specific Gravity:	1.114_4^{60}
Stability:	combustible; Flash point: 152°C (TOC)

7. Production

Most butynediol is used to manufacture 1,4-butanediol and butenediol (Hort, 1978). Current domestic capacity to produce 1,4-butanediol is 380 million pounds per year (SRI International, 1980).

In 1974, roughly 6 to 8 million pounds of butynediol were consumed for purposes other than 1,4-butanediol production (McGreevy, 1975).

Data available from the U.S. EPA (1980) regarding producers of 2-butyne-1,4-diol and production volumes are presented in Table 9.

Table 9. Producers of 2-Butyne-1,4-diol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
BASF Wyandotte		
Geismar, LA	Manufacturer	10-50 million lb.
Parsippany, NJ	Importer	10-100 thousand lb.
GAF Corp.		
Calvert City, KY	Manufacturer	confidential
Texas City, TX	Manufacturer	confidential
DuPont		
LaPorte, TX	Manufacturer	100-500 million lb.
Aceto Chem.		
Flushing, NY	Importer	none

8. Use

Most butynediol produced is consumed domestically, at plant-site, for manufacturing butanediol and butenediol. Small amounts are also coverted to ethers (Hort, 1978).

Butynediol is used to produce the wild oat herbicide Carbyne (Hort, 1978). In 1975, 0.4 million pounds of this herbicide were used domestically (Ayers et al., 1976).

Butynediol is also used in plating and pickling baths (Hort, 1978), as a corrosion inhibitor, as a polymerization accelerator, as a stabilizer for chlorinated hydrocarbons, and as a cosolvent for paint and varnish removal (Hawley, 1977).

9. Manufacturers and Distributors

2-Butyne-1,4-diol is manufactured by (SRI International 1980; USITC, 1980; Hort, 1978):

BASF Wyandotte	Geismar, LA
DuPont	LaPorte, TX
GAF Corp.	Calvert City, KY
	Texas City, TX

In addition to the manufacturers, the distributors include:

Aldrich Chem.	EM Lab
Alfa International	Fisher Sci.
Anachemica Chem.	ICN/K and K
Atomergic Chemetals	Lachat Chem.
Bio-Clinical Lab.	MCB Reagents
Chem. Procurement Lab.	Pfaltz and Bauer
Chem Services	SPG Intl Chem.
Eastman Kodak	Tridom Chem.

10. Manufacturing Processes

Butynediol is commercially manufactured by formaldehyde ethynylation processes (Hort, 1978). In these types of processes, an aqueous solution of formaldehyde and gaseous acetylene are passed through one or more reactors in the

presence of a copper acetylide catalyst. Yields of butynediol can be over 90% with 4-5% of propargyl alcohol formed as a coproduct.

11. Impurities or Additives

Butynediol is available commercially as a 35% aqueous solution specified as 34.0% minimum butynediol with propargyl alcohol limited to 0.2% and formaldehyde to 0.7%.

The commercial flake butynediol is specified as 96.0% minimum purity, with 2% moisture (maximum) content (Hort, 1978).

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 2,175 workers are potentially exposed to 2-butyne-1,4-diol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 2-butyne-1,4-diol were not found in the literature searched.

14. Biological Effects

Little information concerning the potential biological effects of 2-butyne-1,4-diol was available.

a. Animal Studies

(1) Acute Exposures

Lethal dose data for 2-butyne-1,4-diol are summarized in Table 10. No data concerning irritancy were found in the literature searched. Administration of acutely toxic doses of 2-butyne-1,4-diol to experimental animals resulted in signs of depression of the central nervous system (i.e., sedation, loss of motor activity), accelerated breathing, coughing, moist rales, salivation, diarrhea, piloerection, vasodilation of the extremities, hyperemia of the internal organs and brain, marked hypothermia, and death (Tabefner and Pearce, 1974; Knyshova, 1968; Sprince et al., 1966).

Table 10. Acute Effects of 2-Butyne-1,4-diol

Route	Species	Dose (g/kg)	Response[a]	Reference
oral	rats	0.329	LD50, 18 h	Taberner and Pearce, 1974
oral	rats	0.105	LD50, 2 d	Knyshova, 1968
oral	mice	0.105	LD50, 2 d	Knyshova, 1968
oral	rabbits	0.150	LD50, 2 d	Knyshova, 1968
oral	guinea pigs	0.130	LD50, 2 d	Knyshova, 1968

[a] d = day; h = hour

(2) Subchronic Exposures

Knyshova (1968) reported that rats (6) treated with 2 mg/kg 2-butyne-1,4-diol (per day?) for 6 months did not differ from controls in weight gain, behavior, general condition, or hematologic values. The treated animals formed conditioned reflexes more slowly than did controls, however, and had a longer latent period before responding to the stimulus. Histological changes in the cerebrum of treated animals included a reduction in the content of Nissl bodies and the growth of glial elements. Fatty changes and areas of sclerosis were noted in the livers of treated animals.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

Inhibition of alcohol dehydrogenase <u>in vivo</u> by pretreatment of rats with pyrazole prevented the toxic effects of 2-butyne-1,4-diol (Taberner and Pearce, 1974). Hence, the toxicity of 2-butyne-1,4-diol appears to stem from its oxidized metabolites rather than from the parent compound.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of 2-butyne-1,4-diol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2-butyne-1,4-diol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

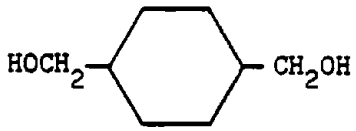
18. Other Pertinent Data

No other information that would aid in the assessment of 2-butyne-1,4-diol as an occupational hazard was found in the literature searched.

E. 1,4-CYCLOHEXANEDIMETHANOL

1. Chemical Name: 1,4-Cyclohexanedimethanol

2. Chemical Structure:



3. Synonyms: CHDM
1,4-CHIDM
1,4-Cyclohexylenedimethanol
1,4-Dimethylolcyclohexane
1,4-Bis-(hydroxymethyl)cyclohexane

4. Chemical Abstract Service (CAS) Number: 105-08-8

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

GU9800000

6. Chemical and Physical Properties:

Description:	white waxy solid
Molecular Weight:	144.24
Boiling Point:	286°C
Melting Point:	45-50°C
Vapor Pressure:	---
Solubility:	miscible with water and low molecular weight alcohols; appreciably soluble in acetone; negligible solubility in hydrocarbons and diethyl ether.
Specific Gravity:	1.150 density (20°C)
Stability:	combustible; Flash point: 330°F (COC)

7. Production

Data available from the U.S. EPA (1980) regarding producers of 1,4-cyclohexanedimethanol and production volumes are presented below:

Tennessee Eastman Co. (Kingsport, TN)
Manufacturer
1977 Production: 10 to 50 million lb

Morton Chem. (Ringwood, IL)
Manufacturer
1977 Production: 1 to 10 thousand lb

8. Use

The most important application for 1,4-cyclohexanedimethanol is in the manufacture of linear polyesters for use as polyester fibers such as the Kodel polyester fibers (Bramer and Davis, 1980).

1,4-Cyclohexanedimethanol is commercially important in the manufacture of polyurethane foams. It also has uses in the manufacture of polyformals for lubricants and hydraulic fluid, in antiopacity agents for paper (Bramer and Davis, 1980), and in reduction of reaction time in esterifications (Hawley, 1977).

9. Manufacturers and Distributors

SRI International (1980) and USITC (1980) list Tenessee Eastman in Kingsport, TN as the only manufacturer. The U.S. EPA (1980) also lists Morton Chem. as a manufacturer.

Distributors include (Chem Sources--USA, 1980):

Aldrich Chem.	Fisher Sci.
Chem. Procurement Lab.	ICN/K and K
Chem. Services	MCB Reagents
Eastman Kodak	Pfaltz and Bauer

10. Manufacturing Processes

1,4-Cyclohexanedimethanol is manufactured by the catalytic hydrogenation under pressure of dimethyl terephthalate in a methanol solution (Bramer and Davis, 1980; Frey and Soder, 1975).

11. Impurities or Additives

Commercial grade 1,4-cyclohexanedimethanol assays at a 99 wt. % minimum (Bramer and Davis, 1980).

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 1,372 workers are potentially exposed to 1,4-cyclohexanedimethanol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 1,4-cyclohexanedimethanol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Lethal and irritant dose data for 1,4-cyclohexanedimethanol are summarized in Table 11. These data are derived primarily from toxicity studies conducted by the Health, Safety, and Human Factors Laboratory of the Eastman Kodak Company (Eastman Chemical Products, 1981a). 1,4-cyclohexanedimethanol was only slightly irritating to the skin and eyes of rabbits and did not produce sensitization reactions during a standarized sensitization test with guinea pigs (Eastman Chemical Products, 1981a). No other information on the effects of acute exposure to 1,4-cyclohexanedimethanol was found in the literature searched.

(2) Subchronic Exposures

When fed to rats at levels of 0.1 or 1% in the diet for 36 days, 1,4-cyclohexanedimethanol had no effect on food consumption, weight gain, behavior, hematologic or serum chemistry values, or relative and absolute liver and kidney weights. No gross pathologic or histopathologic changes were observed in the tissues (Eastman Chemical Products, 1981a).

Exposure of rats to vapor concentrations of 180 to 500 ppm 1,4-cyclohexanedimethanol, 6 hours a day for 10 days, produced no deaths. Examination of these rats 14 days after termination of exposure revealed no histopathological effects attributable to exposure (Eastman Chemical Products, 1981a).

Table 11. Acute Effects of 1,4-Cyclohexanedimethanol

Route[a]	Species	Dose[b] (g/kg)	Response	Reference
oral	rats	3.2-6.4 (10% in water)	LD_{50}	Eastman Chemical Products, 1981a
oral	rats	1.6-3.2 (20% in water)	LD_{50}	Eastman Chemical Products, 1981a
oral	mice	1.6-3.2 (10% or 20% in water)	LD_{50}	Eastman Chemical Products, 1981a
oral	guinea pigs	0.80-1.6	LD_{50}	Eastman Chemical Products, 1981a
i.p.	rats	0.8	LDLo	Deichman and Gerarde, 1969
i.p.	mice	1.6	LDLo	Deichman and Gerarde, 1969
dermal	guinea pigs	Solid compound moistened with water or methanol; or 20% solution in acetone and water; 24 h	Mild irritation	Eastman Chemical Products, 1981a
ocular	rabbits	Not stated	Mild irritation	Eastman Chemical Products, 1981a

[a] i.p. = intraperitoneal

[b] d = day

Daily application of 1,4-cyclohexanedimethanol to the uncovered skin of guinea pigs for 10 days did not produce greater irritation than had been observed with a single application (Eastman Chemical Products, 1981a).

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

1,4-Cyclohexanedimethanol was not mutagenic in the Ames Salmonella assay (tester strains not stated), with or without activation (Eastman Chemical Products, 1981b).

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

After oral administration to rats, 1,4-cyclohexanedimethanol was rapidly absorbed, metabolized, and excreted in the urine. The major urinary metabolite was cyclohexanedicarboxylic acid (70% of dose). The remainder of the dose was excreted primarily in the form of 4-hydroxymethylcyclohexanecarboxylic acid (Divincenzo and Ziegler, 1980).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of 1,4-cyclohexanedimethanol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 1,4-cyclohexanedimethanol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of 1,4-cyclohexanedimethanol as an occupational hazard was found in the literature searched.

F. DIETHYLENE GLYCOL

1. Chemical Name: Diethylene Glycol

2. Chemical Structure: $HO-CH_2-CH_2-O-CH_2-CH_2-OH$

3. Synonyms: Dicol
Diglycol
beta, beta'-Dihydroxydiethyl ether
Ethanol, 2,2' oxydi-
Ethylene diglycol
Glycol ether
Glycol ethyl ether
bis(2-Hydroxyethyl)ether
3-Oxapentane-1,5-diol
3-Oxa-1,5-pentanediol
2,2'-Oxybisethanol
2,2'-Oxydiethanol

4. Chemical Abstracts Service (CAS) Number: 111-46-6

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

ID5950000

6. Chemical and Physical Properties:

Description:	colorless, odorless liquid with sharp sweet taste
Molecular Weight:	106.12
Boiling Point:	244-245°C
Melting Point:	-6.5°≈C
Vapor Pressure:	1.0 mm Hg (at 91.8°C)
Solubility:	complete in water, alcohol, ether, acetone; insoluble in benzene and carbon tetrachlorid
Specific Gravity:	1.118^{20}_{20}
Stability:	combustible; Flash point (open cup): 280°F

7. Production

Production in recent years is as follows (USITC, 1977, 1978, 1979, 1980):

Year	Production (in millions of pounds)
1979	393
1978	372
1977	327
1976	276

CMR (1979a) projects future growth of diethylene glycol to be 4% per year through 1983.

Data available from the U.S. EPA (1980) regarding producers of diethylene glycol and production volumes are presented in Table 12.

8. Use

The following tabulation presents the percentage of the total amount of diethylene glycol produced that is used in each of the applications listed (CMR, 1979a):

	Percentage of Total
Polyurethane and unsaturated polyester resins	35
Triethylene glycol	13
Morpholine	8
Natural gas dehydration	7
Textile agents	6
"Udex" extraction solvent	6
Dioxane	6
Antifreeze blending	5
Exports	5
Miscellaneous	9

9. Manufacturers and Distributors

The manufacturers of diethylene glycol and their estimated capacities are given in Table 13. There are nearly 100 commercial distributors of diethylene glycol.

10. Manufacturing Processes

Diethylene glycol is normally a coproduct in the production of ethylene glycol. The proportion of diethylene glycol produced is controlled by the molar ratio of ethylene oxide to water, with greater amounts of the poly-

Table 12. Producers of Diethylene Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Olin Corp.		
Brandenburg, KY	Manufacturer	0.1-1 million lb
Dow Chemical		
Freeport, TX	Manufacturer	10-50 million lb
Plaquemine, LA	Manufacturer	10-50 million lb
Midland, MI	Importer	1-10 million lb
Fiber Industries Inc.		
Salisbury, NC	Manufacturer	1-10 million lb
Florence, NC	Manufacturer	1-10 million lb
Shelby, NC	Manufacturer	0.1-1 million lb
PPG Industries		
Beaumont, TX	Manufacturer	1-10 million lb
Ponce, PR	Manufacturer	10-50 million lb
Haven Chemical		
Philadelphia, PA	Manufacturer	confidential
Texas Eastman		
Longview, TX	Manufacturer	10-50 million lb
Union Carbide		
Institute, WV	Manufacturer	confidential
Hahnville, LA	Manufacturer	confidential
Ponce, PR	Manufacturer	10-50 million lb
Port Lavaca, TX	Manufacturer	confidential
Shell Chemical		
Geismar, LA	Manufacturer	1-10 million lb
Morganton Plant		
Morganton, NC	Manufacturer	1-10 thousand lb
Northern Petrochemicals		
Morris, IL	Manufacturer	10-50 million lb
BASF Wyandotte		
Geismar, LA	Manufacturer	10-50 million lb
March Chemical		
Denham Springs, LA	Manufacturer	10-100 thousand lb
Hercofina-NC		
Wilmington, NC	Manufacturer	confidential
Celanese Chemical		
Pasadena, TX	Manufacturer	10-50 million lb
Calumet Refining Co.		
Princeton, KA	Manufacturer	none

Table 12. Producers of Diethylene Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Chemical Exchange Co.		
Baytown, TX	Manufacturer	1-10 thousand lb
Houston, TX	Manufacturer	1-10 million lb
Dixie Chemical		
Pasadena, TX	Manufacturer	confidential
Jefferson Chemical		
Port Nechos, TX	Manufacturer	confidential
United Mineral and Chem.		
New York City, NY	Importer	under 1000 lb
Nissho-Iwai Amer.		
New York City, NY	Importer	10-50 million lb
Henkel Inc.		
Teaneck, NJ	Importer	under 1000 lb
Esselen Assoc.		
Stamford, CT	Importer	none
EM Laboratories		
Elmsford, NY	Importer	confidential
Milijac Inc.		
---, CT	Importer	none
Synarome, Corp.		
New York City, NY	Importer	under 1000 lb
Struktol Co.		
Akron, OH	Importer	confidential
Sandoz Color and Chem.		
East Hanover, NJ	Importer	none
Superior Materials		
New York City, NY	Importer	under 1000 lb
Sakai Trading Co.		
New York City, NY	Importer	none
Steuber Co.		
New York City, NY	Importer	none
Montedison USA		
New York City, NY	Importer	none
Mitsubishi International		
New York City, NY	Importer	1-10 million lb
Roure Bertrand DuPont		
Teaneck, NJ	Importer	under 1000 lb

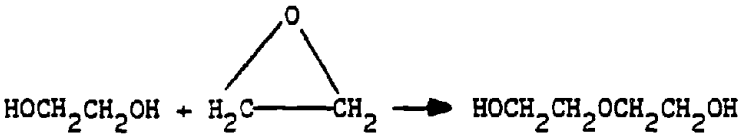
Table 12. Producers of Diethylene Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Proprietary Perfumes Lmt. Maywood, NJ	Importer	under 2000 lb
Ciba-Geigy Corp. Ardsley, NJ	Importer	none
Itah and Co. New York City, NY	Importer	10-100 thousand lb
ICI Americas Wilmington, DC	Importer	confidential
Harper Corp. of Amer. Charlotte, NC	Importer	10-100 thousand lb
Davos Chem. Corp. Fort Lee, NJ	Importer	none

Table 13. Producers of Ethylene Oxide and Estimated Production Ranges

Producer and Location	Estimated Annual Capacity (Millions of Pounds) (SRI International, 1980)	(CMR, 1979a)
BASF Wyandotte Corp.		
Geismar, LA	25	35
Celanese Corp.		
Clear Lake, TX	24	45
Dow Chem. Co.		
Freeport, TX	40	75
Plaquemine, LA	45	
Eastman Kodak Co.		
Longview, TX	18	18
Northern Natural Gas Co.		
Morris, IL	21	15
Olin Corp.		
Brandenburg, KY	10	--
PPG Industries, Inc.		
Beaumont, TX	18	18
Shell Chem. Co.		
Geismar, LA	10	25
Texaco, Inc.		
Post Neches, TX	36	80
Union Carbide Corp.		
Seadrift, TX Taft, LA Texas City, TX Penuelas, PR	215	215
TOTAL	462	526

glycols being produced at higher molar ratios of ethylene oxide to water. Although rarely done commercially, diethylene glycol can be produced from ethylene glycol as follows:



$$HOCH_2CH_2OH + H_2C\!-\!O\!-\!CH_2 \longrightarrow HOCH_2CH_2OCH_2CH_2OH$$

11. Impurities or Additives

Because the manufacturing process for diethylene glycol is similar to that for ethylene glycol, impurities similar to those found in ethylene glycol can be expected in commercially produced diethylene glycol. Specifications for commercial diethylene glycol include a minimum purity of 99 wt. % with 0.005 wt. % max. of acidity, 0.2 wt. % max. water, 0.005 wt. % ash, and 0.2 wt. % max. ethylene glycol (Union Carbide, 1978).

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 660,368 workers are potentially exposed to diethylene glycol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to diethylene glycol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

The acute toxic effects of diethylene glycol are summarized in Table 14. Administration of lethal doses of diethylene glycol resulted in central nervous system depression in rats, mice, rabbits, and guinea pigs (Bornmann, 1955, Haag and Ambrose, 1937; Kesten et al., 1939; Laug et al., 1939; von Oettingen and Jirouch, 1931; Winek et al., 1978). Animals poisoned

Table 14. Acute Effects of Diethylene Glycol

Route[a]	Species	Dose[b] (g/kg)	Response[b]	Reference
oral	rats	31.6	LD50, 14 d	Union Carbide, 1978
oral	rats	16.5	LD50, 8 d	Laug et al., 1939
oral	rats	20.76	LD50, 14 d	Smyth et al., 1941
oral	mice	28.21	LD50	Bornmann, 1955
oral	mice	26.5	LD50, 8 d	Laug et al., 1939
oral	rabbits	4.9	LD50, 8 d	Laug et al., 1939
oral	guinea pigs	8.7	LD50, 8 d	Laug et al., 1939
oral	guinea pigs	13.21	LD50, 14 d	Smyth et al., 1941
inhalation	rats	concentrated vapor, 8 h	No deaths	Union Carbide, 1978
inhalation	mice	0.13 mg/l (30 ppm), 2 h	Lethal dose, 12 d	Sanina and Kochetkova, 1966
i.p.	mice	9.73	LD50 7 d	Karel et al., 1947
s.c.	rats	16.8	LDLo, 14 d	Haag and Ambrose, 1937
s.c.	mice	5.6	LDLo, 24 h; marked irritation at injection site	von Oettingen and Jirouch, 1931
i.v.	rats	4.5	LDLo, 14 d	Haag and Ambrose, 1937
i.v.	rabbits	2.2	LDLo, 14 d	Haag and Ambrose, 1937

Table 14. Acute Effects of Diethylene Glycol (Cont'd)

Route[a]	Species	Dose[b] (g/kg)	Response[b]	Reference
dermal	rabbits	13.3, 24 h, closed dressing	LD50, 14 d	Union Carbide, 1978
dermal	rabbits	0.01 ml (0.011 g)[c], 24 h, open	No irritation	Union Carbide, 1978
ocular	rabbits	0.5 ml (0.56 g)[c]	Little or no irritation, 18-24 h	Carpenter and Smyth, 1946
ocular	rabbits	not stated	No irritation	Union Carbide, 1978

[a] i.p. = intraperitoneal; s.c. = subcutaneous; i.v. = intravenous.

[b] d = day; h = hour.

[c] Total dose.

with diethylene glycol had ruffled coats, a bloated appearance, and refused their food (Laug et al., 1939). Other consequences of diethylene glycol administration included lack of muscular coordination (Winek et al., 1978), convulsions (Hanzlik et al., 1939a), dyspnea (Laug et al., 1939; Winek et al., 1978), depression of respiratory rate and heartbeat (Bornmann, 1955), hypotension (von Oettingen and Jirouch, 1931; Loeser et al., 1954), irritation of the digestive tract (Smyth et al., 1941), hemolysis (Bornmann, 1955), diuresis followed by anuria (Bornmann, 1955; Kesten et al., 1939; Laug et al., 1939), hemoglobinuria (Loeser et al., 1954), metabolic acidosis (Geiling et al., 1937; Hebert et al., 1978), and pronounced lowering of the temperature for 24 hours before death (Laug et al., 1939). Female rats were more sensitive, as judged by the LD50 value, to the toxicity of diethylene glycol than were male rats (Smyth et al., 1941). Symptoms of toxicity appeared less rapidly after administration of diethylene glycol than after administration of ethylene glycol (Laug et al., 1939; Winek et al., 1978).

No pathological changes were observed in the central nervous systems of animals treated with fatal doses of diethylene glycol (Laug et al., 1939; Winek et al., 1978). Cardiac dilatation was noted in a few mice that died within the first 24 hours (Karel et al., 1947). Examination of the lungs occasionally revealed congestion, edema, focal interstitial pneumonia, and hemorrhages in several species (Laug et al., 1939).

Renal lesions were the most commonly reported pathological effect resulting from administration of diethylene glycol to rats, mice, rabbits, guinea pigs, and dogs. Clinical signs of renal damage were marked increases in the nonprotein nitrogen concentrations of the blood (Kesten et al., 1939) and high levels of protein in the urine (Laug et al., 1939). Gross and

microscopic examination of the kidneys revealed edema (Kesten et al., 1939; Laug et al., 1939), congestion (Kesten et al., 1939), occasional hemorrhages (von Oettingen and Jirouch, 1931), deposition of protein near the glomerulus (Laug et al., 1939; Winek et al., 1978), and extensive hydropic degeneration of the epithelium of the convoluted tubules so severe in places that only the basement membranes remained and the tubules were occluded with debris (Laug et al., 1939; Kesten et al., 1939; von Oettingen and Jirouch, 1931; Weatherby and Williams, 1939; Winek et al., 1978). Thrombosis of the renal blood vessels, particularly those of the cortex, was observed in some animals (Laug et al., 1939). In animals that survived at least 5 days, calcification of the necrotic cytoplasm occurred (Kesten et al., 1939) and regeneration began (Kesten et al., 1939; Laug et al., 1939).

Kesten et al. (1939) and Winek et al. (1978) found no deposits of calcium oxalate crystals in the kidneys of rats and rabbits that had been given doses of diethylene glycol high enough to cause tubular degeneration. These authors had reported extensive renal deposition of calcium oxalate crystals after administration of ethylene glycol. Hebert et al. (1978) reported finding calcium oxalate crystals, however, in the kidneys of approximately 50% of rats given acutely toxic doses of diethylene glycol. Laug et al. (1939) reported that fatal doses of diethylene glycol produced widespread centrilobular hydropic degeneration in the livers of experimental animals. The degeneration was mild in some foci and but so severe in others that the cells were completely disintegrated. Kesten et al. (1939) and Weatherby and Williams (1939) observed similar but less severe and less frequent degeneration of hepatic parenchymal cells.

Extensive mitotic activity (Laug et al., 1939) and hydropic changes (Kesten et al., 1939) have occasionally been observed in the

adrenals of animals acutely poisoned with diethylene glycol. Other findings were generalized edema and hemorrhage into the intestines (Laug et al., 1939). The spleens were abnormally small (Loeser et al., 1954) and had phagocytized excessive amounts of blood pigment (Laug et al., 1939; Karel et al., 1947). Karel et al. (1947) reported that diethylene glycol produced a severe toxic reaction in the spleens (white pulp) and other lymphatic tissues of female mice (thymus, lymph nodes, lymphoid follicles of liver). Pyknosis, degeneration, and fragmentation of the lymphocytes of these tissues was followed by proliferation of reticular cells and phagocytosis of cell debris. Although Union Carbide (1978) reported that no rats died from exposure to saturated vapors of diethylene glycol for 8 hours, an abstract from the Russian literature states that mice exposed to 30 ppm diethylene glycol for 2 hours died within 12 days from effects on the hematopoietic and lymphatic systems (Sanina and Kochetkova, 1966).

Topical application of diethylene glycol to the skin and eyes of rabbits was nonirritating (Union Carbide, 1978; Carpenter and Smyth, 1946). Subcutaneous injection of diethylene glycol produced no irritation according to Loeser et al. (1954) and marked irritation according to von Oettingen and Jirouch (1931).

(2) Subchronic Exposures

Daily oral administration of diethylene glycol (2.2 to 4.5 g/kg, 3 times a day to rats; 0.6 to 1.7 g/kg, 3 times a day to rabbits and dogs) resulted in ruffled fur, refusal of food, increased consumption of water, and diuresis, followed by oliguria, anuria, rapid respiration, coma, and death within 9 days (Geiling et al., 1937). In addition, dogs experienced muscular tremors, spasms, and apparent delirium (Geiling et al., 1937). Blood counts on all animals were normal.

Cannon (1937) performed necropsies on the animals from the experiments of Geiling et al. (1937). He observed marked congestion, edema, and bronchopneumonia in the lungs of a few of the animals. The hearts were dilated. The myocardium was essentially normal in most animals, but early fatty degeneration had occurred in some.

The most striking pathological changes in these animals and in those from other subchronic experiments occurred in the kidneys. As in the acute experiments previously described, nonprotein nitrogen concentrations of the blood were elevated (Kesten et al., 1939; Hanzlik et al., 1939a), the epithelium of the renal convoluted tubules underwent severe hydropic degeneration (Cannon, 1937; Hanzlik et al., 1939a; Keston et al., 1939; Weatherby and Williams, 1939), and the glomerular spaces contained albumin (Cannon, 1937). Cannon (1937) noted that swelling of the epithelial cells and formation of casts obstructed the tubules and that the collecting tubules, while relatively unaffected, had undergone some fatty degeneration.

The livers of some of the animals that died from subchronic oral administration of diethylene glycol were also affected. In addition to centrilobular hydropic degeneration (Cannon, 1937; Kesten et al., 1939; Weatherby and Williams, 1939) similar to that described in the Acute Exposures section, fatty degeneration occurred (Hanzlik et al., 1939a; Cannon, 1937) and was most marked at the borders of the hydropic areas (Cannon, 1937). Hydropic degeneration of the adrenals (Kesten et al., 1939), abnormal deposits of pigment in the spleens (Haag and Ambrose, 1937), and marked passive congestion of the body as a whole (Cannon, 1937) were other consequences of subchronic oral administration.

Marchenko (1973a; abstract of Russian paper) noted pathological changes in the central nervous systems of rats and mice after daily

oral administration of low doses of diethylene glycol. These changes, which became marked after 2 to 3 months of treatment, included congestion, hemorrhages, chromatolysis, and hyperplasia of astrocytes.

Exposure of rats and mice by inhalation to 5 mg/m^3 (about 1 ppm) glycol produced mild degenerative changes in their kidneys and livers and hypertrophy of the astrocytes of the cerebral cortex, according to another report by the same author (Marchenko, 1973b; abstract).

Repeated daily applications of diethylene glycol (0.7 to 2.8 g/kg) to the skin of rabbits for 30 days resulted in mild dermatitis, a reduction in food consumption, death of the animals, and marked hydropic degeneration of the renal tubular epitheluim (Hanzlik et al., 1947). This degeneration was more severe than the degeneration observed after application of equal amounts of ethylene glycol. Daily applications of at least 1.1 g/kg diethylene glycol caused hydropic degeneration of the liver cells (Hanzlik et al., 1947).

(3) Chronic Exposures

In the chronic study by Fitzhugh and Nelson (1946) described in the section on Carcinogenicity, feeding of 4% diethylene glycol in the diet resulted in marked retardation of growth and in a slight increase in mortality in male rats in the second year of the experiment. Feeding of 2% or 1% diethylene glycol in the diet retarded growth only during the period of rapid growth. Food consumption was not affected.

The production of bladder stones and tumors by diethylene glycol in the Fitzhugh and Nelson (1946) study is discussed in the Carcinogenicity section. Hemorrhage into the bladder (no stones present) and renal pelvis occasionally occurred. Hydroureter, hydronephrosis, and enlarged kidneys were common findings. Microscopic examination of the kidneys revealed

focal tubular atrophy and hyaline casts and, less frequently, hydropic degeneration, cacification, and glomerular atrophy. Hydropic degeneration of the liver was common; focal necrosis of hepatic cells occurred occasionally. The severity and frequency of these pathological effects decreased with decreasing amounts of diethylene glycol (2% and 1%) in the diet.

In an earlier investigation from the same laboratory, Morris et al. (1942) had found that chronic administration of diethylene glycol (1.71 and 3.42% in the diet) produced bladder stones and chronic cystitis in male rats but not in female rats. The inner portion of the stones was composed mainly of calcium oxalate; the outer portion was composed mainly of phosphate.

(4) Carcinogenicity

In a study of the chronic effects of diethylene glycol, Fitzhugh and Nelson (1946) fed the chemical to groups of 12 Osborne-Mendel male rats at levels of 1, 2, and 4% in the diet for 2 years. The most striking and frequent lesions produced by this treatment were stones and tumors in the animals' urinary bladders (Table 15). Some of the tumors were papillary and generally benign. Others were intramural and, of these, some were malignant. In all but one of the bladders that had tumors, stones were also present, indicating that the tumors may have resulted from chronic irritation. No tumors were reported to occur in the other organs and tissues that were examined. Fitzhugh and Nelson (1946) noted that bladder stones had never been found in untreated rats from their colony and that only 1 bladder tumor had been found in 5000 of their rats that had been variously fed over 50 different substances in chronic experiments.

Weil et al. (1967) investigated the production of tumors in the bladders of a male and female rat fed 2 or 4% diethylene glycol in the diet for periods of 90 days to 2 years. Only the male rats that had been fed

Table 15. Incidence of Stones and Tumors of the Bladder in Rats fed Diethylene Glycol for 2 Years (Adapted from Fitzhugh and Nelson, 1946)

Dosage: % in diet	Number of rats	Number of rats with bladder stones	Number of rats with bladder tumors
1	12	2	0
2	12	7	6
4	12	11	5

4% diethylene glycol for more than 90 days had appreciable incidences of stones (40%) or tumors (5%) in their bladders. Weil et al. (1967) measured the incidence of bladder stones and tumors in rats that had received implants of stones or glass beads in their bladders or had undergone sham operations. Bladder stones and tumors were found in both male and female rats of all three groups and never developed in the absence of a foreign body or prior surgical procedure. The authors concluded that bladder tumors were probably the result of mechanical irritation or trauma rather than a primary result of the ingestion of diethylene glycol.

In contrast to the reports of Fitzhugh and Nelson (1946) and Weil et al. (1967), an abstract (Sanina, 1968) from the Russian literature states that no bladder tumors were produced in mice after "prolonged injection" (intubation?) of diethylene glycol into the stomach. According to Sanina (1968), inhalation of 0.004 to 0.005 mg/l (0.9 to 1.2 ppm) diethylene glycol for 6 to 7 months caused malignant tumors of the mammary glands in 10 of 16 female mice and 1 case of lympholeukosarcoma. These malignancies were detected 2.5 to 11 months after cessation of treatment. This report cannot be evaluated because the incidence of tumors in controls was not stated.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

Holck (1937) reported that pregnancy did not occur when a small number of male and female rats that were receiving 0.5% diethylene glycol in the drinking water were caged together. Whether the animals actually mated was not stated. This level of diethylene glycol retarded the animals weight

gain. When the females were mated with untreated males, there was some evidence, according to Holck, of smaller and fewer litters. Wegener (1953) found that daily oral administration of 2.2 g/kg of diethylene glycol to rats over a period of 12 weeks had no effect on the reproductive ability of the animals or of their offspring.

(8) Other Relevant Information

Although much of the diethylene glycol administered to animals is excreted unchanged in the urine, small amounts may be metabolized to oxalic acid. Concentrations of oxalate in blood, kidneys, and urine rose after administration of diethylene glycol (Winek et al., 1978; Hanzlik et al., 1939a). The cores of bladder stones formed during chronic diethylene glycol treatment were composed mainly of oxalic acid (Morris et al., 1942), and there is one report of deposition of calcium oxalate crystals in the kidney after acute administration of this glycol (Hebert et al., 1978). Diethylene glycol was eliminated from the blood more slowly than was ethylene glycol (Winek et al., 1978).

b. Human Studies

No reports of illness or injury from industrial exposure were found in the literature searched. Information on the toxicity of diethylene glycol to humans has been derived almost entirely from the approximately 365 cases of poisoning caused by the ingestion of Elixer of Sulfanilamide-Massengill, a medicine that contained 72% diethylene glycol (Schoeffel et al., 1937). Comparison of the effects of this elixir with the effects of sulfanilamide in humans (Calvery and Klumpp, 1939) and toxicologic studies with animals (Geiling et al., 1937; Cannon, 1937; Geiling and Cannon, 1938) established that diethylene glycol was the toxic agent in Elixir of Sulfanilamide-Massengill. The mean cumulative fatal dose for adults of this

elixir of sulfanilamide was 98.6 ml (about 1.14 g diethylene glycol/kg) and the minimum fatal dose was 20 ml (about 0.23 g diethylene glycol/kg) (Calvery and Klumpp, 1939).

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

As reviewed by Geiling and Cannon (1938) and Calvery and Klump (1939), about 24 hours after the first dose was taken, patients ingesting elixir of sulfanilamide (72% diethylene glycol) experienced vomiting, abdominal cramps, headaches, dizziness, and occasionally diarrhea. Starting 2 or more days after the initial dose, transient polyuria often occurred, followed by oliguria, anuria, and pain over the kidneys and in the abdomen. Patients died within 2 to 7 days after the onset of anuria. Edema of the face and extremities, coma, slow respiration and pulse, tremors and (in a few children) convulsions, and subnormal body temperatures usually preceeded death. Other findings were moderate leukocytosis and hematuria. Progressive anemia was noted by Hagebusch (1937) but not by others (Geiling and Cannon, 1938; Calvery and Klumpp, 1939).

(3) Target Organ Toxicity

Autopsies of patients who died from ingesting diethylene glycol (elixir of sulfanilamide) revealed pulmonary edema and, less frequently, bronchopneumonia and hemorrhage into the lungs and pericardium (Geiling and Cannon, 1938). No lesions of the central nervous system were reported.

The most common and severe pathological changes involved the kidneys. In most cases, the cause of death appeared to be renal insufficiency (Calvery and Klumpp, 1939; Rowe, 1963). Clinical evidence of severe impairment of renal function included extremely high levels of urea

nitrogen and creatinine in the blood, and high levels of albumin in the urine (Geiling and Cannon, 1938; Calvery and Klumpp, 1939). Swelling of the kidneys and bilateral cortical necrosis with hemorrhage were frequently observed at autopsy. The blood vessels in these necrotic areas contained hyaline thrombi and their walls were necrotic. Characteristically, hydropic degeneration of the epithelium of the convoluted tubules produced obliteration of the lumens. Necrosis and complete disintegration of the tubular epithelium had sometimes occurred (Geiling and Cannon, 1938).

The livers were sometimes enlarged and hemorrhagic. Histological examination revealed centrilobular hydropic degeneration of the hypatic cells with some necrosis. Fatty degeneration occurred in cells at the margins of the hydropic areas. Other pathological changes included congestion and hemorrhage of the gastrointestinal tract and generalized edema (Geiling and Cannon, 1938).

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of diethylene glycol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for diethylene glycol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

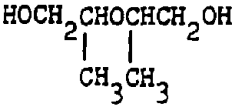
18. Other Pertinent Data

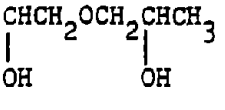
The vapor pressure of diethylene glycol is low enough at room temperature that this glycol should not present an inhalation hazard unless used at high temperatures or sprayed (Rowe, 1963; Browning, 1965).

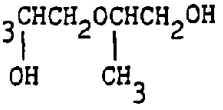
G. DIPROPYLENE GLYCOL

1. Chemical Name: Dipropylene Glycol

2. Chemical Structure (3 isomers):

(1) 

(2) 

(3) 

3. Synonyms: (1) 1-Propanol, 2,2'-oxybis-

(2) 2,2'-Dihydroxy dipropyl ether
2,2'-Dihydroxy isopropyl ether
1,1'-Oxydi-2-propanol
2-Propanol, 1,1'-oxybis-

(3) 1-Propanol, 2-(2-hydroxpropoxy)-

4. Chemical Abstract Service (CAS) Number: (1) 108-61-2
(2) 110-98-5
(3) 106-62-7
mixture: 25265-71-8

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

(2) UB8785000

6. Chemical and Physical Properties (Commercial Product):

Description:	colorless liquid
Molecular Weight:	134.18
Boiling Point:	231.0°C
Melting Point:	supercools
Vapor Pressure:	<0.01 mm Hg (20°C)
Solubility:	completely soluble in water; soluble in alcohol and toluene; completely soluble in ether and methanol
Specific Gravity:	1.020^{25}_{25}
Stability:	combustible; Flash point: 256°F (CC)

7. Production

Production of dipropylene glycol in recent years is as follows (USITC, 1977, 1978, 1979, 1980):

Year	Production (in millions of pounds)
1979	57.830
1978	51.987
1977	54.266
1976	49.615

CMR (1978a) estimates the future growth rate of the dipropylene glycol demand to be 5% per year through 1982.

Data available from the U.S. EPA (1980) regarding producers of dipropylene glycol and production volumes are presented in Table 16.

8. Use

The following tabulation presents the percentage of the total amount of dipropylene glycol produced that is used in each of the applications listed (CMR, 1978a):

	Percentage of Total
Polyester resins	60%
Plasticizers	30%
Alkyd resins, hydrocarbon extraction, urethane polyols and other	10%

Miscellaneous uses of dipropylene glycol include its use as a component of hydraulic fluids, in textile lubricants, in ink formulations, and as a selective solvent (Union Carbide, 1978).

9. Manufacturers and Distributors

SRI International (1980) and CMR (1978) list the following manufacturers:

		Annual Capacity (in millions of lbs)
Dow Chemical	Freeport, TX	25
	Plaquemine, LA	16
Olin Corp.	Brandenburg, KY	10
Oxirane Int.	Bayport, TX	18
Texaco (Jefferson)	Port Neches, TX	7
Union Carbide	South Charleston, WV	10
		86

Table 16. Producers of Dipropylene Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
		CAS No. 25265-71-8
Olin Corp.		
Brandenburg, KY	Manufacturer	1-10 million lb
Dow Chemical		
Freeport, TX	Manufacturer	10-50 million lb
Plaquemine, LA	Manufacturer	10-50 million lb
Oxirane Chem.		
Pasadena, TX	Manufacturer	10-50 million lb
March Chemical		
Denham Springs, LA	Manufacturer	10-100 thousand lb
Givaudan Corp.		
Clifton, NJ	Manufacturer	none
Jefferson Chemical		
Port Nechos, TX	Manufacturer	confidential
Austin, TX	Manufacturer	confidential
JPM Imports		
Astoria, NY	Importer	confidential
Synarome, Corp.		
New York City, NY	Importer	under 1000 lb
V. Mane Fils, Inc.		
Fairfield, NJ	Importer	confidential
Roure Bertrand DuPont		
Teaneck, NJ	Importer	under 1000 lb
ICI Americas		
Wilmington, DE	Importer	confidential
		CAS No. 110-98-5
Union Carbide		
South Charleston, WV	Manufacturer	confidential
EM Laboratories		
Elmsford, NY	Importer	confidential

In addition to the manufacturers, the distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Chemical Buyers' Guide, 1980; Chem Sources--USA, 1980):

Alpha International	C.P. Hall Co.
Anachemia Chem.	J.F. Henry Chem.
Ashland Chem.	Kessler Chem.
Atomergic Chemetals	Lachat Chem.
J.T. Baker Chem.	Legion Export and Import
BASF Wyandotte	Lux Chem.
Bentley Chem.	MCB Reagents
Berje Chem.	McKesson Chem.
Chem Services	Mitsubishi Intern.
Coyne Chem.	Pioneer Salt and Chem.
CPS Chem.	Robinson Bros. Chem.
Dynamic Chem.	Suburban Chem.
EM Lab	Thompson-Hayward Chem.
Eastman Kodak	Tridom Chem.
FBC Chem.	Union Chem.
Fehr Bros. Chem.	Universal Preservachem.
Fisher Sci.	Van Waters and Rogers
GSL Chem.	Worth Chem.

10. Manufacturing Processes

Dipropylene glycol is produced as a coproduct in the manufacture of propylene glycol via propylene oxide hydrolysis (Brown et al., 1980); see propylene glycol profile for a process description.

The approximate isomer distribution in the dipropylene glycol product is by CAS number (Brown et al., 1980):

(1) 108-61-2 4%

(2) 110-98-5 43%

(3) 106-62-7 53%

11. Impurities or Additives

Commercial dipropylene glycol has the following specifications (Union Carbide, 1978):

acidity by wt. max., as acetic acid	0.01%
water by wt., max.	0.1%
ash by wt., max.	0.005%
suspended matter	substantially free
iron, max.	0.5 ppm
chlorides, max.	1 ppm

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 227,916 workers are potentially exposed to dipropylene glycol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to dipropylene glycol were not found in the literature searched.

14. Biological Effects

As presented in Section 2, 3, 4, and 10, there are three isomers of dipropylene glycol; the commerical product consists of all three isomers. The authors of the papers discussed in Section 14 did not specify the identity or isomer composition of the dipropylene glycol that they tested. In most instances, it appears to have been the commercial product.

a. Animal Studies

(1) Acute Exposures

Lethal and irritant dose data for dipropylene glycol are summarized in Table 17. Oral, intraperitoneal, or intravenous administration of lethal doses of dipropylene glycol to rats (Shaffer et al., 1951) and intravenous administration to dogs (Hanzlik et al., 1939a) resulted in depression of the central nervous system. Rats given the chemical orally also suffered tremors and convulsions (Shaffer et al., 1951).

Few pathological changes were found in animals that received acutely toxic doses of dipropylene glycol. Oral administration of this glycol to rats in lethal doses produced ischemia of the kidney, minor pulmonary

Table 17. Acute Effects of Dipropylene Glycol

Route[a]	Species	Dose[b] (g/kg)	Response[b]	Reference
oral	rats	14.85	LD50, 14d	Shaffer et al., 1951
oral	rats	15.1	LD50, 14 d	Union Carbide, 1978
inhalation	rats	concentrated vapor, 8 h	No deaths	Union Carbide, 1978
i.p.	rats	10.59	LD50, 14 d	Shaffer et al., 1951
i.p.	mice	4.5	LD50, 7 d	Karel et al., 1947
i.v.	dogs	11.7 (by slow infusion)	Lethal dose, average	Hanzlik et al., 1939a
i.v.	rats	5.80	LD50, 14d	Shaffer et al., 1951
dermal	rabbits	>20.4, 24 h closed dressing	LD50, 14 d	Union Carbide, 1978
dermal	rabbits	undiluted, 24 h, closed dressing, intact or abraded skin	Slightly irritating	Moreno, 1974
dermal	rabbits	0.01 ml (0.01 g)[c] 24 h, open	No irritation	Union Carbide, 1978
ocular	rabbits	0.5 ml (0.51 g)[c]	Little or no irritation, 18-24 h	Carpenter and Smyth, 1946
ocular	rabbits	not stated	Mild irritation	Union Carbide, 1978

[a] i.p. = intraperitoneal; i.v. = intravenous

[b] d = day; h = hour

[c] Total dose

hemorrhage, congestion of liver and spleen, and injection of intestinal blood vessels (Shaffer et al., 1951). Intraperitoneal administration of dipropylene glycol to mice resulted in slight renal tubular degeneration (Karel et al., 1947). Intravenous injection of this glycol into rabbits produced extensive hydropic degeneration in the renal epithelium, an occasional hemoglobin-containing cast in the collecting tubules of the kidneys, and elevation of the nonprotein nitrogen level of the blood (Kesten et al., 1939).

Undiluted dipropylene glycol produced little or no irritation when applied to the skin or eyes of rabbits (Moreno, 1974; Union Carbide, 1978; Carpenter and Smyth, 1946).

(2) Subchronic Exposures

Dogs given repeated oral doses of dipropylene glycol showed no outward signs of toxicity, and had minimal liver damage and insignificant to moderate degeneration of the renal convoluted tubules (Hanzlik et al., 1939a). The dogs had received four to six doses of 1.5, 2.0, or 5.0 ml/kg (1.53, 2.04, or 5.10 g/kg).

Dipropylene glycol, given to rats for 77 days as a 5% solution in their drinking water, produced no detectable effects (Kesten et al., 1939). According to the authors the treated animals' organs appeared to be normal. A concentration of 10% dipropylene glycol in the drinking water, however, produced renal lesions in almost half the 25 rats tested. Many of the rats with renal damage died. The renal lesions consisted of extensive hydropic degeneration of the epithelium, with, occasionally a hemoglobin-containing cast in the collecting tubules.

Ten applications of dipropylene glycol to the skin of rabbits in 12 days produced negligible irritation. No signs of systemic toxicity were observed (Dow Chemical Co., n.d.).

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

Unlike propylene glycol, dipropylene glycol was not glycogenic. Administration of dipropylene glycol to fasted rats failed to increase the content of glycogen in the liver (Hanzlik et al., 1939b).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

Dipropylene glycol (20% in petrolatum) was non-irritating in a 48-hour closed-patch test on human subjects (Epstein, 1974). Also, this preparation of dipropylene glycol did not produce sensitization reactions in a maximization test with human volunteers (Epstein, 1974).

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of dipropylene glycol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for dipropylene glycol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of dipropylene glycol as an occupational hazard was found in the literature searched.

H. ETHYLENE GLYCOL

1. Chemical Name: Ethylene Glycol

2. Chemical Structure: $HO-CH_2-CH_2-OH$

3. Synonyms: 1,2-Dihydroxyethane
Ethane-1,2-diol
1,2-Ethandiol
1,2-Ethanediol
Ethylene alcohol
Ethylene dihydrate glycol
Glycol alcohol
Monoethylene glycol

4. Chemical Abstracts Service (CAS) Number: 107-21-1

5. Registry of Toxic Effects of Chemical Substance (RTECS) Number:

KW2975000

6. Chemical and Physical Properties:

Description:	viscous liquid with a sweet taste
Molecular Weight:	62.07
Boiling Point:	197.6°C
Melting Point:	-12.7°C
Vapor Pressure:	0.06 mm Hg (at 20°C)
Solubility:	completely soluble in water, alcohol, acetone, acetic acid, glycerol, pyridine, slightly soluble in ether; practically insoluble in benzene and homologs, chlorinated solvents
Specific Gravity:	1.1155^{20}_{20}
Stability:	combustible; Flash point (open cup): 240°F

7. Production

Production in recent years is as follows (USITC, 1977, 1978, 1979, 1980):

Year	Production (in millions of pounds)
1979	4,729
1978	3,904
1977	3,675
1976	3,335

CMR (1978b) estimates future growth of ethylene glycol to be 6% per year through 1982.

Data available from the U.S. EPA (1980) regarding producers of ethylene glycol and production volumes are presented in Table 18.

8. Use

The annual sales of ethylene glycol amounted to 3348 million pounds in 1979 (USITC, 1980). Ethylene glycol is used primarily as antifreeze for water-cooled motor vehicles (50% of total production) and in the production of synthetic fibers and films (35% of total production). Other markets for ethylene glycol include its use as hydraulic brake fluid, heat transfer fluid, industrial humectant, ingredient of electrolyte condensers, solvent in paint and plastics industry, softening agent for cellophane, stabilizer in fire extinguishers, safety explosives, alkyd resins, plasticizers, elastomers, and synthetic waxes. All these uses amount to 8% of the total production. Approximately 7% is exported (CMR, 1978b; The Merck Index. 1976).

9. Manufacturers and Distributors

The manufacturers of ethylene glycol and their estimated capacities are shown in Table 19. There are over 100 commercial distributors of ethylene glycol.

10. Manufacturing Processes

The major source of ethylene glycol is the hydration of ethylene oxide by a catalytic or a noncatalytic process. The catalytic process employs a large excess of a dilute aqueous acid and the noncatalytic process uses high temperatures and pressures in the presence of a large excess of water. Figure 2 outlines the manufacturing process for the production of ethylene glycol from ethylene oxide.

Table 18. Producers of Ethylene Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Eastman Kodak		
Rochester, NY	Manufacturer-Not Distributed	1-10 million lb
Olin Corp.		
Brandenburg, KY	Manufacturer	1-10 million lb
Dow Chemical		
Freeport, TX	Manufacturer	100-500 million lb
Plaquemine, LA	Manufacturer	100-500 million lb
Midland, MI	Importer	0.1-1 million lb
Fiber Industries Inc.		
Salisbury, NC	Manufacturer-Not Distributed	100-500 million lb
Florence, NC	Manufacturer-Not Distributed	50-100 million lb
Shelby, NC	Manufacturer-Not Distributed	10-50 million lb
PPG Industries		
Beaumont, TX	Manufacturer	50-100 million lb
Ponce, PR	Manufacturer	100-500 mllion lb
Haven Chemical		
Philadelphia, PA	Manufacturer	0.1-1 million lb
Newbern Polyester Plant		
New Bern, NC	Manufacturer	1-10 million lb
Texas Eastman		
Longview, TX	Manufacturer	100-500 million lb
Union Carbide		
Institute, WV	Manufacturer	confidential
Port Lavaca, TX	Manufacturer	confidential
Ponce, PR	Manufacturer	0.5-1 billion lb
Hahnville, LA	Manufacturer	confidential
New York City, NY	Importer	1-10 million lb
BASF Wyandotte		
Geismar, LA	Manufacturer	100-500 million lb
ABC Compounding Co.		
Atlanta, GA	Manufacturer	under 1000 lb
E.I. DuPont de Nemours		
Brevard, NC	Manufacturer	0.1-1 million lb
Parlin, NJ	Manufacturer	0.1-1 million lb
Shell Chemical		
Geismar, LA	Manufacturer	100-500 million lb
Houston, TX	Importer	10-50 million lb
Sunolin Chemical Co.		
Claymont, DE	Manufacturer	1-10 million lb

Table 18. Producers of Ethylene Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
3M Company		
Greenville, SC	Manufacturer	confidential
Decatur, Al	Manufacturer	confidential
St. Paul, MN	Manufacturer	confidential
Morganton Plant		
Morganton, NC	Manufacturer	none
Northern Petrochemicals		
Morris, IL	Manufacturer	100-500 million lb
March Chemical		
Denham Springs, LA	Manufacturer	10-100 thousand lb
Oxirane Chem. Co.		
Channelview, TX	Manufacturer	none
Calcasiecal Corp.		
Lake Charles, LA	Manufacturer	0.1-1 million lb
Chemical Exchange Co.		
Houston, TX	Manufacturer	100-1000 thousand lb
Dow Badische Co.		
Anderson, SC	Manufacturer	1-10 million lb
Dixie Chemical		
Pasadena, TX	Manufacturer	confidential
Jefferson Chemical		
Port Nechos, TX	Manufacturer	confidential
United Mineral and Chem.		
New York City, NY	Importer	under 1000 lb
Nissho-Iwai Amer.		
New York City, NY	Importer	100-500 million lb
Henkel Inc.		
Teaneck, NJ	Importer	under 2000 lb
Esselen Assoc.		
Stamford, CT	Importer	none
Cemco Inc.		
New Cahaan, CT	Importer	none
Milijac Inc.		
---, CT	Importer	none
Thorson Chem.		
New York City, NY	Importer	under 1000 lb
Struktol Chem.		
Akron, OH	Importer	confidential

Table 18. Producers of Ethylene Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Sandoz Color and Chem. East Hanover, NJ	Importer	none
Steuber Co. New York City, NY	Importer	none
Montedison USA New York City, NY	Importer	none
Mitsubishi International New York City, NY	Importer	1-10 million lb
Mitsui and Co. New York City, NY	Importer	10-50 million
J.E. Halma Co. Lodi, NJ	Importer	confidential
Hercules Inc. Wilmington, DE	Importer	confidential
Ciba-Geigy Corp. Ardsley, NJ	Importer	none
Itoh and Co. New York City, NY	Importer	10-100 thousand lb

Table 19. Producers of Ethylene Glycol and Estimated Production Ranges

Producer and Location	Estimated Annual Capacity (Millions of Pounds) (SRI International, 1980)	(CMR, 1978b)
BASF Wayandotte Corp.		
Geismar, LA	250	245
Calcasieu Chem. Corp.		
Lake Charles, LA	180	200
Celanese Corp.		
Clear Lake, TX	500	500
Dow Chem. Co.		
Freeport, TX	255	240
Plaquemine, LA	350	470
Eastman Kodak Co.		
Longview, TX	180	180
Northern Natural Gas Co.		
Morris, IL	200	230
Olin Corp.		
Brandenburg, KY	50	40
Oxirane International		
Channelview, TX	800	800
PPG Indust. Inc.		
Beaumont, TX	180	200
Guayanilla, TX	---	400
Shell Chem. Co.		
Geismar, LA	340	140
Texaco Inc.		
Port Neches, TX	330	380
Union Carbide Corp.		
Seadrift, TX	750	850
Taft, LA	1250	1100
Penuclas, PR	600	600
TOTAL	6215	6575

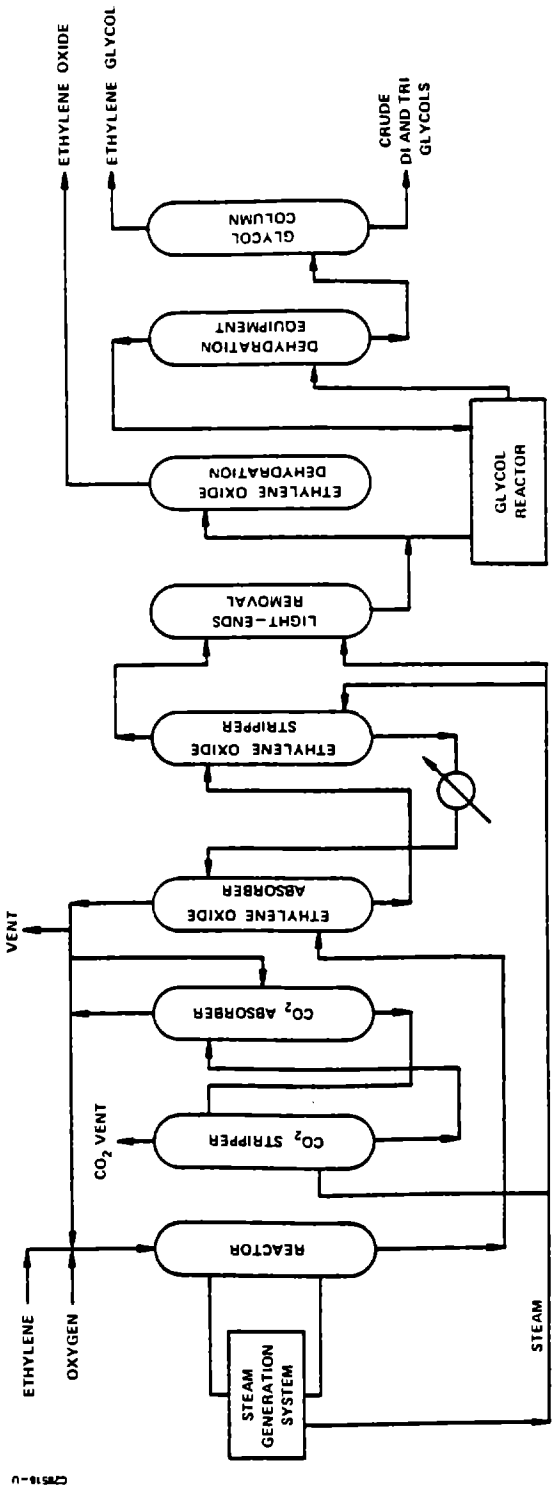


Figure 2. Production of Ethylene Oxide and Ethylene Glycol, (licensed by Shell Development Co.) (Miller, 1979)

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 Oxiran plant in Channelview, TX. 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 atmospheres pressure. Acetic acid is recycled. The overall ethylene glycol yield by this process is 95% of the theoretical yield, compared to 67% via ethylene oxide hydration.

Union Carbide has patented ethylene glycol production from synthesis gas. The reaction is carried out at 200°C and 8000 psi and is as follows:

$$3CO + 5H_2 \longrightarrow HOCH_2CH_2OH + CH_3OH$$

It is predicted that this process will be of major importance in the mid-1980s.

Three other commercial processes that were employed in the past--the reaction of CO and formaldehyde; the fermentation of molasses; and the vapor phase oxidation of propane--have been discontinued.

11. Impurities of Additives

Both industrial (99.0% pure) and polyester grade ethylene glycol contain acetic acid, ash, and diethylene glycol as impurities (Union Carbide, 1978).

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 1,806,810 workers are potentially exposed to ethylene glycol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to ethylene glycol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Lethal dose and irritancy data for ethylene glycol are summarized in Table 20. Numerous investigators have reported that administration of lethal doses of ethylene glycol to rats, mice, rabbits, guinea pigs, and monkeys resulted in central nervous system depression (Bornmann, 1955; Beck et al., 1936; Clay and Murphy, 1977; Hanzlik et al., 1931; Kersting and Nielsen, 1966; Laug et al., 1939; von Oettingen and Jirouch, 1931; Winek et al., 1978). Ethylene glycol produced weakness (Laug et al., 1939), lack of muscular coordination (Kersting and Nielsen, 1966; Laug et al., 1939; Winek et al., 1978), loss of equilibrium (Hanzlik et al., 1931; Latvin and Molitor, 1939), and convulsions (Hanzlik et al., 1931, 1939a; Kersling and Nielsen, 1966; Beckett and Shields, 1971) in a variety of species. Other consequences of acute poisoning with ethylene glycol were an initial acceleration of respiration (Kersting and Nielsen, 1966; Hanzlik et al., 1931), dyspnea (Winek et al., 1978), respiratory failure (Latven and Molitor, 1939; Bornmann, 1955), tachycardia followed by bradychardia (Kersting and Nielsen, 1966; Bormann, 1955), hypotension (von Oettingen and Jirouch, 1931), irritation of the digestive tract (Smyth et al., 1941), hemolysis (Bornmann, 1955), hematuria (Winek et al., 1978), diuresis (Bornmann, 1955; Beckett and Shields, 1971), hypocalcemia (Beckett and Shields, 1971), and uncompensated metabolic acidosis (Clay and Murphy, 1977). In monkeys and dogs, metabolic acidosis resulted primarily from the accumulation of glycolate (a metabolite of ethylene glycol) in the blood (Clay and Murphy, 1977).

Administration of ethylene glycol to experimental animals has produced pathological changes in their brains, lungs, and hearts.

Table 20. Acute Effects of Ethylene Glycol

Route[a]	Species	Dose[b] (g/kg)	Response[b]	Reference
oral	rats	8.26	LD50, 14 d	Union Carbide, 1978
oral	rats	6.14	LD50, 8 d	Laug et al., 1939
oral	rats	8.54	LD50, 14 d	Smyth et al., 1941
oral	rats	7.21	LD50, 14 d; median of samples tested	Smyth et al., 1969
oral	rats	11.94 9.06 7.89	LD50's, 14 d; 3 different samples of ethylene glycol	Smyth et al., 1970
oral	mice	9.93	LD50, 6 d	Holman et al., 1979
oral	mice	14.6	LD50, 8 d	Laug et al., 1939
oral	mice	15.39	LD50	Bornmann, 1955
oral	mice	13.38	LD50	Mundy et al., 1974
oral	mice	8.37	LD50, 24 h	Latven and Molitor, 1939
oral	guinea pigs	8.20	LD50, 8 d	Laug et al., 1939
oral	guinea pigs	6.61	LD50, 14 d	Smyth et al., 1941
oral	dogs	4.91	Lethal dose	Beckett and Shields, 1971
inhalation	rats	concentrated vapor, 8 h	No deaths	Union Carbide, 1978
i.p.	mice	5.62	LD50, 7 d	Karel et al., 1947
i.p.	mice	17-19	LD50 (approximate)	Beck et al., 1936
i.p.	monkeys	4	LDLo	Clay and Murphy, 1977

Table 20. Acute Effects of Ethylene Glycol (Cont'd)

Route[a]	Species	Dose[b] (g/kg)	Response[b]	Reference
i.m.	rats	3.3	LDLo	Hanzlik et al., 1931
i.m.	rabbits	5.5	LDLo	Hanzlik et al., 1931
s.c.	rats	5.3	LD50	Mason et al., 1971
s.c.	mice	5.02	LD50, 24 h	Latven and Molitor, 1939
s.c.	mice	2.79	LDLo, 24 h; marked irritations at site of injection	von Oettingen and Jirouch, 1931
i.v.	rats	2.8	LDLo	Hanzlik et al., 1931
i.v.	mice	3.3	LD50, 24 h	Latven and Molitor, 1939
i.v.	rabbits	5.0	LDLo	Hanzlik et al., 1931
intradermal	guinea pigs	0.1 ml (0.11 g)[c]	Moderate irritation	Latven and Molitor, 1939
dermal	rabbits	>22.3, 24 h, closed dressing	LD50, 14 d	Union Carbide, 1978
dermal	rabbits	0.01 ml (0.011 g)[c], 24 h, open	No irritation	Union Carbide, 1978
dermal	rabbits	not stated; closed dressing	No irritation, 24 h	Latven and Molitor, 1939
mucosal (penile)	rabbits	≈0.2 ml of 15% solution[c]	No irritation, 2 and 24 h	Draize et al., 1944
ocular	rabbits	≈0.5 ml (0.56 g)[c]	Mild irritation (edema and hyperemia)	Latven and Molitor, 1939

Table 20. Acute Effects of Ethylene Glycol (Cont'd)

Route[a]	Species	Dose[b] (g/kg)	Response[b]	Reference
ocular	rabbits	0.5 ml (0.56 g)[c]	Little or no irritation, 18-24 h	Carpenter and Smyth, 1946
ocular	rabbits	0.1 ml (0.11 g)[c]	Mild irritation at 1 and 24 h	Draize et al., 1944
ocular	rabits	not stated	Mild irritation (edema) at 1 h; complete recovery by 4 h	Hanzlik et al., 1931
ocular	rabbits	not stated	No irritation	Union Carbide, 1978
ocular	rabbits	0.1 ml of 15% solution[c]	No irritation	Draize et al., 1944
ocular	rabbits	≈0.05 ml of 4% solution every 10 min for 6 h	Irritation	McDonald et al., 1972

[a] i.p. = intraperitoneal; i.m. = intramuscular; s.c. = subcutaneous; i.v. = intravenous.

[b] d = day; h = hour; min = minute.

[c] total dose.

Bove (1966) and Kersting and Nielsen (1966) observed calcium oxalate crystals within the walls and perivascular spaces of the blood vessels of the brains of rats and dogs that had been given fatal doses of ethylene glycol. Mild meningitis and hyperemia and edema of the brain occurred occasionally (Kersting and Nielsen, 1966; Winek et al., 1978). Effects on the lungs included edema, congestion, hemorrhage, and mild pneumonitis (Kersting and Nielsen, 1966; Laug et al., 1939). Kersting and Nielsen (1966) have reported that fatal doses of ethylene glycol produced focal hemorrhages of the myocardium in a few dogs.

Damage to the kidneys was the most striking and commonly reported pathological effect resulting from the administration of ethylene glycol to rats, mice, rabbits, guinea pigs, and dogs. Clinical signs of renal damage were marked increases in the nonprotein nitrogen (Kesten et al., 1939) and urea nitrogen (Beckett and Shields, 1971) concentrations of the blood and high levels of protein in the urine (Laug et al., 1939; Kersting and Nielsen, 1966). Gross and microscopic examination of the kidneys revealed edema (Kersting and Nielsen, 1966), occasional hemorrhage (von Oettingen and Jirouch, 1931; Kersting and Nielsen, 1966), hydropic degeneration of the epithelium of the convoluted tubules (Beckett and Shields, 1971; Bove, 1966; Laug et al., 1939; Kersting and Nielsen, 1966; Kesten et al., 1939; Hanzlik et al., 1939a; von Oettingen and Jirouch, 1931), and deposition of calcium oxalate crystals, primarily in the lumens of the convoluted tubules but also within the epithelial cells and in the lumens of the collecting tubules (Bove, 1966; Kesten et al., 1939; Kersting and Nielsen, 1966; Winek et al., 1978). Dilation of the tubules sometimes occurred proximal to blockage by crystals and the extent and severity of the dilatation appeared to parallel the extent of crystal deposition (Kesten et al., 1939; Bove, 1966).

Degenerative changes in the tubular epithelium sometimes occurred in the absence of crystals (Bove, 1966; Gershoff and Andrus, 1962; Wiley et al., 1938). Conversely, heavy deposition of calcium oxalate crystals with little cellular pathology has been observed (Winek et al., 1978). Sequential biopsies showed that calcium oxalate crystals persisted in the kidneys of dogs after the dogs had recovered clinically from sublethal doses of ethylene glycol (Kersting and Nielsen, 1966). These findings indicate that the toxicity of ethylene glycol to the kidney is not due solely to the deposition of calcium oxalate crystals.

Oral administration of ethylene glycol to animals occasionally caused edema, centrilobular hemorrhage, and (focal) necrosis of the liver (Kersting and Nielsen, 1966; Hanzlik et al., 1939a; Laug et al., 1939). High oral doses produced hemorrhagic areas in the stomachs and congestion of other internal organs (Kersting and Nielsen, 1966; Laug et al., 1939).

In tests with rabbits, ethylene glycol was mildly irritating to the eye (Carpenter and Smyth, 1946; Draize et al., 1944; Hanzlik et al., 1931; Latven and Molitor, 1939) and nonirritating to the skin (Latven and Molitor, 1939; Union Carbide, 1978). Intradermal injection of the glycol into guinea pigs and subcutaneous injection into mice (von Oettingen and Jirouch, 1931) produced irritation at the site of injection.

Smyth et al. (1969, 1970) investigated the joint toxic action of pairs of 27 industrial organic chemicals, including ethylene glycol, intubated into rats. In the first study, LD50 values were determined for 50% by volume mixtures; in the second study, LD50 values were determined for mixtures of 2 chemicals in volumes directly proportional to their respective LD50 values. For mixtures containing ethylene glycol, results of both studies indicated that the joint toxicity of the 2 chemicals was additive (rather than synergestic or antagonistic).

(2) Subchronic Exposures

Administration of ethylene glycol in the drinking water at levels of 0.5 and 1% for 130 days caused stunted growth in rats (food consumption was normal) (Hanzlik et al., 1931), and levels of 10% for 4 to 6 days or 0.25 to 1% for up to 157 days caused decreased food consumption, weight loss, and anemia in monkeys (Roberts and Siebold, 1969). Monkeys receiving the 10% solution were less active than those receiving lower doses. None of the monkeys appeared to suffer cardiopulmonary effects. Calcium oxalate crystals appeared in the walls of cerebral blood vessels and in adjacent tissues of some of the monkeys.

The principal pathological findings in rats and monkeys that had ingested ethylene glycol in their drinking water were deposition of calcium oxalate crystals in the renal convoluted tubules (both in the lumens and within the epithelial cells) and hydropic degeneration of the renal tubular epithelium (Kesten et al., 1939; Fonck-Cussac et al., 1971; Hanzlik et al., 1931; Roberts and Siebold, 1969). Dilation of the tubules sometimes occurred (Kesten et al., 1939). Female monkeys were more resistant to the renal effects than were male monkeys (Roberts and Siebold, 1969). Impaired kidney function (elevated blood urea nitrogen levels), abnormal glomerular permeability (protein precipitate in Bowman's space), and hydropic degeneration of the epithelium of the proximal renal tubules occurred in some monkeys that had no calcium oxlate crystals in their kidneys (Roberts and Siebold, 1969).

Oral administration of ethylene glycol in daily doses of 1/5 of the acute LD50 produced aberrations in hepatic carbohydrate metabolism (Rajogopal and Ramakrishna, 1978) and aberrations in calcium and phosphorous metabolism that were probably associated with the chelation of calcium by oxalic acid (Rajagopal et al., 1977).

Exposure of several species of animals to vapors of ethylene glycol (up to 398 mg/m^3 (157 ppm), 8 hours/day, 5 days/week for 16 weeks) was reported to produce no pathological changes (Coon et al., 1970; Wiley et al., 1936) except severe eye irritation including corneal damage after continous exposure to 12 mg/m^3 (4.7 ppm) for 8 days (Coon et al., 1970). The ACGIH (1979) suggested, however, that this eye irritation may have been caused by oxidation products of ethylene glycol.

Repeated daily applications of ethylene glycol (0.70 to 2.8 g/kg) to the skin of rabbits for 30 days resulted in mild dermatitis, a reduction in food consumption, death of the animals, and hydropic degeneration of the renal tubular epithelium (Hanzlik et al., 1947). The degeneration was less severe than that seen after application of equal amounts of diethylene glycol.

(3) Chronic Exposures

In the chronic study by Mason et al. (1971) described in the Carcinogenicity section, subcutaneous injections of up to 1000 mg/kg ethylene glycol twice a week for 12 months had no effect on the body weight gain or mortality of male rats during the treatment period or for 6 months thereafter. No lesions "severe enough to warrant comment" were found during gross and histopathological examinations.

In the chronic feeding study of Blood (1965), also mentioned under Carcinogenicity, levels of 0.1 to 0.5% ethylene glycol in the diet produced decreases in the weights of kidneys, lungs, and livers of male (but not female) rats, with no effect on body weight. Higher doses (1% and 4% in the diet) resulted in increased water consumption, significant inhibition of growth, and early mortality. Male rats were affected at both 1% and 4% ethylene glycol; females were affected only at the 4% concentration. Just before death, the affected rats excreted protein in the urine, indicating renal damage (Blood,

1965). Histopathological examination revealed degeneration of the renal tubular epithelium and deposition of crystals on the basement membranes and within the convoluted tubules and, to a lesser extent, in the collecting tubules and pelvis (Blood, 1965). The incidence and severity of crystal deposition appeared to be roughly proportional to the dose; again, males were affected at lower doses than were females. Oxalate stones were found in the kidneys, and 1 female rat developed a large magnesium phosphate stone after 1 year on the 0.1% diet.

Morris et al. (1942), in a 2-year chronic feeding study (1% and 2% ethylene glycol, 10 male and female rats per dose level), found not only evidence of renal damage and crystal deposition but also formation of stones, composed primarily of calcium oxalate, in the bladders of some of the animals. Marked chronic cystitis accompanied the stones. Stones and cystitis were found in the males only. Slight damage to the liver (diffuse or centrilobular atrophy, bile duct proliferation, fatty degeneration) was noted.

Ethylene glycol fed to 2 male monkeys at a level of 0.2% and to 1 female monkey at a level of 0.5% in the diet for 3 years produced no toxic effects (Blood et al., 1962). Slight microscopic changes were observed in the kidneys of 1 male; no other gross or microscopic changes were observed in any of the organs of the 3 animals.

(4) Carcinogenicity

Mason et al. (1971) investigated the potential carcinogenicity of ethylene glycol administered subcutaneously to Cesarean-derived Fischer 344 rats of both sexes. Injection of 30, 100, 300, and 1000 mg ethylene glycol/kg body weight were given twice weekly for 12 months to 20, 40, 60, and 80 rats, respectively, starting when the animals were 6 weeks old. Controls included 120 rats that received injections of vehicle and 120 rats that received

no treatment. Animals were killed and examined at 12 or 18 months from the start of treatment. Although a number of tumors occurred in both control and treated animals, there was no significant increase in incidence of tumors in ethylene glycol-treated animals.

Blood (1965) found that feeding ethylene glycol to male and female Sprague-Dawley rats (17 rats of each sex per dose level) at levels of 0.1 to 4% in the diet for 2 years produced no changes in tumor incidence that could be correlated with the treatment.

(5) Mutagenicity

Ethylene glycol, with and without microsomal activation, was not mutagenic for Salmonella typhimurium TA98, TA100, TA1535, and TA1537 (McCann et al., 1975). Similarly, in testing performed under the National Toxicology program (NTP, 1980), ethylene glycol was not mutagenic for Salmonella typhimurium TA98, TA100, TA1535, and TA1537 with or without metabolic activation.

Conan et al. (1979) found significant increases in the number of polychromatic (newly formed) erythrocytes bearing Howell-Jolly bodies in mice treated with ethylene glycol. The mice were given 2 oral or intraperitoneal doses of ethylene glycol (1.25-12.5 ml/kg/dose) spaced 24 hours apart, the second dose occurring 6 hours before the mice were killed. According to the authors, Howell-Jolly bodies are fragments arising from previous breakage of chromosomes. Thus, the results indicate that ethylene glycol caused chromosome breakage. In the same study, ethylene glycol did not, however, induce increases in the number of chromosome anomalies in bone marrow cells (Conan et al., 1979).

An abstract (Rapaport, 1948) from the Russian literature states that ethylene glycol produced 0.8% mutations in Drosophila. Because control levels were not given, this result cannot be evaluated.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

The metabolism of ethylene glycol in animals and the role of its metabolites in toxicity have been well reviewed by Parry and Wallach (1974) and by Vale (1979). According to these authors, ethylene glycol is oxidized to aldehydes (principally glycoaldehyde) and, subsequently, to acids (glyoxylic acid, glycolic acid, oxalic acid) and to carbon dioxide. Ethylene glycol itself does not appear to be toxic, and compounds (e.g., ethanol) that inhibit the metabolism of ethylene glycol diminish its toxicity. Hence, the toxicity of ethylene glycol may be mediated through its metabolites. The aldehyde metabolites are thought to be toxic to the central nervous system; the accumulation of glycolic acid appears (as previously discussed) to account for metabolic acidosis, and oxalic acid, although it is formed in small quantities, may be at least partially responsible for renal damage, and it produces hypocalcemia by chelating calcium. According to Bachman and Goldberg (1971), glyoxylic acid inhibits mitochondrial processes and, therefore, may be responsible for some of the toxic effects observed after administration of ethylene glycol.

b. Human Studies

The ready availability of ethylene glycol in antifreeze solutions, its sweet taste, and its intoxicating effects have led to many cases of human poisoning. Ethylene glycol has been ingested as an alcohol substitute, a suicide agent, and accidentally by children. The estimated lethal oral dose of ethylene glycol for an adult is 100 ml (1.6 g/kg) (Hunt, 1932, Rowe, 1963;

Browning, 1965; Parry and Wallach, 1974), although Gaultier et al. (1976) reported that an individual died after ingesting 50 ml and another recovered (with appropriate treatment including hemodialysis) after drinking 1000 ml.

(1) Pharmacokinetics

In a study by Wills et al. (1974), men exposed to about 30 mg/m^3 (≈12 ppm) aerosolized ethylene glycol for 20 to 22 hours a day for 30 days did not absorb appreciable amounts of ethylene glycol. The concentrations of ethylene glycol in serum and urine of the 20 exposed men were not different from concentrations in serum and urine of 10 unexposed men. The authors estimated that the subject who consistently had the highest urinary levels of ethylene glycol (18 mg/100 ml) may have absorbed approximately 0.8 g of ethylene glycol per day. A report of adverse health effects from exposure to vapors of (heated) ethylene glycol (Triosi, 1950), however, indicates that toxic amounts can be absorbed through the respiratory tract under certain conditions.

The ethylene glycol content of tissues and body fluids of a 14-year old boy who died within 24 hours of ingesting an antifreeze solution containing ethylene glycol were as follows: blood, 21 mg %; urine, 56 mg %; brain, 26 mg %; kidney, 17 mg %, liver, 15 mg % and pancreas, 13 mg % (Moriarty and McDonald, 1974). Ethylene glycol contents of tissues of a 22-year old man who died 48 hours after ingestion of antifreeze containing ethylene glycol were: liver, 165 mg %; brain, 107 mg %; and kidney, 45 mg % (Siew et al., 1975). The concentration of ethylene glycol in his blood before he died was 300 mg %.

The major components detected in ether extracts of blood and urine from an ethylene glycol-intoxicated patient were ethylene glycol and glycolic acid (Clay and Murphy, 1977). No other metabolites of ethylene glycol were found.

An end product of ethylene glycol metabolism is oxalic acid, which forms a relatively insoluble chelate with calcium. Crystals of calcium oxalate are commonly found in the kidneys and brains of persons who died after ingesting ethylene glycol, and occasionally in other organs such as the liver (Siew et al., 1975; Moriarty and McDonald, 1974; Pons and Custer, 1946; Gaultier et al., 1976). Calcium oxalate crystals and elevated levels of oxalic acid have been detected in the urine of persons who ingested ethylene glycol (Parry and Wallach, 1974; Siew et al., 1975; Schreiner and Maher, 1965; Clay and Murphy, 1977).

(2) Health Effects

The clinical events following ingestion of toxic amounts of ethylene glycol have been grouped by Berman et al. (1957) into three stages. Their description has been generally accepted and elaborated by others (Schreiner and Maher, 1965; Moriarty and McDonald, 1974; Parry and Wallach, 1974; Vale, 1979). In the first stage, central nervous system effects occur within 30 minutes to 12 hours of ingestion of ethylene glycol. With lower doses, the person appears intoxicated. With higher doses, stupor, diffuse neurological abnormalities, depression of deep reflexes, coma, convulsions, grand mal seizures, and death may occur. Vomiting, hematemesis, metabolic acidosis (compensated or uncompensated), hypocalcemia, hypercalemia, moderate leukocytosis, slight fever, proteinuria, microscopic hematuria, and profuse calcium oxalate crystalluria are frequently observed during this stage (Berman et al., 1957; Friedman et al.,1962; Gaultier et al., 1976; Moriarty and McDonald, 1974; Parry and Wallach, 1974; Pons and Custer, 1946; Schreiner and Maher, 1965; Siew et al., 1975).

In the second stage, cardiopulmonary effects may become prominent in patients who survive after the first 12 to 24 hours. Tachypnea,

mild hypertension, tachycardia, and finally cyanosis, hypotension, and cardiac or respiratory failure and death may occur (Gaultier et al., 1976; Hagemann and Chiffelle, 1948; Moriarty and McDonald, 1974; Parry and Wallach, 1974; Siew et al., 1975).

In the third stage, those patients who survive beyond the second or third day usually suffer renal impairment. Bilateral flank pain, tenderness over the kidneys, proteinuria, oliguria or anuria followed by diuresis, elevated blood urea nitrogen levels, and oxaluria are characteristic of this phase. Death may result from renal failure. Patients who survive this phase often recover completely (Berman et al., 1957; Schreiner and Maher, 1965; Moriarty and McDonald, 1974; Parry and Wallach, 1974; Friedman et al., 1962). Muscle tenderness and elevated creatine phosphokinase levels (which may indicate necrosis of muscle) have been noted in a few cases (Friedman et al., 1962; Parry and Wallach, 1974).

Only one instance of adverse effects from industrial exposure to ethylene glycol was found in the literature searched. Thirty-eight women were chronically exposed to vapors of ethylene glycol in an electrolytic condensor factory while using a mixture of 40% ethylene glycol, 55% boric acid, and 5% ammonia heated to 105°C (Triosi, 1950). Nine of these women suffered recurrent attacks of unconsciousness lasting 5 to 10 minutes. All 9 had nystagmus, as did 5 others who had no other symptoms. The 5 women who had the most frequent spells of unconsciousness (almost every day) were given blood tests and found to have lymphocytosis. Nystagmus and episodes of unconsciousness ceased in 2 of the women when they were transferred to alternative work and in the others when the process was enclosed and internally drafted. There had been no such attacks in women employed in other areas of the same factory.

In experiments with volunteers, Wills et al. (1974) found that nearly continuous exposure to approximately 30 mg/m^3 (≈ 12 ppm) of aerosolized ethylene glycol for 30 days (as described under Pharmacokinetics) made no difference in the performance of 20 men as compared to that of unexposed men on a battery of psychological tests. These tests were designed to detect effects on reaction time, visual motor coordination, perception, and mental ability. Differences were also not detected in hematologic, clinical chemistry, or urinalysis values. Higher levels of exposure (140 mg/m^3) provoked complaints of irritation of the upper respiratory tract. Concentrations above 200 mg/m^3 proved to be intolerable because of a burning sensation in the trachea and coughing. The authors concluded that the irritative effects of ethylene glycol make it highly unlikely that an individual would remain in an atmosphere of ethylene glycol concentrated enough to cause toxic effects. This conculsion would not necessarily apply, however, to vapors of ethylene glycol.

(3) Target Organ Toxicity

Autopsies of individuals who had died within 44 hours of ingesting ethylene glycol revealed edema and congestion of the brain, petechiae throughout the cerebrum and cerebellum, exudative meningoencephalitis and degeneration of the ganglion cells of the cerebral cortex, cerebellum, and brain stem with satellitosis (Pons and Custer, 1946; Hagemann and Chiffelle, 1948; Friedman et al., 1962; Moriarty and McDonald, 1974). Crystals (presumed to be calcium oxalate) were seen in the brain and leptomeninges. The crystals usually appeared in the vessel walls and perivascular spaces, and occasionally in the vascular lumina and within the brain substance itself (Pons and Custer, 1946; Siew et al., 1975). Crystals have also been observed in the inflammatory exudate (Moriarty and McDonald, 1974).

Pathological changes in the lungs included edema, acute passive congestion, widespread petechial hemorrhages in both pleura and lungs, decreased crepitation, consolidation, and bronchopneumonia (Friedman et al., 1962; Hagemann and Chiffelle, 1948; Moriarty and McDonald, 1974; Pons and Custer, 1946). Pons and Custer (1946) found a few isolated crystals in the lungs. Occasional evidence of damage to the heart included cardiac dilatation, hemorrhage in the heart and pericardium, and interstitial myocarditis (Friedman et al., 1962; Hagemann and Chiffelle, 1948).

The most striking changes occurred in the kidneys. Individuals who died within 44 hours of ingesting ethylene glycol had little evidence of renal pathology other than congestion and the presence of calcium oxalate crystals in the renal tubules (Pons and Custer, 1946; Hagemann and Chiffelle, 1948). Persons who survived beyond the second or third day, however, were found during biopsy or autopsy to have suffered renal damage. Clinical evidence of impaired function has been presented in the Health Effects section. Gross and histological examination of the kidneys revealed edema, hyperemia, various degrees of hemorrhage, degeneration and desquamation of the tubular epithelium with preservation of the basement membranes, and focal regeneration. Calcium oxalate crystals appeared both within the epithelial cells and within the lumens of the proximal tubules and in a few of the collecting and distal tubules (Berman et al., 1957; Schreiner and Maher, 1965; Pons and Custer, 1946; Siew et al., 1975; Friedman et al., 1962; Gaultier et al., 1976).

Hepatic damage has been reported in a few cases. Congestion (Moriarty and McDonald, 1974; Pons and Custer, 1946), edema (Hagemann and Chiffelle, 1948), central hydropic degeneration (Friedman et al., 1962; Pons and Custer, 1946), fatty change (Hagemann and Chiffelle, 1948), and occasional crystals (Siew et al., 1975; Friedman et al., 1962) have been observed in a few livers at autopsy.

The spleen and other internal organs sometimes appeared congested with occasional petechial hemorrhages (Friedman et al., 1962; Moriarty and McDonald, 1974; Hagemann and Chiffelle, 1948). Friedman et al. (1962) noted histological evidence of parenchymatous and interstitial myositis in 2 fatal cases of ethylene glycol poisoning.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

According to the NTP (1980), ethylene glycol is scheduled for teratology and reproductive toxicology assays in fiscal years 1981-1983 and for carcinogenicity bioassay starting in fiscal year 1981. The carcinogenicity bioassay will involve administering this glycol in the diet to rats and mice.

Ethylene glycol is being tested (in-house) for mutagenicity and genetic toxicity by the Food and Drug Administration (FDA) Bureau of Medical Devices (NTP, 1981). Reproductive and developmental toxicity testing are to be started in fiscal year 1981 by the FDA National Center for Toxicological Research (NTP, 1981).

16. Exposure Standards

The ACGIH (1981) has adopted a Threshold Limit Value-Time-Weighted Average (TLV-TWA) for ethylene glycol of 125 mg/m^3 (50 ppm) for the vapor and 10 mg/m^3 for the particulate (mist). The tentative Threshold Limit Value-Short-Term Exposure Limit (TLV-STEL) proposed by the ACGIH (1981) for the particulate is 20 mg/m^3 (7.9 ppm).

17. Sources of Additional Relevant Information

The chemistry, environmental aspects, and health effects of ethylene glycol have been reviewed by Miller (1979).

NIOSH Health Hazard Evaluations (HHEs) relating to ethylene glycol have been conducted at the following facilities:

Location	HHE No.
Air products and Chemicals, Inc., Hometown, PA	74-23-216
Bamber Bait Co., Gainsville, TX	78-27-551
Formica Corporation, Cincinnati, OH	75-145-327

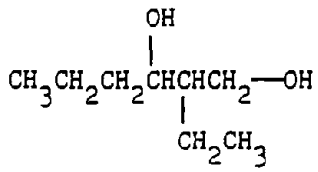
18. Other Pertinent Data

The vapor pressure of ethylene glycol is low enough at room temperature that this glycol should not present an inhalation hazard unless used at high temperatures or sprayed (Rowe, 1963; Browning, 1965).

I. 2-ETHYL-1,3-HEXANEDIOL

1. Chemical Name: 2-Ethyl-1,3-hexanediol

2. Chemical Structure:



3. Synonyms: Carbide 6-12
Compound 6-12 Insect Repellent
ENT 375
Ethohexadiol
2-Ethylhexane-1,3-diol
Ethyl hexanediol
Ethyl hexyleneglycol
2-Ethyl-3-propyl-1,3-propanediol
1,3-Hexanediol, 2-ethyl-
3-Hydroxymethyl-n-heptan-4-ol
6-12 Insect Repellent
Octylene glycol
Repellent 612
Rutgers 612

4. Chemical Abstract Service (CAS) Number: 94-96-2

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

MO2625000

6. Chemical and Physical Properties:

Description:	colorless, slightly viscous, odorless liquid
Molecular Weight:	146.26
Boiling Point:	243.2°C
Melting Point:	-40°C (sets to glass below this temperature)
Vapor Pressure:	<0.01 mm Hg (20°C)
Solubility:	4.2% by wt. in water (20°C); soluble in alcohol, ether, and chloroform
Specific Gravity:	0.9422_{20}^{20}
Stability:	combustible

7. Production

Production figures are not available; however, based upon uses, it is judged that annual production is on the order of one million pounds or more (SRC Estimate).

Data available from the U.S. EPA (1980) regarding producers of 2-ethyl-1,3-hexanediol and production volumes are presented in Table 21.

8. Use

2-Ethyl-1,3-hexanediol is used in two-package urethanes as a viscosity reducer and, more importantly, as a reactive diol (Union Carbide, 1978). At room temperatures it acts as a conventional solvent, but at elevated temperatures it reacts to eliminate or minimize solvent emissions. Urethane coatings utilizing 2-ethyl-1,3-hexanediol are used in the automobile, appliance, and thermoplastics industries.

Due to its useful blending, lubricity, and emollient properties, 2-ethyl-1,3-hexanediol is a useful component of cosmetic creams, lotions, hair dressings, shampoos, and liquid cleansing creams (Union Carbide, 1978).

2-Ethyl-1,3-hexanediol is used as an ingredient in insect repellents (Martin and Worthing, 1977; Sherman, 1978). In 1971, less than a million pounds were produced for this purpose (Johnson, 1972). As an insect repellent, it is widely formulated with dimethyl phthalate and butopyrononxyl in the ratio of 2:6:2 (Martin and Worthing, 1977).

2-Ethyl-1,3-hexanediol is also used as a conditioning agent for cork products, as a film coalescing aid for various latexes, as a specialty ink solvent, and as an intermediate for producing anti-oxidants and corrosion inhibitors (Union Carbide, 1978).

9. Manufacturers and Distributors

2-Ethyl-1,3-hexanediol is commercially manufactured by Union Carbide Corp. (USITC, 1980).

Distributors include (1980-81 OPD Chemical Buyers' Directory, 1980; Chem Sources--USA, 1980):

Table 21. Producers of 2-Ethyl-1,3-Hexanediol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Union Carbide South Charleston, WV	Manufacturer	confidential
Henley and Co. New York City, NY	Importer	confidential
American Hoechst Bridgewater, NJ	Importer	confidential

Aldrich Chem.	EM Lab
Alltech Assoc.	Fisher Sci.
American Hoechst	Gallard-Schelsinger
Anachemica Chem.	Henley and Co.
Atomergic Chemetals	ICN/K and K
Chem. Procurement Lab.	Lachat Chem.
Chemsampo	MCB Reagents
Chem. Services	Tridom Chem.
Eastman Kodak	George Uhe and Co.

10. Manufacturing Processes

2-Ethyl-1,3-hexanediol is manufactured by the hydrogenation of butyraldol (Sherman, 1978). It can also be prepared by the condensation of butyraldehyde with magnesium aluminum ethoxide and the hydrolysis of the ester so formed (Martin and Worthing, 1977).

11. Additives or Impurities

2-Ethyl-1,3-hexanediol has the following specifications (Union Carbide, 1978):

Purity % by wt., min.	97.0
Acidity % by wt., max., as acetic	0.02
Water % by wt., max.	0.05
Color, Pt-Co Units, max.	20
Suspended matter	substantially free

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 2-ethyl-1,3-hexanediol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 2-ethyl-1,3-hexanediol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Lethal and irritant dose data for 2-ethyl-1,6-hexanediol are summarized in Table 22. This glycol was irritating to the skin and eyes of rabbits. No other information on the effects of acute exposure to 2-ethyl-1,3-hexanediol were found in the literature searched.

(2) Subchronic Exposures

Rats (N=10) given 0.7 g/kg body weight/day of 2-ethyl-1,3-hexanediol in their food for 30 days experienced a reduction in growth but had no reduction in "appetite" (food intake?). Liver and kidney weights were unaffected by the treatment and no microscopic lesions were produced in liver, kidney, spleen, or testis. A dosage of 0.48 g/kg/day had no effect on any of the above parameters (Smyth et al., 1951).

Daily application of 0.5, 1.0, 2.0, or 4.0 ml/kg (0.47, 0.94, 1.88, or 3.77 g/kg) 2-ethyl-1,6-hexanediol to the uncovered clipped skin of rabbits for 90 days resulted in slight to moderate hydropic degeneration of hepatic and renal cells, and moderate tubular atrophy of the testes in animals that died (Draize et al., 1948). No lesions were found in survivors. The LD50 was 1.88 g/kg/day. Irritation of the skin was moderate to marked in rabbits that died and slight in survivors. According to the authors, this glycol was poorly absorbed through the skin but the small amounts absorbed produced a narcosis.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

Stenbach and Shubick (1974) tested the effect on tumor incidence of twice weekly applications of 0.02 ml of 10, 50, or 100% 2-ethyl-

Table 22. Acute Effects of 2-Ethyl-1,3-Hexanediol

Route	Species	Dose[a] g/kg	Response[a]	Reference
oral	rats	2.71	LD50, 14 d	Smyth et al., 1951
oral	rats	2.5	LD50, estimated, 6 d	Draize et al., 1948
oral	rats	6.12	LD50, 14 d	Union carbide, 1978
oral	mice	4.2	LD50, estimated, 6 d	Draize et al., 1948
oral	guinea pigs	1.9	LD50, estimated, 6 d	Draize et al., 1948
inhalation	rats	concentrated vapor, 8 h	No deaths	Union Carbide, 1978
dermal	rabbits	14.3, 24 h, closed dressing	LD50, 14 d	Union Carbide, 1978
dermal	rabbits	9.4, 24 h, closed dressing	LD50, 14 d	Draize et al., 1944
dermal	rabbits	0.5 ml[b] (0.47 g), 24 h, closed dressing	Moderate irritation	Draize et al., 1948
dermal	rabbits	0.01 ml (0.009 g)[b],	Mild irritation	Union Carbide, 1978
ocular	rabbits	24 h, open 0.02 (0.018 g)[b]	Severe irritation, 18-24 h	Carpenter and Smyth, 1946
ocular	rabbits	not stated	Moderate irritation	Union Carbide, 1978

[a] d = day; h = hour

[b] Total dose

1,3-hexanediol to the shaved skin of female Swiss mice. Each dosage group consisted of 50 mice. Treatment for the lifespan of the animals produced no statistically significant differences in incidence of skin tumors or any other tumors as compared to appropriate controls.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

In 24-hour closed-patch tests with human subjects, 2-ethyl-1,3-hexanediol (0.1 ml) produced no irritation (Draize et al., 1948).

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of 2-ethyl-1,3-hexanediol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2-ethyl-1,3-hexanediol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of 2-ethyl-1,3-hexanediol as an occupational hazard was found in the literature searched.

J. 1,6-HEXANEDIOL

1. Chemical Name: 1,6-Hexanediol

2. Chemical Structure: $HO-CH_2(CH_2)_4CH_2-OH$

3. Synonyms: Hexamethylene glycol
1,6-Dihydroxyhexane

4. Chemical Abstract Service (CAS) Number: 629-11-8

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

MO2100000

6. Chemical and Physical Properties:

Description:	crystalline solid
Molecular Weight:	118.18
Boiling Point:	243.9°C
Melting Point:	41°C
Vapor Pressure	---
Solubility:	miscible with water and alcohol; slightly soluble in ether; insoluble in benzene
Specific Gravity:	0.95^{20}_{20}
Stability:	combustible; Flash point: 210°F (TCC)

7. Production

In 1971, roughly 43 million pounds of 1,6-hexanediol were produced as an intermediate in the production hexamethylenediamine (Blackford, 1973).

Data available from the U.S. EPA (1980) regarding producers of 1,6-hexanediol and production volumes are presented in Table 23.

8. Use

By volume, the most important use of 1,6-hexanediol is as an on-site intermediate in the production of hexamethylenediamine. Hexanethylenediamine is manufactured via 1,6-hexanediol by Celanese Chemical Corp. at their 85 million lb/year capacity plant in Bay City, TX (SRI International, 1980).

Table 23. Producers of 1,6-Hexanediol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Celanese Chem. Co. Bay City, TX	Manufacturer	50-100 million lb
Haven Chemical Philadelphia, PA	Manufacturer	confidential
Morton Chemical Ringwood, IL	Manufacturer	1-10 thousand lb
BASF Wyandotte Parsippany, NJ	Importer	none

1,6-Hexanediol is also used as an intermediate in the production of polyester, polyurethanes, and resins, as a plasticizer, as a coupling agent, as a solvent, and in gasoline refining (Hawley, 1977; The Merck Index, 1976).

9. Manufacturers and Distributors

1,6-Hexanediol is commercially produced by Celanese Chemical Corp. in Bay City, TX (SRI International, 1980; USITC, 1980).

The U.S. EPA (1980) also lists Haven Chem. and Morton Chem. as manufacturers.

Distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Chemical Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Accurate Chem. and Sci.	Columbia Organics
Aldrich Chem.	Eastern Chem.
Atomergic Chemetals	Eastman Kodak
BASF Wyandotte	Fisher Sci.
Bio-Clinical Lab.	ICN/K and K
California Aromatics and Flavors	Lachat Chem.
	MCB Reagents
Chem. Procurement Lab.	Pfaltz and Bauer
Chemsampo, Inc.	Tridom Chem.
Chem Services	Well Chem.

10. Manufacturing Processes

1,6-Hexanediol is commercially produced by hydrogenating the air oxidation product of cyclohexane (Blackford, 1973).

11. Impurities or Additives

Commercial 1,6-hexanediol has the following specifications (Chemical Week: 1981 Buyers' Guide Issue, 1980):

Purity, wt. %	98.8
Water content, wt. %, max.	0.05
Iron, ppm max.	1
Acidity, wt. %, max.	0.02

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 6,123 workers are potentially exposed to 1,6-hexanediol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 1,6-hexanediol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Lethal and irritant dose data for 1,6-hexandiol are presented in Table 24. The LD50 value calculated from deaths occurring during the first 24 hours was virtually identical to the LD50 value calculated from deaths occurring the first 6 days after intraperitoneal injection, indicating a lack of delayed toxicity (Holman et al., 1979). 1,6-Hexanediol produced ataxia in rats when administered intraperitoneally in a high but sublethal dose (McCreery and Hunt, 1978). This glycol was irritating to the skin and eyes of rabbits when applied in an unpurified vehicle (Carpenter et al., 1974).

(2) Subchronic Exposures

Although a related diol, 2,5-hexanediol, has been found to be neurotoxic to rats when administered subchronically 1,6-hexanediol was not neurotoxic when tested in the same manner (Spencer and Schaumberg, 1977; Spencer et al., 1978). Rats (N=6) that received 0.5% 1,6-hexanediol in their drinking water for 12 weeks gained weight normally and had "normal clinical signs" (Spencer et al., 1978). The histological appearance of tissues from the nervous system of these treated animals was similar to that of controls.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

Table 24. Acute Effects of 1,6-Hexanediol

Route[a]	Species	Dose[b] (g/kg)	Response[b]	Reference
oral	rats	3.73	LD50, 14 d	Holman et al., 1979
inhalation	rats	concentrated vapor, 8 h	no deaths	Carpenter et al., 1974
i.p.	mice	1.76	LD50, 24 h	Holman et al., 1979
i.p.	mice	1.74	LD50, 6 d	Holman et al., 1979
dermal	rabbits	>10 (in vehicle[c])	LD50	Carpenter et al., 1974
dermal	rabbits	0.01 g[d] in vehicle[c], 24 h, open	mild irritation	Carpenter et al., 1974
ocular	rabbits	0.5 g[d] in vehicle[c]	severe irritation, 18-24 h	Carpenter et al., 1974
ocular	rabbits	0.1 g[d] in vehicle[c]	mild to moderate 18-24 h	Carpenter et al., 1974

[a] i.p. = intraperitoneal

[b] d = day; h = hour

[c] The vehicle used by Carpenter et al. (1974) was not specified.

[d] total dose

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

Following oral administration to rabbits, 4 to 9% of a dose of 1,6-hexanediol was excreted as a glucuronide in the urine. Another urinary metabolite of this glycol was adipic acid, the product resulting from oxidation of both hydroxyl groups (Gessner et al., 1960).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of 1,6-hexanediol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 1,6-hexanediol were found.

17. Sources of Additional Relevant Information

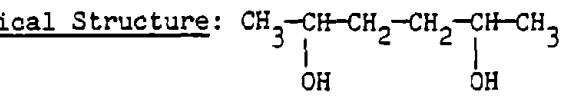
No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of 1,6-hexanediol as an occupational hazard was found in the literature searched.

K. 2,5-HEXANEDIOL

1. Chemical Name: 2,5-Hexanediol

2. Chemical Structure: 

3. Synonyms: Hexane-2,5-diol

4. Chemical Abstract Service (CAS) Number: 2935-44-6

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number: MO2275000

6. Chemical and Physical Properties:

Description:	solid
Molecular Weight:	118.17
Boiling Point:	216-218°C (750 mm Hg)
Melting Point:	43°C
Vapor Pressure:	---
Solubility:	soluble in water, alcohol, and ether
Specific Gravity:	0.9610_4^{20}
Stability:	combustible; Flash point: 215°F (CC)

7. Production

Data available from the U.S. EPA (1980) regarding producers of 2,5-hexanediol and production volumes are presented below:

BASF Wyandotte Corp. (Parsippany, NJ)
Importer
1977 Production: 10-100 thousand lb.

8. Use

2,5-Hexanediol is used in a variety of organic syntheses and esterfications and is useful as an anti-icing agent for gasoline and as a stabilizer for pesticides (various patent literature).

9. Manufacturers and Distributors

There are no known commercial manufacturers of 2,5-hexanediol in the U.S.; however, it is imported in commercial quantities.

Distributors include (1980-81 OPD Chemical Buyers' Directory, 1980; Chem Sources--USA, 1980):

Aldrich Chem.	Eastern Chem.
Atomergic Chem.	Fisher Sci.
BASF Wyandotte	ICN/K and K
Bio-Clinical Lab.	International Enzymes
Chem. Procurement Lab.	Koch Chem.
Chemsampo	Lachat Chem.
Chem. Services	MCB Reagents
Columbia Organics	Polysciences
Crompton and Knowles Corp.	Tridom Chem.

10. Manufacturing Processes

The commercial manufacturing process was not available from the literature searched.

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 2,5-hexanediol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 2,5-hexanediol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Lethal and irritant dose data for 2,5-hexanediol are presented in Table 25. When administered intraperitoneally in a high but sublethal dose, 2,5-hexanediol produced ataxia in rats (McCreery and Hunt, 1978). In rabbits, lethal amounts of this glycol (dissolved in carbitol) were absorbed through the skin (Smyth and Carpenter, 1948). 2,5-Hexanediol (dissolved in

Table 25. Acute Effects of 2,5-Hexanediol

Route	Species	Dose[a] (g/kg)	Response[a]	Reference
oral	rats	5.0 (in cellosolve)	LD50; 14 d	Smyth and Carpenter, 1948
inhalation	rats	saturated vapor, 8 h	no deaths	Symth and Carpenter, 1948
dermal	rabbits	16.3 (in carbitol), 24 h, closed dressing	LD50; 14 d	Symth and Carpenter, 1948
ocular	rabbits	0.5 g[b] (in ethanol)	Severe irritation	Symth and Carpenter, 1948
ocular	rabbits	0.1 g[b]	Mild to moderate irritation	Symth and Carpenter, 1948

[a] d = day; h = hour

[b] total dose

ethanol) was found to be irritating to the eyes of rabbits (Smyth and Carpenter, 1948).

(2) Subchronic Exposures

Three different laboratories (Spencer and Schamburg, 1977, reported more fully in Spencer et al., 1978; Krasavage et al., 1979; Eben et al., 1979), have reported that subchronic oral administration of 2,5-hexanediol to rats produced neurotoxic effects similar to those produced by n-hexane and methyl-n-butyl ketone in experimental animals and in humans. The neuropathology condition produced by these chemicals has been termed central-peripheral distal axonopathy, dying-back disease, and giant axonal neuropathy. Clinical signs in rats included weakness of the hind limbs, followed by the dragging of the hind fat, and ultimately paralysis of the hind limbs. Histopathological changes were characterized by distal, retrograde axonal degeneration of the giant axonal type in the long and large fiber tracts of the peripheral and central nervous systems (Spencer et al., 1978; Eben et al., 1979).

The onset of clinical signs of neuropathy was about 6 to 10 weeks after initiation of treatment by gavage with 40 mg/kg/day (Eben et al., 1979) or 780 mg/kg/day, 5 days a week (Krasavage et al., 1979), or by administration of 0.5% 2,5-hexanediol in the drinking water (Spencer et al., 1978). All three laboratories reported that food consumption and body weight gain decreased as signs of neurotoxicity became pronounced. Clinical chemistry tests for liver damage and kidney function gave values for treated rats that were within the normal range (Eben et al., 1979).

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

Atrophy of the germinal epithelium of the testis was observed in male rats gavaged with 780 mg/kg/day of 2,5-hexanediol, 5 days a week for 90 days (Krasavage et al., 1979). These rats also experienced neurotoxic effects and a decrease in food consumption and weight gain as previously described.

(8) Other Relevant Information

The neurotoxicity of 2,5-hexanediol appears to be mediated through its metabolite 2,5-hexanedione (Eben et al., 1979; Krasavage et al., 1979).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

Research to evaluate the effect of n-hexane and related hydrocarbons such as 2,5-hexanediol in the production of delayed neurotoxicity by EPN (o-ethyl-o-4-nitrophenyl phenylphosphonothionate) is currently being conducted

by Donia and Graham at Duke University, School of Medicine, Dept. of Pharmacology (SSIE, 1981). The project is sponsored by NIOSH.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2,5-hexane were found.

17. Sources of Additional Relevant Information

Spencer and coworkers (1980) have recently published a review of hexacarbon neurotoxicity which includes information on 2,5-hexanediol.

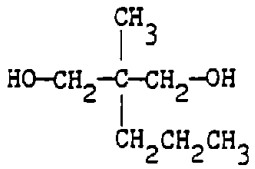
18. Other Pertinent Data

No other information that would aid in the assessment of 2,5-hexane as an occupational hazard was found in the literature searched.

L. 2-METHYL-2-PROPYL-1,3-PROPANEDIOL

1. Chemical Name: 2-Methyl-2-propyl-1,3-propanediol

2. Chemical Structure:



3. Synonyms: 2,2-Bis(hydroxymethyl)pentane
2-Methyl-2-n-propyl propanediol-1,3
1,3-Propanediol, 2-methyl-2-propyl-

4. Chemical Abstract Service (CAS) Number: 78-26-2

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not listed

6. Chemical and Physical Properties:

Description:	crystalline solid
Molecular Weight:	132.20
Boiling Point:	234°C
Melting Point:	62-63°C
Vapor Pressure	---
Solubility:	soluble in water and in organic solvents
Specific Gravity:	---
Stability:	combustible

7. Production

Data available from the U.S. EPA (1980) regarding producers of 2-methyl-2-propyl-1,3-propanediol and production volumes are presented below:

Millmaster Chem. Co. (Berkeley Heights, NJ)
Manufacturer - Not Distributed
1977 Production: 0.1 to 1 million pounds

American Hoechst (Bridgewater, NJ)
Importer
1977 Production: confidential

8. Use

2-Methyl-2-propyl-1,3-propanediol is used in the manufacture of the tranquilizer Meprobamate, the coronary vasodilator Nitral (The Merck Index,

1976), and in other organic syntheses. It is captively used by its manufacturer Millmaster Chemical (U.S. EPA, 1980).

9. Manufacturers and Distributors

It is commercially made by Millmaster Chemical in Berkely Heights, NJ (USITC, 1980; U.S. EPA, 1980).

Distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Aceto Chem.	Crompton and Knowles
Aldrich Chem.	ICN/K and K
BASF Wyandotte	Orlex Chem.
Chemical Dynamics	Pfaltz and Bauer
Chem. Procurement Lab.	Polyscienes Inc.
Columbia Organics	Tridom Chem.

10. Manufacturing Processes

The commercial process is not available; however, it can be manufactured by the reaction of an aqueous mixture of formaldehyde and methylproply-CHCHO (Müller, 1957).

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 2-methyl-2-propyl-1,3-propanediol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 2-methyl-2-propyl-1,3-propanediol were not found in the literature searched.

14. Biological Effects

The only information found in the literature searched was data on the metabolism of this glycol in animals. After oral administration of 2-methyl-2-propyl-1,3-propanediol to rabbits, 23 to 49% of the dose was excreted in the urine as the glucuronide conjugation of the glycol (Gessner et al., 1960).

15. Ongoing Studies

No current toxicological or environmental studies of 2-methyl-2-propyl-1,3-propanediol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2-methyl-2-propyl-1,3-propanediol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of 2-methyl-2-propyl-1,3-propanediol as an occupational hazard was found in the literature searched.

M. NEOPENTYL GLYCOL

1. Chemical Name: Neopentyl Glycol

2. Chemical Structure: $HOCH_2C(CH_3)_2CH_2OH$

3. Synonyms: Dimethylolpropane
2,2-Dimethyl-1,3-propanediol
Dimethyltrimethylene glycol
Neopentylene glycol
NPG
1,3-Propanediol, 2,2-dimethyl-

4. Chemical Abstract Service (CAS) Number: 126-30-7

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

TY5775000

6. Chemical and Physical Properties:

Description:	white crystalline solid
Molecular Weight:	104.15
Boiling Point:	208°C
Melting Point:	120-130°C
Vapor Pressure:	---
Solubility:	65% w/w in water; soluble in alcohols, ethers, ketones, and benzene; relatively insoluble in alkanes
Specific Gravity:	1.066_4^{25}
Stability:	combustible; Flash point: 120°C (COC); Autoignition temp.: 399°C

7. Production

Data available from the U.S. EPA (1980) regarding producers of neopentyl glycol and production volumes are presented in Table 26.

8. Use

Neopentyl glycol is used extensively as a chemical intermediate in the manufcture of polyester and alkyd resins (Bramer and Davis, 1980). In 1976, the estimated demand for neopentyl glycol intermediate in unsaturated polyester was 10.1 million pounds (Frey, 1976).

Table 26. Producers of Neopentyl Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Texas Eastman Longview, TX	Manufacturer	10-50 million lb
Stauffer Chemical Gallipolils Ferry, WV	Manufacturer	confidential
Henkel Inc. Teaneck, NJ	Importer	under 1000 lb
Ashland Chem. Dublin, OH	Importer	none
BASF Wyandotte Parsippany, NJ	Importer	1-10 million lb
Sakai Trading NY Inc. New York City, NY	Importer	none

Neopentyl glycol is also used extensively as a chemical intermediate in the manufacture of polyurethane polyols, synthetic lubricants, polymeric plasticizers, and other polymers (Bramer and Davis, 1980).

9. Manufacturers and Distributors

SRI International (1980) and USITC (1980) list Eastman Kodak (Texas Eastman) in Longview, TX as the sole manufacturer. Bramer and Davis (1980) also list the Badische Division of BASF as a manufacturer.

Distributors of neopentyl glycol include (Chemical Week: 1981 Chemical Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Aldrich Chem.	Helm NY Chem.
Anachemia Chem.	ICN/K and K
Atomergic Chemetals	Lachat Chem.
Chem. Procurement Lab.	MCB Reagents
Chem Services	Mitsubishi Gas Chem.
Columbia Organics	Monomer-Polymer and Dajac Lab.
Eastern Chem.	Pfaltz and Bauer
EM Lab	Thorson Chem.
Fisher Sci.	Tridom Chem.

10. Manufacturing Processes

Commercial preparation of neopentyl glycol can be via an alkali-catalyzed condensation of isobutyraldehyde with 2 moles of formaldehyde (crossed Cannizzaro reaction) (Bramer and Davis, 1980).

11. Impurities or Additives

Commercial grade assays at 97 wt. % minimum (Bramer and Davis, 1980).

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 19,523 workers are potentially exposed to neopentyl glycol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to neopentyl glycol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Lethal and irritant dose data for neopentyl glycol are summarized in Table 27. These data are from toxicity studies conducted by the Health, Safety, and Human Factors Laboratory of the Eastman Kodak Company (Eastman Chemical Products, 1981c). Neopentyl glycol, when dissolved in acetone/corn oil or an unspecified vehicle, was irritating to the skin and eyes of experimental animals (Eastman Chemical Products, 1981c). No other information on the effects of acute exposure to neopentyl glycol was found in the literature searched.

(2) Subchronic Exposures

Rats fed 0.1% neopentyl glycol in the diet for 36 days had no effects on food consumption, weight gain, behavior, hematologic and serum chemistry values, urinalysis, or relative and absolute liver and kidney weights. This treatment produced no gross pathologic or histopathologic changes in the tissues. Results were similar when rats were fed 1.0% neopentyl glycol in the diet for 36 days, except that food consumption and weight gain were depressed at this higher dosage (Eastman Chemical Products, 1981c).

Rats exposed to an atmosphere of 17 mg/l (=4000 ppm) neopentyl glycol 6 hours a day for 10 days had signs (unspecified) of irritation, but their behavior was otherwise normal. Their weight gain was unaffected by the exposures (Eastman Chemical Products, 1981c).

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

Table 27. Acute Effects of Neopentyl Glycol

Route	Species	Dose[a] (g/kg)	Response	Reference
oral	rats	6.4-12.8	LD50	Eastman Chemical Products, 1981c
oral	mice	3.2-6.4	LD50	Eastman Chemical Products, 1981c
inhalation	rats	167 mg/l (40,000 ppm), 6 h	Irritation; lethal to 1 of 3	Eastman Chemical Products, 1981c
dermal	guinea pigs	4 (as 20% solution in acetone and corn oil), 24 h, closed dressing	Slight to moderate irritation	Eastman Chemical Products, 1981c
ocular	rabbits	not stated	Mild irritation	Eastman Chemical Products, 1981c

[a] h = hour

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

In rabbits, orally administered neopentyl glycol was rapidly excreted in the urine conjugated with glucuronic acid. A minor urinary metabolite of this glycol was the monocarboxylic acid 3-hydroxy-2,2-dimethylpropionic acid (Gessner et al., 1960).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of neopentyl glycol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for neopentyl glycol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

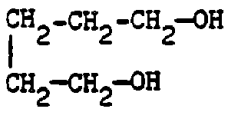
18. Other Pertinent Data

No other information that would aid in the assessment of neopentyl glycol as an occupational hazard was found in the literature searched.

N. 1,5-PENTANEDIOL

1. Chemical Name: 1,5-Pentanediol

2. Chemical Structure:



3. Synonyms: 1,5-Dihydroxy pentane
Pentamethylene glycol
Pentane-1,5-diol
1,5-Pentylene glycol

4. Chemical Abstract Service (CAS) Number: 111-29-5

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

SA0480000

6. Chemical and Physical Properties:

Description:	colorless, viscous, oil liquid
Molecular Weight:	104.15
Boiling Point:	242.4°C
Melting Point:	-15.6°C
Vapor Pressure:	<0.01 mm Hg (20°C)
Solubility:	completely soluble in water; miscible with methanol, alcohol, acetone, ethyl acetate; solubility in ether: 11% w/w; limited solubility in benzene, trichloroethylene, methylene chloride, petroluem ether, heptane.
Specific Gravity:	0.9921_{20}^{20}
Stability:	combustible; Flash point: 296°F (CC)

7. Production

Data available from the U.S. EPA (1980) regarding producers of 1,5-pentanediol and production volumes are presented in Table 28.

8. Use

1,5-Pentanediol is used as a chain extender or reactive diluent in urethane elastomers and coatings (Union Carbide, 1978). Esters of 1,5-Pentanediol are plasticizers for vinyl and other resins and are important

Table 28. Producers of 1,5-Pentanediol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Union Carbide Corp. South Charleston, WV	Manufacturer	10-100 thousand lb
Morton Chemical Ringwood, IL	Manufacturer	1-10 thousand lb
Thorson Chemical New York City, NY	Importer	under 2000 lb

intermediates for the manufacture of alkyd resins and urethane polymers (Hess et al., 1978).

1,5-Pentanediol is also used in hydraulic fluids, as a lube oil additive, and in antifreezes (Hawley, 1977).

9. Manufacturers and Distributors

The manufacturers are listed in Table 28.

The distributors include (Chem Sources--USA, 1980):

Aldrich Chem.	Eastman Kodak
Anachemia Chem.	EM Lab.
Atomergic Chemetals	Fairfield Chem.
BASF Wyandotte	Fisher Sci.
Chemical Procurement Lab.	Lachat Chem.
Chemsampo	MCB Reagents
Chem Services	Pfaltz and Bauer
Columbia Organics	Tridom Chem.

10. Manufacturing Processes

1,5-Pentanediol is manufactured by the hydrogenation of glutaraldehyde (Hess et al., 1978).

11. Impurities or Additives

Commercial grade 1,5-pentanediol has the following specifications (Union Carbide, 1978):

Purity % by wt., min.	96.0
Acidity % by wt., max., as acetic	0.01
Water % by wt., max.	0.2
Color, Pt-Co Units, max.	30
Suspended matter	substantially free
Carbonyl content, glutaraldehyde by wt., max.	0.5
Ester Content by wt., max. as valerolactone	1.5

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 65,721 workers are potentially exposed to 1,5-pentanediol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to 1,5-pentanediol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Lethal and irritant dose data for 1,5-pentanediol are summarized in Table 29. LD50 values were the same whether calculated for a 24-hour or a 6-day observation period after intraperitoneal injection (i.e., all deaths occurred during the first 24 hours), indicating a lack of delayed toxicity (Holman et al., 1979). 1,5-Pentanediol produced ataxia in rats when administrered intraperitoneally in a high but sublethal dose (McCreery and Hunt, 1978). Topical administration of this glycol resulted in little or no irritation to the skin and eyes of rabbits (Union Carbide, 1978; Smyth et al., 1962).

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

Table 29. Acute Effects of 1,5-Pentanediol

Route[a]	Species	Dose[b]	Response[b]	Reference
oral	rats	5.89	LD50, 14 d	Union Carbide, 1959, 1978; Smyth et al., 1962
i.p.	mice	2.25	LD50, both 24 h and 6 d	Holman et al., 1979
inhalation	rats	concentrated vapor, 8 h	No deaths, 14 d	Smyth et al., 1962; Union Carbide, 1978
dermal	rabbits	>19.8, 24 h covered dressing	LD50, 14 d	Union Carbide, 1959; Smyth et al., 1962
dermal	rabbits	0.01 ml (0.01 g)[c], 24 h, open	No irritation	Smyth et al., 1962; Union Carbide, 1978
ocular	rabbits	0.5 ml (0.5 g)[c]	Mild or moderate irritation, 18-24 h	Smyth et al., 1962
ocular	rabbits	not stated	Mild irritation	Union Carbide, 1978

[a] i.p. = intraperitoneal

[b] d = day; h = hour

[c] total dose

(8) Other Relevant Information

Following oral administration to rabbits, 1,5-pentanediol was not excreted in the urine as a conjugate with glucuronic acid. Small amounts of glutaric acid appeared in the urine and the rest of the compound appeared to have been "destroyed" in vivo, presumably by metabolism to carbon dioxide (Gessner et al., 1960).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of 1,5-pentanediol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 1,5-pentanediol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

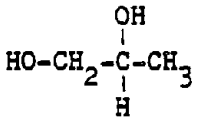
18. Other Pertinent Data

No other information that would aid in the assessment of 1,5-pentanediol as an occupational hazard was found in the literature searched.

O. PROPYLENE GLYCOL

1. Chemical Name: Propylene Glycol

2. Chemical Structure:



3. Synonyms: 1,2-Dihydroxypropane
1,2-Propanediol
Methyl ethylene glycol
Methyl glycol
Monopropylene glycol
Propane-1,2-diol
α-Propylene glycol
1,2-Propylene glycol
Sirline
Trimethyl glycol

4. Chemical Abstracts Service (CAS) Number: 57-55-6

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

TY2000000

6. Chemical and Physical Properties:

Description:	colorless viscous liquid with slightly acrid taste
Molecular Weight:	76.09
Boiling Point:	188.2°C
Melting Point:	-59°C
Vapor Pressure:	0.22 mm Hg (at 25°C)
Solubility:	completely soluble in water, acetone, chloroform, alcohol; soluble in ether
Specific Gravity:	1.036_4^{25}
Stability:	combustible; Flash point (open cup): 225°F

7. Production

Production in recent years is as follows (USITC, 1977-1980):

Year	Production (in millions of pounds)
1979	610
1978	547
1977	489
1976	517

CMR (1980) projects a future growth rate of 4% per year through 1984.

Data available from the U.S. EPA (1980) regarding producers of propylene glycol and production volumes are presented in Table 30.

8. Use

The following tabulation presents the percentage of the total amount of propylene glycol produced that is used in each of the applications listed (CMR, 1980):

	Percentage of Total
Unsaturated polyester resins	42
Exports	12
Semi-moist pet food	11
Food and pharmaceutical use	9
Cellophane	7
Humectant for cigarette tobacco	6
Polymerce plasticizers	6
Miscellaneous	7

9. Manufacturers and Distributors

Table 31 lists the major manufacturers and their estimated annual production capacity for propylene glycol.

There are nearly 100 commercial distributors of propylene glycol.

10. Manufacturing Processes

Propylene glycol is manufactured commercially by the hydrolysis of propylene oxide by a process analogous to that used to produce ethylene glycol from ethylene oxide. The manufacturing process is outlined in Figure 3.

Propylene glycol is also manufactured in industry from propylene obtained in the cracking of propane. The propylene is converted to the chlorohydrin by chlorine water and the chlorohydrin is converted to the glycol by

Table 30. Producers of Propylene Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Olin Corp.		
Brandenburg, KY	Manufacturer	10-50 million lb
Dow Chemical		
Freeport, TX	Manufacturer	50-100 million lb
Plaquemine, LA	Manufacturer	100-500 million lb
Oxirane Chem. Co.		
Pasadena, TX	Manufacturer	100-500 million lb
Haven Chemical		
Philadelphia, PA	Manufacturer	under 1000 lb
Union Carbide		
South Charleston, WV	Manufacturer	confidential
BASF Wyandotte		
Spartanburg, SC	Manufacturer	none
Parsippany, NJ	Importer	none
Ashland Chemical		
Great Meadows, NJ	Manufacturer	10-100 thousand lb
ABC Compounding Co.		
Atlanta, GA	Manufacturer	1-10 thousand lb
March Chemical		
Denham Springs, LA	Manufacturer	10-100 thousand lb
Hercules Inc.		
Harbor Beach, MI	Manufacturer	confidential
Haarman and Reimer		
Springfield, NJ	Manufacturer	confidential
Jefferson Chemical		
Port Nechos, TX	Manufacturer	confidential
Conroe, TX	Manufacturer	confidential
United Mineral and Chem.		
New York City, NY	Importer	under 1000 lb
Henkel Inc.		
Teaneck, NJ	Importer	under 1000 lb
EM Laboratories		
Elmsford, NY	Importer	confidential

Table 30. Producers of Propylene Glycol and Production Ranges (U.S. EPA, 1980) (Cont'd)

Producer	Type of Production	1977 Production Range
Milijac Inc. ---, CT	Importer	none
Symarome Corp. New York City, NY	Importer	none
Sakai Trading New York City, NY	Importer	none
Mitsubishi International New York City, NY	Importer	1-10 million lb
Prochimie International New York City, NY	Importer	1-10 million lb
J.E. Halma Co. Lodi, NJ	Importer	confidential
Rohm and Haas Co. Philadelphia, PA	Importer	none
Ciba-Geigy Corp. Ardsley, NJ	Importer	none
ICC Industries New York City, NY	Importer	1-10 thousand lb
ICI Amer. Wilmington, DE	Importer	confidential

Table 31. Producers of Propylene Glycol and Estimated Production Ranges

Producer and Location	Estimated Annual Capacity (Millions of Pounds) (SRI International, 1980)	(CMR, 1980)
Dow Chem.		
Freeport, TX	250	250
Plaquemine, LA	150	150
Olin Corp.		
Brandenburg, KY	90	70
Oxirane International		
Bayport, TX	250	230
Texaco Inc.		
Port Neches, TX	50	40
Union Carbide Corp.		
South Charleston, WV	100	100
TOTAL	890	840

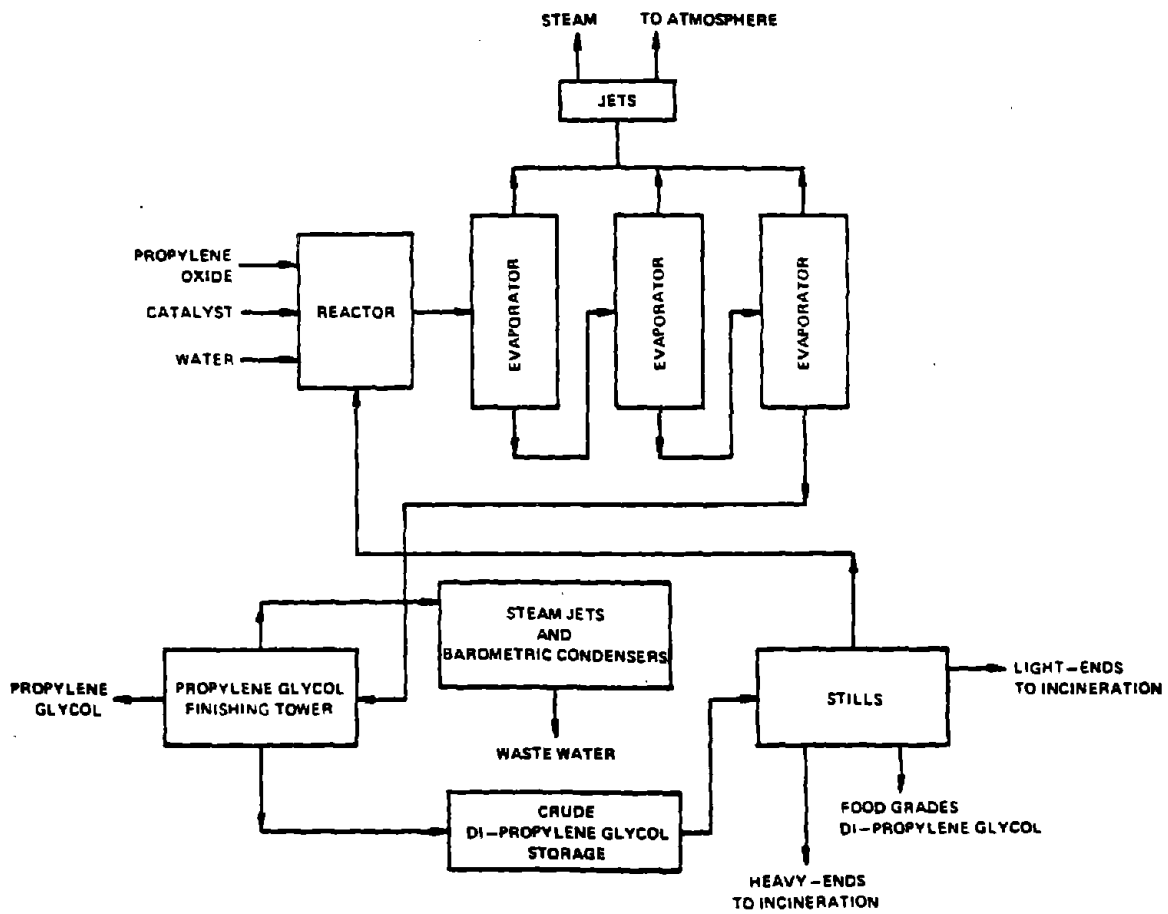


Figure 3. Propylene Glycol Manufacture from Propylene Oxide

Na_2CO_3 solution. It can also be obtained by heating glycerol with NaOH. Levorotatory propylene glycol can be synthesized from hydroxyacetone by yeast reduction.

11. Impurities or Additives

Both U.S.P. (99.5% purity) and industrial grade propylene glycol contain acetic acid (20 ppm, max.), water (0.2%, by wt., max.), chlorides (1 ppm, max.), and trace amounts of lead, arsenic, and iron as impurities (Union Carbide, 1978).

12. Occupational Exposure

The National Occupational Survey indicates that 2,749,747 workers are potentially exposed to propylene glycol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to propylene glycol were not found in the literature searched.

14. Biological Effects

Propylene glycol is a generally recognized as safe (GRAS) food additive [21 CFR 172.850 and 21 CFR 182.1666]. The use of propylene glycol in foods and pharmaceuticals has prompted much of the following research on its health effects.

A. Animal Studies

(1) Acute Exposures

Lethal dose and irritancy data for propylene glycol are summarized in Table 32. Numerous investigators have reported that administration of lethal and sublethal doses of propylene glycol to rats, mice, rabbits, guinea pigs, and dogs resulted in central nervous system depression (Braun and Cartland, 1936; Bornmann, 1955; Hickman, 1965; Hillman and Schneider, 1975; Laug et al., 1939; Lehman and Newman, 1937; Seidenfeld and Hanzlik, 1932; Zaroslinsky

Table 32. Acute Effects of Propylene Glycol

Route[a]	Species	Dose[b] (g/kg)	Response[b]	Reference
oral	rats	33.5	LD50 (approximate), 2 d	Weatherby and Haag, 1938
oral	rats	21.8	LD50, 8 d	Laug et al., 1939
oral	rats	29	LD50 (approximate), 24 h	Thomas et al., 1949
oral	rats	26.38	LD50, 14 d	Smyth et al., 1941
oral	rats	45.9	LD50, 14 d; median of samples tested	Smyth et al., 1969
oral	rats	44.4	LD50, 14 d	Smyth et al., 1970
oral	rats	25.9	LD50, 24 h	Bartsch et al., 1976
oral	rats	35.8	LD50, 14 d	Union Carbide, 1978
oral	mice	24.8	LD50, 8 d	Laug et al., 1939
oral	mice	22.8	LD50, 24 h	Latven and Molitor, 1939
oral	mice	31.87	LD50	Bornmann, 1955
oral	guinea pigs	19.6	LD50, 8 d	Laug et al., 1939
oral	guinea pigs	18.35	LD50, 14 d	Smyth et al., 1941
inhalation	rats	concentrated vapor, 8 h	No deaths	Union Carbide, 1978
i.p.	rats	14.7	LD50, 5 d	Hickman, 1965
i.p.	rats	13.5	LD50 (approximate), 24 h	Thomas et al. 1949
i.p.	rats	13.5	LD50, 24 h	Bartsch et al., 1976
i.p.	mice	13.5	LD50, 24 h	Holman et al., 1979
i.p.	mice	12.8	LD50, 6 d	Holman et al., 1979
i.p.	mice	9.73	LD50, 7 d	Karel et al., 1947
i.p.	mice	17.2	LD50, 24 h	Zaroslinski et al., 1971
i.p.	mice	11.2	LD50	Budden et al., 1978

Table 32. Acute Effects of Propylene Glycol (Cont'd)

Route[a]	Species	Dose[b] (g/kg)	Response[b]	Reference
i.m.	rats	14	LD50 (approximate), 2 d	Weatherby and Haag, 1938
i.m.	rats	20.8	LD50 (approximate), 24 h	Thomas et al., 1949
s.c.	rats	22.5	LD50 (approximate), 2 d	Weatherby and Haag, 1938
s.c.	rats	29	LD50 (approximate), 24 h	Thomas et al., 1949
s.c.	mice	19.2	LD50, 24 h	Latven and Molitor, 1939
i.v.	rats	6.8	LD50 (approximate), 2 d	Weatherby and Haag, 1938
i.v.	rats	6.4	LD50, 24 h	Bartsch et al., 1976
i.v.	mice	6.6	LD50, 24 h	Bartsch et al., 1976
i.v.	mice	8.3	LD50, 24 h	Latven and Molitor, 1939
i.v.	rabbits	6.5	LD50 (approximate)	Weatherby and Haag, 1938
i.v.	dogs	25.9 (by slow infusion)	Lethal dose, average	Hanzlik et al., 1939a
intradermal	guinea pigs	0.1 ml (0.1 g)[c]	Moderate irritation	Latven and Molitor, 1939
dermal	rabbits	>20.7, 24 h, closed dressing	LD50, 14 d	Union Carbide, 1978
dermal	rabbits	0.01 ml (0.01 g)[c], 24 h, open	No irritation	Union Carbide, 1978
dermal	rabbits	not stated, 24 h, closed dressing (2 cm^2)	No irritation, 24 h	Latven and Molitor, 1939

Table 32. Acute Effects of Propylene Glycol (Cont'd)

Route[a]	Species	Dose[b] (g/kg)	Response[b]	Reference
mucosal (penile)	rabbits	about 0.2 ml (0.21 g) 15% solution[c]	No irritation, 2 and 24 h	Draize et al., 1944
ocular	rabbits	0.5 ml (0.52 g)[c]	Moderate irritation (edema, hyperemia)	Latven and Molitor, 1939
ocular	rabbits	0.5 ml (0.52 g)[c]	Little or no irritation, 18-24 h	Carpenter and Smyth, 1946
ocular	rabbits	0.1 ml (0.1 g)[c]	Mild irritation, 1 h; practically no irritation, 24 h	Draize et al., 1944
ocular	rabbits	not stated	Mild irritation	Union Carbide, 1978
ocular	rabbits	not stated	Mild transient irritation	Seidenfeld and Hanzlik, 1932

[a] i.p. = intraperitoneal; i.m. = intramuscular; s.c. = subcutaneous; i.v. = intravenous.

[b] d = day; h = hour.

[c] Total dose.

et al., 1971). Propylene glycol produced lack of muscular coordination (Hickman, 1965; Lehman and Newman, 1937), loss of equilibruim (Braun and Cartland, 1936; Latven and Molitor, 1939; Laug et al., 1939; Seidenfeld and Hanzlik, 1932), analgesia (Braun and Cartland, 1936; Laug et al., 1939; Seidenfeld and Hanzlik, 1932), muscle tremors (Braun and Cartland, 1936; Seidenfeld and Hanzlik, 1932; Weatherby and Haag, 1938), and, occasionally, convulsions (Hickman, 1965; Weatherby and Haag, 1938). Other consequences of acute poisoning with propylene glycol were an increase in the respiratory rate (Braun and Cartland, 1936), depression of the respiratory rate (Seidenfeld and Hanzlik, 1932; Bornmann, 1955) and heartbeat (Bornmann, 1955), hypotension (Seidenfeld and Hanzlik, 1932), irritation of the digestive tract (Smyth et al., 1941), hemolysis (Bornmann, 1955), and diuresis (Bornmann, 1955).

Administration of propylene glycol to mice prior to training for an inhibitory avoidance task was reported to impair their retention of this training 72 hours later (Vasquez et al., 1977). According to these investigators, this effect may have been due to depression of the central nervous system.

Pathological changes after administration of propylene glycol to experimental animals were minimal. Oral administration of this glycol to rats, mice, and guinea pigs produced slight hydropic degeneration of the kidney with debris and casts in a few cortical tubules, slight congestion of the liver, and hemorrhagic areas in the small intestine (Laug et al., 1939). Intravenous injection into rabbits resulted in evidence of hemolysis (hemoglobin-containing casts throughout the renal tubulules), and, occasionally, in focal necrosis of the renal convoluted tubules with regeneration of adjacent areas and a high nonprotein nitrogen content in the blood (indicating renal insufficiency) (Kesten et al., 1939). Inhalation of 10% propylene glycol produced degeneration

of the ciliated cells and goblet cells of the tracheas of rabbits (Konradova et al., 1978).

In tests with rabbits, propylene glycol produced mild to moderate irritation of the eye (Draize et al., 1944; Seidenfeld and Hanzlik, 1932; Union Carbide, 1978; Latven and Molitor, 1939) and no irritation of the skin (Latven and Molitor, 1939; Union Carbide, 1978). Injections (intradermal, intraperitoneal, intramuscular, or into the foot pads of mice) were reported to produce various degrees of local irritation, inflammation, and edema (Latven and Molitor, 1939; Hickman, 1965; Wittman and Bawin, 1974; Mogre et al., 1977).

Smyth et al. (1969, 1970) investigated the joint toxic action of pairs of 27 industrial organic chemicals, including propylene glycol, intubated into rats. In the first study, LD50 values were determined for 50% by volume mixtures; in the second study, LD50 values were determined for mixtures of 2 chemicals in volumes directly proportional to their respective LD50 values. For mixtures containing propylene glycol, results of both studies indicated that the joint toxicity of the 2 chemicals was additive, with the exception of the mixture of propylene glycol and propylene oxide, for which the joint toxicity was less than additive.

(2) Subchronic Exposures

Oral administration of propylene glycol in drinking water (1-10%) to rats for up to 234 days (Kesten et al., 1939; Seidenfeld and Hanzlik, 1932; Weatherby and Haag, 1938) or by gavage (1-8.4 g/kg/day) to rabbits for 50 days (Braun and Cartland, 1936) produced no effects other than, with higher doses, a transient inhibition of growth at the beginning of the experiment. No gross or microscopic evidence of pathologic effects ascribable to propylene glycol was observed.

Daily applications of up to 2.5 ml/kg propylene glycol to the skin of rabbits for 30 days did not appear to affect the animals' health and resulted in no histopathological changes (Hanzlik et al., 1947).

(3) Chronic Exposures

In the study of Gaunt et al. (1972) described in the section on Carcinogenicity, rats that consumed up to 2.5 g propylene glycol/kg body weight/day for 2 years had no statistically significant differences from control rats in mortality, body weight gain, food consumption, hematologic values, urinalysis, and histopathological findings.

Morris et al. (1942) reported that the feeding of 2.45 or 4.9% propylene glycol in the diet to groups of 10 male and female rats produced no renal pathology or bladder stones (in contrast to ethylene glycol and diethylene glycol). Hepatic damage was slight, consisting of mild diffuse or centrilobular atrophy, bile duct proliferation, and fatty degeneration.

In a study by Weil et al. (1971), groups of 5 male and 5 female beagle dogs were fed, for 2 years, diets containing propylene glycol at levels that produced approximate daily intakes of 2.0 and 5.0 g/kg propylene glycol body weight. Controls received comparable caloric amounts of dextrose or no treatment. Weil et al. (1971) monitored mortality, organ and body weights, histopathology, hematology, blood chemistry, and urinalysis. Dogs that received the higher dose of propylene glycol had slightly lower hemoglobin values, hematocrits, and total erythrocyte counts relative to controls. In addition, blood counts indicated accelerated replacement from bone marrow. Changes did not appear to be irreversible; there was no apparent damage to bone marrow or spleen. A slight increase in total bilirubin values was noted in dogs that received 5 g/kg propylene glycol. These effects were attributed by Weil et al., (1971) to hemolysis of erythrocytes by propylene glycol. No histopathological or biochemical evidence of hepatic damage was observed.

In a series of experiments by Robertson et al. (1947), white rats of both sexes were continuously exposed to a supersaturated atmosphere of propylene glycol for up to 18 months. The rats exposed to propylene glycol gained weight more rapidly than did control rats. Complete blood counts, hemoglobin determinations, microscopic examination of urine, and gross and histological examination of lungs, kidneys, livers, and spleens revealed no differences between treated and control animals.

Similar experiments with monkeys (Robertson et al., 1947) revealed no differences attributable to the inhalation of propylene glycol except that the treated monkeys had discoloration of the facial skin while controls did not, and treated monkeys had less anemia than did controls. (The anemia, according to the authors, was due in part to a roundworm infection).

(4) Carcinogenicity

Gaunt et al. (1972) investigated the potential carcinogenicity of propylene glycol in a study with Charles River CD rats fed 0, 6250, 12,500, 25,000, or 50,000 ppm of this glycol in the diet for 2 years. There were 30 male and 30 female rats per dose level. At the 50,000 ppm level, rats consumed about 2.5 g propylene glycol/kg body weight/day. Propylene glycol produced no statistically significant or dose-related effects on tumor incidence.

Stenbach and Shubick (1974) tested the effect on tumor incidence of twice weekly applications of 0.02 ml of 10, 50, and 100% propylene glycol to the shaved skin of female Swiss mice. Each dosage group consisted of 50 mice. Treatment for the lifespan of the animals produced no statistically significant differences in incidence of skin tumors or any other tumors.

Several carcinogenicity studies in which propylene glycol was administered to rats and mice as a vehicle control were reviewed by

Miller (1979). In these studies, the glycol was injected subcutaneously or applied topically to the oral mucosa repeatedly for at least 8 months. No increase in tumor incidence was observed.

(5) Mutagenicity

Litton Bionetics (1974) investigated the potential mutagenicity of propylene glycol in the following assays:

1. Microorganisms: Salmonella typhimurium TA1530 and G46 (bacteria) and Saccharomyces cerevisiae D3 (yeast)
   a. In vitro (without microsomal activation)
   b. In host-mediated assay with mice.
2. Mammals:
   a. Cytogenetics
      in vivo - bone marrow of rats
      in vitro - human embryonic lung culture W138
   b. Dominant lethal assay - rats

Both positive and negative controls were included in each assay. At the highest dose only, propylene glycol produced a questionable increase in mutation frequency in S. typhimurium D3 in the host mediated assay. Propylene glycol appeared to be weakly mutagenic for Saccharomyces D3 both in vitro and in the host-mediated assay, but was also toxic for this organism, so results are difficult to interpret. Results of the cytogenetic and dominant lethal assays were negative.

In testing performed under the National Toxicology Program (NTP, 1980), propylene glycol was not mutagenic for Salmonella typhimurium TA98, TA100, TA1535, and TA1537 with or without metabolic activation. These results were obtained independently by 2 different laboratories (NTP, 1980).

Razvi et al. (1979) stated that the intraperitoneal injection of 0.1 ml propylene glycol into mice caused markedly higher levels of chromosome aberrations in spermatocytes than did the injection of saline.

(6) Teratogenicity

The Food and Drug Research Laboratories (1973) have evaluated the teratogenicity of propylene glycol in mice, rats, hamsters, and rabbits. Propylene glycol was administered by intubation according to the following schedule:

Species	Dose levels (mg/kg/day)	No. pregnant animals/dose level	Days gestation on which doses given
mice	0, 16.0, 74.3, 345, 1600	25-28	6 through 15
rats	0, 16.0, 74.3, 345, 1600	25-28	6 through 15
hamsters	0, 15.5, 72.0, 334.5, 1550	24-27	6 through 10
rabbits	0, 12.3, 57.1, 267, 1230	15-20	6 through 18

In all four species, propylene glycol had no apparent effect on nidation, maternal survival, or fetal survival and body weight. The incidence of abnormalities of soft and skeletal tissues in fetuses from treated dams did not differ from the incidence observed in fetuses from control dams.

According to Robertson et al. (1947), male and female white rats exposed continuously to a supersaturated atmosphere of propylene glycol for up to 18 months bred as regularly and produced as large litters as did the control animals. There were no differences in appearance or weight gain between the offspring of the two groups.

(8) Other Relevant Information

As reviewed by Miller (1979), propylene glycol is metabolized in animals to lactic acid or pyruvic acid, which can enter the

tricarboxylic acid cycle or the glycolytic pathway. Entry into the glycolytic pathway can contribute to glycogen synthesis.

Intramuscular or oral administration of a single dose of propylene glycol to fasted rats caused dose-related increases in total hepatic glycogen, rate of glycogen synthesis, and blood glucose concentrations (Wittman and Bawin, 1974; Wittman et al., 1975; Hanzlik et al., 1939b). Oral administration of 5 or 10% propylene glycol (presumably in the drinking water) to rats for 5 weeks was reported to increase liver weight and induce hyperglycemia (Vaille et al., 1971).

Farsund (1978) reported that subcutaneous administration of 0.2 ml propylene glycol to 12 hairless mice 3 times a week for 3 months slightly increased the proportion of diploid cells, slightly reduced the proportion of tetraploid cells, and virtually eliminated the octaploid class of cells in the bladder mucosa. DNA synthesis in tetraploid cells ceased. According to the author, the bladder mucosa is normally composed of diploid, tetraploid, and octaploid cells; the polyploid cells are thought to arise from cycles of DNA synthesis without mitosis. Farsund (1978) stated that the changes produced by propylene glycol in the cells of bladder mucosa indicated cytotoxicity and were qualitatively similar to but less severe than those he had observed after administration of the bladder carcinogen dibutylnitrosamine and the alkylating agent cyclophosphamide.

b. Human Studies

(1) Pharmacokinetics

In 3 human subjects, each of whom took 1 ml (1 g) propylene glycol/kg by mouth, blood concentrations of propylene glycol reached a maximum in 0.5 hour and remained at that level for about 4 hours before decreasing (Hanzlik et al., 1939a). Within 10 hours of ingestion, 20 to 25% of

the dose was excreted unchanged in the urine. The concentration of propylene glycol in the saliva was approximately 3 times the concentration in blood.

(2) Health Effects

The oral administration of vitamin preparations containing high percentages of propylene glycol to children has produced symptoms of toxicity to the central nervous system and other disturbances. Administration of vitamin C suspended in propylene glycol (dose not clear) 3 times daily to a 15-month old child resulted in an irregular apical heart rate (sinus arrhythmia) after 8 days of treatment (Martin and Finberg, 1970). The child began to have episodes of unresponsiveness with tachypnea, tachycardia, diaphoresis, and hypoglycemia after 10 days of treatment. When administration of the vitamin C-propylene glycol preparation was discontinued, these episodes ceased.

Martin and Finberg (1970) noted personal communications from two physicians, each of whom had reported that administration of about 60 ml of propylene glycol (as a vehicle for vitamin D) to an infant produced stupor lasting a number of hours. The infants appeared to recover completely. An 11-year old child who ingested 2-4 ml propylene glycol (as a vehicle for vitamin D) twice daily suffered grand mal seizures followed by periods of unconsciousness starting in the 13th month of treatment (Arulanantham and Genel, 1978). When vitamin D was given in a different vehicle, no more seizures occurred.

Ingestion of an unknown amount of propylene glycol produced coma with metabolic acidosis in a person of unspecified age and sex (Cate and McGlothlin, 1976).

Applications of propylene glycol to the tongue and subcutaneous and intramuscular injections of as little as 0.1 ml of this glycol caused temporary local burning sensations in human subjects (Braun and Cartland, 1936; Seidenfeld and Hanzlik, 1932).

Miller (1979) has reviewed reports of skin irritation and sensitization tests on propylene glycol; the information presented here is taken from that review. Propylene glycol produced little irritation and no sensitization when applied in diluted form or when applied undiluted without an occlusive dressing. Positive reactions were more likely when an occlusive dressing was used, when the glycol was undiluted, or when surface active agents were present in the test mixture.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

Propylene glycol is being tested for systemic and organ toxicity at the University of Minnesota (Project No. S07RR05385-53998). This project is sponsored by the Division of Research Resources, Biomedial Research Support, National Institutes of Health (NTP, 1981).

16. Exposure Standards

No recommended or promulgated occupational exposure standards for propylene glycol were found.

17. Sources of Additional Relevant Information

Miller (1979) and Auerbach Associates (1977) have reviewed the chemistry, environmental aspects, and biological effects of propylene glycol. The biological effects have also been reviewed by Informatics (1973).

NIOSH Health Hazard Evaluations (HHEs) relating to propylene glycol have been conducted at the following facilities:

Location	HHE No.
Cromwell Paper Co., Chicago, IL	74-63-364
Union Electric Co., St. Louis, MO	77-7A, 7B-486

18. Other Pertinent Data

No other information that would aid in the assessment of propylene glycol as an occupational hazard was found in the literature searched.

P. TETRAETHYLENE GLYCOL

1. Chemical Name: Tetraethylene Glycol

2. Chemical Structure: $HO(CH_2CH_2O)_4H$

3. Synonyms: Ethanol, 2,2'-[oxybis(2,1-ethanediyloxy)]bis-
Ethanol, 2,2'-(oxybis(ethyleneoxyl)di-
Hi-Dry
TEG

4. Chemical Abstract Service (CAS) Number: 112-60-7

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

XC2100000

6. Chemical and Physical Properties:

Description:	colorless hygroscopic liquid
Molecular Weight:	194.23
Boiling Point:	decomposes
Melting Point:	-41°C
Vapor Pressure:	<0.01 mm Hg (20°C)
Solubility:	completely soluble in water; insoluble in benzene, toluene, gasoline; soluble in dioxane
Specific Gravity:	1.1247^{20}_{20}
Stability:	combustible; Flash point: 376°F (CC)

7. Production

Production in recent years is as follows (USITC, 1977-1980):

Year	Production (in millions of pounds)
1979	23.328
1978	22.707
1977	---
1976	13.663

Data available from the U.S. EPA (1980) regarding producers of tetraethylene glycol and production volumes are presented in Table 33.

Table 33. Producers of Tetraethylene Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
CPS Chem. Co.		
Old Bridge, NJ	Manufacturer	10-100 thousand lb
Olin Corp.		
Brandenburg, KY	Manufacturer	0.1-1 million lb
Dow Chemical		
Freeport, TX	Manufacturer	1-10 million lb
Plaquemine, LA	Manufacturer	1-10 million lb
PPG Industries		
Beaumont, TX	Manufacturer	1-10 thousand lb
Ponce, PR	Manufacturer	10-100 thousand lb
Haven Chemical		
Philadelphia, PA	Manufacturer	0.1-1 million lb
Texas Eastman		
Longview, TX	Manufacturer	1-10 million lb
Union Carbide		
Ponce, PR	Manufacturer	confidential
Calumet Refining		
Princeton, LA	Manufacturer	none
Chemical Exchange Co.		
Baytown, TX	Manufacturer	0.1-1 million
Houston, TX	Manufacturer	0.1-1 million
Dixie Chem. Co.		
Pasadena, TX	Manufacturer	confidential
Jefferson Chemical		
Port Nechos, TX	Manufacturer	confidential
Nissho-Iwai Amer. Corp.		
New York City, NY	Importer	100-500 million lb
Nichimen Co.		
New York City, NY	Importer	10-100 thousand lb
Itoh and Co.		
New York City, NY	Importer	0.1-1 million lb
Davos Chem.		
Fort Lee, NJ	Importer	none

8. Use

Tetraethylene glycol is used to separate aromatic from non-aromatic hydrocarbons (particularly in higher molecular weight alkylbenzenes separations) by selective extraction (Brown et al., 1980).

Other uses are similar to those of triethylene glycol (Brown et al., 1980); see triethylene glycol profile.

9. Manufacturers and Distributors

SRI International (1980) and USITC (1980) list the following manufacturers:

Dow Chemical (Freeport, Tx)

Union Carbide (Seadrift, TX)
(South Charleston, W VA)
(Texas City, TX)

Eastman Kodak, Texas Eastman (Longview, TX)

Olin Corp. (Brandenburg, KY)

In addition to the manufacturers, the distributors include (1980-81 OPD Chemical Buyers Director, 1980; Chemical Week: 1981 Chemical Buyers' Guide, 1980; Chem Sources--USA, 1980):

Aldrich Chem.	Lachat Chem.
Alpha International	MCB Reagents
Atomergic Chemetals	McKesson Chem.
Chem. Ind.	Pfaltz and Bauer
Chem. Procurement Lab.	Pioneer Salt and Chem.
Chem. Services	Toyomanka (Amer.)
CPS Chem.	Tridom Chem.
Eastman Chem.	Joseph Turner and Co.
EM Lab.	Union Chem.
Fisher Sci.	Van Waters and Rogers
Koch Chem.	Worth Chem.

10. Manufacturing Processes

Like triethylene glycol, tetraethylene glycol is also produced commercially by the direct reaction of ethylene oxide with the lower glycols (Brown et al., 1980).

11. Impurities or Additives

Commercial tetraethylene glycol has the following specifications (Union Carbide, 1978):

acidity by wt., max. as acetic acid	0.01%
water by wt., max.	0.15%
suspended matter	substantial free
diethylene glycol by wt., max.	0.5%
triethylene glycol by wt., max.	3.0
pentaethylene glycol by wt., max.	0.5%

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 6,068 workers are potentially exposed to tetraethylene glycol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to tetraethylene glycol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Lethal and irritant dose data for tetraethylene glycol are summarized in Table 34. Lethal or near-lethal doses of this glycol resulted in sluggish, depressed functioning and in some degree of irritation of the digestive tract in rats and guinea pigs (Smyth et al., 1941). Tetraethylene glycol was not irritating to the skin and eyes of rabbits (Union Carbide, 1978; Carpenter and Smyth, 1946).

(2) Subchronic Exposures

No information was found in the literature searched.

(3) Chronic Exposures

No information was found in the literature searched.

Table 34. Acute Effects of Tetraethylene Glycol

Route	Species	Dose[a] g/kg	Response[a]	Reference
oral	srats	32.5	LD50, 14 d	Union Carbide, 1969, 1978
oral	rats	32.77	LD50, 14 d	Smyth et al., 1941
inhalation	rats	concentrated vapor, 8 h	No deaths	Union Carbide, 1978
dermal	rabbits	>22.5, 24 h, covered dressing	LD50, 14 d	Union Carbide, 1969
dermal	rabbits	0.01 ml (0.01 g)[b], 24 h, open	No irritation	Union Carbide, 1978
ocular	rabbits	not stated	No irritation	Union Carbide, 1978
ocular	rabbits	0.5 ml (0.56 g)[b]	Little or no irritation, 18-24 h	Carpenter and Smyth, 1946

[a] d = day; h = hour

[b] total dose

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of tetraethyl glycol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for tetraethyl glycol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of tetraethyl glycol as an occupational hazard was found in the literature searched.

Q. TRIETHYLENE GLYCOL

1. Chemical Name: Triethylene Glycol

2. Chemical Structure: $HO-CH_2-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-OH$

3. Synonyms: Di-beta-hydroxyethoxyethane
Dihydroxydiethyl ether
3,6-Dioxaoctane-1,8-diol
Ethanol, 2,2'-(ethylenedioxy), di-
2,2'-Ethylenedioxyethanol
Glycol bis(hydroxyethyl)ether
Triglycol

4. Chemical Abstracts Service (CAS) Number: 112-27-6

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

YE4550000

6. Chemical and Physical Properties:

Description:	colorless, hygroscopic, practically odorless liquid
Molecular Weight:	150.17
Boiling Point:	285°C
Melting Point:	-7.2°C
Vapor Pressure:	<0.01 mm Hg (20°C)
Solubility:	completely soluble in water, alcohol, benzene, toluene; slightly soluble in ether
Specific Gravity:	1.1274_4^{15}
Stability:	combustible; Flash point: 350°F (CC)

7. Production

Production in recent years is as follows (USITC, 1977, 1978, 1979, 1980):

Year	Production (in millions of pounds)
1979	131
1978	120
1977	130
1976	---

CMR (1979b) projects future growth of triethylene glycol to be 2% per year through 1983.

Data available from the U.S. EPA (1980) regarding producers of triethylene glycol and production volumes are presented in Table 35.

8. Use

The following tabulation presents the percentage of the total amount of triethylene glycol produced that is used in each of the applications listed (CMR, 1979b):

	Percentage of Total
Natural gas dehydration	34
Vinyl plasticizer	16
Solvent	15
Humectant	14
Polyester resin and polyols	6
Export and other	15

9. Manufacturers and Distributors

The major manufacturers of triethylene glycol are listed in Table 36. As with ethylene and diethylene glycol, there are many commercial distributors of triethylene glycol.

10. Manufacturing Processes

Triethylene glycol is normally a coproduct of the manufacture of ethylene glycol and diethylene glycol and is only very rarely produced directly from a lower glycol. DuPont patented the manufacturing of triethylene glycol by forming an ether-ester of $OHCH_2COOH$ with glycol and then hydrogenating the product.

Table 35. Producers of Triethylene Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Olin Corp.		
Brandenburg, KY	Manufacturer	1-10 million lb
Dow Chemical		
Freeport, TX	Manufacturer	10-50 million lb
Plaquemine, LA	Manufacturer	10-50 million lb
PPG Industries		
Beaumont, TX	Manufacturer	0.1-1 million lb
Ponce, PR	Manufacturer	1-10 million lb
Haven Chemical		
Philadelphia, PA	Manufacturer	1-10 thousand lb
Texas Eastman		
Longview, TX	Manufacturer	1-10 million lb
Union Carbide		
Institute, WV	Manufacturer	confidential
Ponce, PR	Manufacturer	confidential
Shell Chemical		
Geismar, LA	Manufacturer	1-10 million lb
Northern Petrochemicals		
Morris, IL	Manufacturer	0.1-1 million lb
March Chemical		
Denham Springs, LA	Manufacturer	10-100 thousand lb
Celanese Chemical		
Pasadena, TX	Manufacturer	1-10 million lb
Calumet Refining		
Princeton, UT	Manufacturer	none
Chemical Exchange Co.		
Baytown, TX	Manufacturer	0.1-1 million lb
Houston, TX	Manufacturer	0.1-1 million lb
Dixie Chemical		
Pasadena, TX	Manufacturer	confidential
Jefferson Chemical		
Port Nechos, TX	Manufacturer	confidential

Table 35. Producers of Triethylene Glycol and Production Ranges (U.S. EPA, 1980) (Cont'd)

Producer	Type of Production	1977 Production Range
United Mineral and Chem. New York City, NY	Importer	under 1000 lb
Nissho-Iwai Amer. New York City, NY	Importer	100-500 million lb
Nichimen Co. New York City, NY	Importer	1-10 million lb
Proprietary Perfumes Lmt. Maywood, NJ	Importer	under 2000 lb
C. Itoh and Co. New York City, NY	Importer	1-10 million lb
ICI Americas Wilmington, DE	Importer	confidential

Table 36. Producers of Triethylene Glycol and Estimated Production Ranges

Producer and Location	Estimated Annual Capacity (Millions of Pounds)	
	(SRI International, 1980)	(CMR, 1979b)
Celanese Corp. Clear Lake, TX	10	10
Dow Chem. Freeport, TX Plaquemine, LA	40	50
Eastman Kodak Co. Longview, TX	7	1
Olin Corp. Brandenburg, KY	15	5
PPG Indust. Inc. Beaumont, TX	1	1
Shell Chemical Co. Geismar, LA	25	25
Texaco Inc. Port Neches, TX	15	15
Union Carbide Corp. Seadrift, TX Taft, LA Penuelas, PR	80	75
Others	--	10
TOTAL	193	192

11. Impurities or Additives

Commercial grade triethylene glycol has the following specifications (Union Carbide, 1978; Chemical Week: 1981 Buyers' Guide Issue, 1980):

purity	98.0%, min.
acidity	0.01%, max.
water	0.1%, max.

It is also likely to contain some ethylene and diethylene glycol.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 25,986 workers are potentially exposed to triethylene glycol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to triethylene glycol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Lethal and irritant dose information for triethylene glycol are summarized in Table 37. Administration of lethal doses of triethylene glycol to laboratory animals resulted in sluggishness (Smyth et al., 1941), loss of equilibrium (Latven and Molitor, 1939), irritation of the digestive tract (Smyth et al., 1941), leukocytosis (Karel et al., 1947), depression of the respiratory rate (Latven and Molitor, 1939), and, in the experiments of Latven and Molitor (1939), death from respiratory failure.

Karel et al. (1947) described the pathological changes that followed intraperitoneal administration of fatal doses of triethylene glycol to female mice. Autopsy revealed pulmonary congestion, atelectasis, and, occasionally, in animals that died within the first 24 hours, cardiac dilatation. The central nervous systems were not examined. Kidney damage was reported to be

Table 37. Acute Effects of Triethylene Glycol

Route[a]	Species	Dose[b] (g/kg)	Response[b]	Reference
oral	rats	31.8	LD50, 14 d	Union Carbide, 1978
oral	rats	22.06	LD50, 14 d	Smyth et al., 1941
oral	rats	18.9	LD50	Woodard, n.d.
oral	mice	20.8	LD50, 24 h	Latven and Molitor, 1939
oral	mice	21.1	LD50	Woodard, n.d.
oral	rabbits	9.5	LD50	Woodard, n.d.
oral	guinea pigs	14.66	LD50, 14 d	Smyth et al., 1941
oral	guinea pigs	8.9	LD50	Woodard, n.d.
inhalation	rats	concentrated vapor, 8 h	No deaths	Union Carbide, 1978
i.p.	mice (female)	8.15	LD50, 7 d	Karel et al., 1947
i.m.	rats	8.4	LDLo, considerable irritation at injection site	Lauter and Vrla, 1940
s.c.	mice	9.86	LD50, 24 h	Latven and Molitor, 1939
i.v.	mice	7.3	LD50, 24 h	Latven and Molitor, 1939
intradermal	guinea pigs	0.1 ml (0.11 g)[c]	Moderate irritation	Latven and Molitor, 1939
dermal	rabbits	>22.5, 24 h, closed dressing	LD50, 14 d	Union Carbide, 1978
dermal	rabbits	0.01 ml (0.011 g)[c], 24 h, open	No irritation	Union Carbide, 1978

Table 37. Acute Effects of Triethylene Glycol (Cont'd)

Route[a]	Species	Dose[b] (g/kg)	Response[b]	Reference
dermal	rabbits	not stated; closed dressing, 24 h	No irritation	Latven and Molitor, 1939
ocular	rabbits	0.5 ml (0.56 g)[c]	Little or no irritation	Carpenter and Smyth, 1946
ocular	rabbits	0.5 ml (0.56 g)[c]	Mild irritation (edema, hyperemia)	Latven and Molitor, 1939
ocular	rabbits	not stated	No irritation	Union Carbide, 1978

[a] i.p. = intraperitoneal; i.m. = intramuscular; s.c. = subcutaneous; i.v. = intravenous

[b] h = hour; d = day

[c] Total dose

mild. Histopathological findings consisted of a protein precipitate in and dilation of Bowman's space and the proximal tubules, and hydropic degeneration of the epithelial cells of the convoluted tubules and loops of Henle. No crystals were observed. Damage to the liver (pyknosis or mild necrosis of hepatic cells) occurred in a few animals.

Karel et al. (1947) reported that triethylene glycol produced a severe toxic reaction in the spleens and other lymphatic tissues of female mice. Pyknosis, degeneration, and fragmentation of the lymphocytes of the white pulp of the spleen were followed by proliferation of reticular cells and phagocytosis of cell debris. Similar reactions were observed in the thymus, lymph nodes, and lymphoid follicles of the liver. The red pulp of spleen was congested with lesser amounts of lymphocyte fragmentation and, occasionally, increased amounts of hemosiderin.

Triethylene glycol, applied topically, produced no dermal irritation and little or no ocular irritation in rabbits (Latven and Molitor, 1939; Carpenter and Smyth, 1946; Union Carbide, 1978). Local irritation did occur, however, after intradermal and intramuscular injection of this glycol (Latven and Molitor, 1939; Lauter and Vrla, 1940).

(2) Subchronic Exposures

Lauter and Vrla (1940) reported that administration of 5% (by volume) triethylene glycol in the drinking water for 30 days caused severe symptoms of toxicity in albino rats and the death of 3 out of 5 adult rats and 1 out of 5 weanling rats.

No apparent adverse effects were produced in weanling rats by 3% triethylene glycol in the drinking water for 30 days. When triethylene glycol was administered daily by gastric intubation, 3.4 g/kg/day produced no apparent ill effects, 11.3 g/kg/day produced symptoms of toxicity such

as loss of hair and diarrhea (but no deaths), and 22.5 g/kg/day killed all 5 rats within 48 hours (Lauter and Vrla, 1940).

(3) Chronic Exposures

In the chronic study by Fitzhugh and Nelson (1946) described in the section on Carcinogenicity, feeding of 1, 2, or 4% diethylene glycol in the diet to male rats produced no discernible effects on weight gain or mortality. The gross or microscopic appearance of the internal organs of treated rats was no different from that of controls.

In a series of experiments by Robertson et al. (1947), white rats of both sexes were continuously exposed to a supersaturated atmosphere of triethylene glycol, or ingested 3.00 g triethylene glycol/kg body weight/day in their drinking water for up to 13 months. Rats inhaling triethylene glycol had the same growth rate as controls for the first 7 months and then continued to grow while controls did not; both groups appeared healthy. Rats ingesting triethylene glycol had weight gains similar to those of controls. Complete blood counts, hemoglobin determinations, and microscopic examination of urine gave similar results for treated and control groups. At autopsy, gross and histological examination of lungs, kidneys, livers, and spleens revealed no differences attributable to the inhalation or ingestion of triethylene glycol.

Similar experiments were performed with Macacus Rhesus monkeys (Robertson et al., 1947). Monkeys exposed to a supersaturated atmosphere of triethylene glycol grew less well than unexposed monkeys, had discoloration of the facial skin, and were more frequently infested with an unidentified ectoparasite of the external ear. Daily ingestion of 0.5 ml/kg/day also depressed weight gain. Blood counts, hemoglobin determinations, urinalyses, and gross and microscopic examination of the internal organs revealed no differences between control and treated groups except that monkeys

taking the glycol orally had less anemia at the end of the experiment. (Anemia was thought to result from infestation with nematodes.) In a follow-up experiment, monkeys exposed to triethylene glycol vapor at 65 to 75% saturation had slightly higher rates of weight gain than did controls, but had no discoloration of the skin or changes in the external ears.

(4) Carcinogenicity

Feeding of triethylene glycol at levels of 1, 2, and 4% in the diet for 2 years to male Osborne Mendel rats (12 per dose level) did not produce tumors (or stones) of the bladder (in contrast to diethylene glycol, which produced both stones and tumors) (Fitzhugh and Nelson, 1946). No tumors were reported to occur in the other organs and tissues that were examined.

White rats that inhaled supersaturated atmospheres (fogs) of triethylene glycol (35 rats) or ingested 0.16 to 3.00 g triethylene glycol/kg body weight/day in the drinking water (18 rats) for 8-13 months had no pathological changes in lungs, kidneys, livers, or spleens attributable to the treatment (Robertson et al., 1947).

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

According to Robertson et al. (1947), male and female white rats exposed to triethylene glycol for up to 13 months either by continuously inhaling a supersaturated atmosphere of triethylene glycol or by daily ingesting 3.00 g triethylene glycol/kg body weight in the drinking water had frequent large litters. The pups were normal in appearance and weight gain. In the limited experiments of Lauter and Vrla (1940), an amount of triethylene

glycol (11.3 g/kg/day for 30 days) that caused noticeable sickness in rats also appeared to decrease the number and size of litters.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

In a test of the use of vapors of triethylene glycol for air sterilization, persons exposed to 0.002 to 0.003 mg/l (0.5 to 1 ppm) triethylene glycol made no complaints regarding the odor or of discomfort (Jennings et al., 1944); the incidence of upper respiratory infections among patients whose air supply contained triethylene glycol was significantly lower than the incidence among patients whose air supply did not contain this chemical (Harris and Stokes, 1945).

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of triethylene glycol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for triethylene glycol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

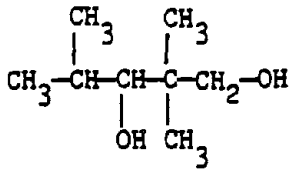
18. Other Pertinent Data

No other information that would aid in the assessment of triethylene glycol as an occupational hazard was found in the literature searched.

R. 2,2,4-TRIMETHYL-1,3-PENTANEDIOL

1. Chemical Name: 2,2,4-Trimethyl-1,3-pentanediol

2. Chemical Structure:



3. Synonyms: 1,3-Pentanediol, 2,2,4-trimethyl-
TMPD
Trimethylpentanediol

4. Chemical Abstract Service (CAS) Number: 144-19-4

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

SA1400000

6. Chemical and Physical Properties:

Description:	white crystalline solid
Molecular Weight:	146.23
Boiling Point:	215-235°C
Melting Point:	46-55°C
Vapor Pressure:	---
Solubility:	slightly soluble in water; soluble in most alcohols, other glycols, aromatic hydrocarbons, ketones and ether.
Specific Gravity:	0.928^{55}_{15}
Stability:	combustible; Flash point: 113°C (COC); Autoignition temp.: 346°C

7. Production

Data available from the U.S. EPA (1980) regarding producers of 2,2,4-trimethyl-1,3-pentanediol and production volumes are presented below:

Texas Eastman Co. (Longview, TX)
Manufacturer
1977 Production: 1-10 million lb.

8. Use

Trimethylpentanediol has many commercial applications (Bramer and Davis, 1980). It is used in the production of both saturated and unsaturated

polyester resins which have diverse industrial uses. The monoisobutyrate ester of trimethylpentanediol is especially useful as a coalescing aid in flat and semigloss latex paint formulations. The diisobutyrate ester is a primary plasticizer for use in surface coatings, vinyl flooring, molding, and other vinyl products. Various other diesters, and mixed esters, and polyesters are also used as monomeric or polymeric plasticizers.

Other applications involving trimethylpentanediol or derivatives are uses in urethane elastomers, in foams, as a reactive diluent in urethane coatings, as a sound insulating glass laminating adhesive, as a bacteria-fungicide, as a pigment homogenizer, in paper sizing, as a cross-linking agent in PVC adhesive, as an ink solvent, in synthetic lubricant production (Bramer and Davis, 1980), and as an insect repellant (Sherman, 1978).

9. Manufacturers and Distributors

Eastman Kodak (Texas Eastman) in Longview, TX is the sole commercial manufacturer of trimethylpentanediol (SRI International, 1980; USITC, 1980; Bramer and Davis, 1980).

Distributors include (Chem Sources-USA, 1980)

Chem Services	Lachat Chem.
Fisher Sci.	MCB Reagents
ICN/K and K	Pfaltz and Bauer
	Tridom Chem.

10. Manufacturing Processes

Trimethylpentanediol is manufactured by the hydrogenation of the aldehyde trimer resulting from the aldol condensation of isobutyraldehyde (Bramer and Davis, 1980; Hagemeyer, 1958). The continuous process begins by feeding isobutyraldehyde and an aqueous base, such as sodium hydroxide, to a reactor which forms isobutyraldol. The reactor is allowed to overflow and the overflow is neutralized with an aliphatic acid. This product is distilled to remove impurities, allow for recycling of unreacted isobutyraldehyde, and

isolate the isobutyraldol. The isobutyraldol is taken from the base of the distillation column, again by intentional overflow, decanted, and extended with ether. The ether and water are removed and the residue is distilled to yield 94% isobutyraldol which is fed to a hydrogenator containing a Raney nickel catalyst. The hydrogenator product is filtered and distilled to yield the trimethylpentanediol product.

11. Impurities or Additives

Commercial grade trimethylpentanediol has a minimum wt. % assay of 96% (Bramer and Davis, 1980).

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to 2,2,4-trimethyl-1,3-pentanediol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to chemical were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Lethal and irritant dose data for 2,2,4-trimethyl-1,3-pentanediol are summarized in Table 38. These data are taken primarily from toxicity studies conducted by the Health, Safety, and Human Factors Laboratory of the Eastman Kodak Company (Eastman Chemical Products, 1981d) and also from studies by Smyth et al. (1962). Trimethylpentanediol was somewhat irritating to the skin and eyes of rabbits but produced no sensitization in standardized tests with guinea pigs (Eastman Chemical Products, 1981d). No other information concerning the effects of acute exposure to trimethylpentanediol was found in the literature searched.

Table 38. Acute Effects of 2,2,4-Trimethyl-1,3-pentanediol

Route	Species	Dose[a] g/kg	Response[a]	Reference
oral	rats, male	2.0	LD50	Eastman Chemical Products, 1981d
oral	rats, female	2.5	LD50	Eastman Chemical Products, 1981d
oral	rats	3.73	LD50, 14 d	Smyth et al., 1962
oral	mice	2.2	LD50	Eastman Chemical Products, 1981d
oral	guinea pigs	1.8	LD50	Eastman Chemical Products, 1981d
inhalation	rats	dust, 4.5 mg/l (≈750 ppm; 34% respirable-size particles), 6 h	Irritation, but no signs of toxicity, 14 d	Eastman Chemcial products, 1981d
dermal	rabbits	6.3 in vehicle	LD50, 14 d	Smyth et al., 1962
dermal	guinea pigs	1.0 (solid moistened with water), 24 h, closed dressing	Mild irriation, no signs of toxic effects	Eastman Chemical Products, 1981d
dermal	rabbits	0.01 g[b], 24 h, open	Mild irritation	Smyth et al., 1962
ocular	rabbits	excess of 15% solution	Irritation (mild or moderate)	Smyth et al., 1962
ocular	rabbits	not stated	Moderate irritation	Eastman Chemical Products, 1981d

[a] d = day; h = hour

[b] total dose

(2) Subchronic Exposures

Male and female rats that consumed 2.0% trimethylpentanediol in the diet for 57 days ate slightly less food and gained slightly less weight than did controls and had slight to moderate hypertrophy of the liver and moderate hypertrophy of the adrenals. Slight hypertrophy of the kidneys occurred in the males. Behavior, hematologic values, serum chemistry values, and the weights of other organs were not significantly affected by this treatment. No gross pathologic or histopathologic changes were noted. No significant changes in any of the above parameters were observed in rats fed 0.5% trimethylpentanediol in the diet for 57 days (Eastman Chemical Products, 1981d).

In tests with guinea pigs and rabbits, repeated topical application of trimethylpentanediol to the uncovered skin for 2 months produced no cumulative irritant or toxic effects (Eastman Chemical Products, 1981d). No experimental details, such as dosage, were specified.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

In a three-generation fertility study with rats, briefly reported by Eastman Chemical Products (1980), trimethylpentanediol at 1% in the diet produced no adverse effects on the number of inseminations and pregnancies, the mean gestation time, or the average litter size. No gross pathologic changes were found in any of the treated litters.

(8) Other Relevant Information

Eastman Chemical Products (1981d) reports that radioactive tracer and metabolism studies of trimethylpentanediol indicate significant percutaneous absorption of this glycol in rabbits, moderate percutaneous absorption in guinea pigs, and poor percutaneous absorption in humans.

b. Human Studies

(1) Pharmacokinetics

The studies mentioned in Section 14.a.(8) indicate that trimethylpentanediol is poorly absorbed through the skin of humans (Eastman Chemical Products, 1981d).

(2) Health Effects

Repeated application of trimethylpentanediol to the skin of humans produced no evidence of irritation, sensitization, photosensitization, or systemic toxicity (Eastman Chemical Products, 1981d). No experimental details, such as dosage, were given.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of 2,2,4-trimethyl-1,3-pentanediol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for 2,2,4-trimethyl-1,3-pentanediol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of 2,2,4-trimethyl-1,3-pentanediol as an occupational hazard was found in the literature searched.

S. TRIPROPYLENE GLYCOL

1. Chemical Name: Tripropylene Glycol

2. Chemical Structure: $HO(C_3H_6O)_2C_3H_6OH$

3. Synonyms: 2-(2-(2-Hydroxypropoxy)propoxy-1-propanol
Propanol, [(1-methyl-1,2-ethanediyl)bis(oxy)]bis-
2-propanol, 1,1'-[(1-methyl-1,2-ethanediyl)bis(oxy)]bis-

4. Chemical Abstract Service (CAS) Number: 1638-16-0
24800-44-0

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

YK6825000

6. Chemical and Physical Properties:

Description:	colorless liquid
Molecular Weight:	192.29
Boiling Point:	268°C
Melting Point:	supercools
Vapor Pressure:	---
Solubility:	completely soluble in water, methanol, and ether
Specific Gravity:	1.019^{25}_{25}
Stability:	combustible; Flash point: 285°F

7. Production

Sales of triproplyene glycol were 1.837 million pounds in 1973 (USITC, 1975).

Data available from the U.S. EPA (1980) regarding producers of tripropylene glycol and production volumes are presented in Table 39.

8. Use

Tripropylene glycol is used as an intermediate in the production of resins, plasticizers, pharmaceuticals, insecticides, dyestuffs, and mold lubricants (Hawley, 1977).

Table 39. Producers of Tripropylene Glycol and Production Ranges (U.S. EPA, 1980)

Producer	Type of Production	1977 Production Range
Dow Chemical		
Freeport, TX	Manufacturer	1-10 million lb
Plaquemine, LA	Manufacturer	1-10 million lb
Union Carbide		
South Charleston, WV	Manufacturer	confidential
March Chemical		
Denham Springs, LA	Manufacturer	10-100 thousand lb
ICI Americas		
Wilmington, DE	Importer	confidential

9. Manufacturers and Distributors

Tripropylene glycol is commercially manufactured by (SRI International, 1980; USITC, 1980);

Dow Chem.	Freeport, TX Plaquemine, LA
Union Carbide	South Charleston, WV
Hodag Chem.	Skokie, IL
Olin Corp.	Brandenburg, KY

Distributors include (1980-81 OPD Chemical Buyers Directory, 1980; Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem Sources--USA, 1980):

Alfa Prod.	C.P. Hall Co.
Ashland Chem.	ICN/K and K
Atomergic Chemetals	Pfaltz and Bauer
CPS Chem.	Pioneer Salt and Chem.
EM Lab.	McKesson Chem.
	Joseph Turner and Co.

10. Manufacturing Processes

Tripropylene glycol is obtained as a by-product of propylene glycol manufacture (Bradley, 1975); see propylene glycol profile for a process description.

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey indicates that 12,110 workers are potentially exposed to tripropylene glycol.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to tripropylene glycol were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Range-finding studies by the Dow Chemical (n.d.) indicate that the oral LD50 for tripropylene glycol rats is between 3 and 10 g/kg. This glycol was not irritating to the skin or eyes of rabbits and was not absorbed through the skin in acutely toxic quantities even when contact was prolonged and repeated (Dow Chemical Co., n.d.)

(2) Subchronic Exposures

As mentioned in Section 14.a.(1), tripropylene glycol produced no signs of acute toxicity when applied to the skin repeatedly (Dow Chemical Co., n.d.).

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of tripropylene glycol were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for tripropylene glycol were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of tripropylene glycol as an occupational hazard was found in the literature searched.

APPENDIX A - GLYCOLS

The following list includes all of the glycols considered under the class definition. The list was primarily compiled from the following sources: U.S. EPA TSCA list and U.S. EPA (1980), SRI International (1980), USITC (1980), and the Kirk-Othmer Encyclopedia of Chemical Technology.

CAS numbers are included to aid in identification.

	CAS No.
1,2-Butanediol (1,2-butylene glycol)	584-03-2
1,3-Butanediol (1,3-butylene glycol)	107-88-0
1,4-Butanediol (1,4-butylene glycol)	110-63-4
2,3-Butanediol	513-85-9
1,3-Butanediol, 2,2-dimethyl-	76-35-7
2,3-Butanediol, 2,3-dimethyl-	76-09-5
1,4-Butanediol, 2-methyl-	2938-98-9
1,4-Butanediol, 1,1,4,4-tetraphenyl-	63469-15-8
Butene-1,4-diol	29733-86-6
2-Butene-1,4-diol	110-64-5
2-Butyne-1,4-diol	110-65-6
3-Butyne-1,2-diol, 2-methyl-1-phenyl-	2033-94-5
1,4-Cyclohexanedimethanol	105-08-8
1,4-Cyclohexanedimethanol, 1-ethyl-	67663-05-2
1,2-Cyclohexanediol	931-17-9
1,10-Decanediol	112-47-0
Diethylene glycol	111-46-6
Dipropylene glycol	25265-71-8
	108-61-2
	110-98-5
	106-62-7
1,2-Ethanediol, 1,2-diphenyl	492-70-6
	579-43-1
	655-48-1
1,2-Ethanediol, 1-phenyl-	93-56-1
1,2-Ethanediol, 1,1,2,2-tetraphenyl-	464-72-2
Ethylene glycol (1,2-ethanediol)	107-21-1

	CAS No.
1,7-Heptanediol	629-30-1
2,4-Heptanediol	
Hexanediol	26762-52-7
1,5-Hexanediol	928-40-5
1,6-Hexanediol	629-11-8
2,4-Hexanediol	19780-90-6
2,5-Hexanediol	2935-44-6
2,5-Hexanediol, 2,5-dimethyl-	110-03-2
Hexanediol, 2-ethyl-	1321-34-2
1,3-Hexanediol, 2-ethyl-	94-96-2
1,6-Hexanediol, 2,2,4-trimethyl-	2089-24-5
Neopentyl glycol	126-30-7
1,9-Nonanediol	3937-56-2
1,8-Octanediol	629-41-4
1,7-Octanediol, 3,7-dimethyl-	107-74-4
3,6-Octanediol, 3,6-dimethyl-	78-65-9
4-Octyne-3,6-diol, 3,6-dimethyl-	78-66-0
1,4-Pentanediol	626-95-9
1,5-Pentanediol	111-29-5
2,4-Pentanediol	626-69-4
1,5-Pentanediol, 3-methyl-	4457-71-0
1,3-Pentanediol, 2-methyl-	149-31-5
1,3-Pentanediol, 2,2,4-trimethyl-	144-19-4
1,2-Propanediol (1,2-Propylene glycol)	57-55-6
1,3-Propanediol	504-63-2
1,3-Propanediol, 2-allyl-2-ethyl-	27606-26-4
1,3-Propanediol, 2-butyl-2-ethyl-	115-84-4
1,3-Propanediol, 2-sec-butyl-2-methyl-	813-60-5
1,3-Propanediol, 2,2-diethyl-	115-76-4
1,3-Propanediol, 2-ethyl-2-methyl-	77-84-9
1,3-Propanediol, 2-methyl-2-propyl-	78-26-2
1,2-Propanediol, 1-phenyl-	1855-09-0
Tetraethylene glycol	112-60-7
Tetramethyl cyclobutanediol	3010-96-6
Triethylene glycol	112-27-6
Tripropylene glycol	24800-44-0
	1638-16-0

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