Literature Review for Glycerol and Glycols

for

Entertainment Services & Technology Association

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Table of Contents

I. PURPOSE

The purpose of this report is to review all applicable literature concerning the safe inhalation exposure concentrations for the glycols listed below and glycerol. A proposal outlining additional research needs to define safe inhalation exposure concentrations for the listed substances is also presented.

	Chemical Abstracts Registry Service (CAS) #
Glycerol	56-81-5
<u>Glycols</u>	
1,4-Butylene glycol	110-63-4
Diethylene glycol	111-46-6
Dipropylene glycol	110-98-5
Propylene glycol	57-55-6
Triethylene glycol	112-27-6

A number of databases were searched to review the available scientific literature for each of the above substances. The list of databases is located in Appendix A. As a priority, inhalation toxicity was searched in each database. If no inhalation data was found, then a general toxicology search was done by CAS number and/or name for each compound. The information obtained from the databases was reviewed and the relevant scientific literature selected and incorporated into the summary report for each substance. All references are footnoted and can be found in the Bibliography. Copies of each database search will be forwarded to the Entertainment Services & Technology Association.

II. INTRODUCTION

Glycol is a general term for dihydric alcohol (compounds having two hydroxyl [-OH] moieties). Glycol is also commonly a synonym for ethylene glycol. Ethylene glycol contains a two carbon backbone with a hydroxyl group on each carbon. All of the compounds reported within this document are dihydric alcohols with the exception of glycerol. Glycerol (glycerin) is a trihydric alcohol with chemical and physical properties similar to glycols.[1]

As a group, glycols are used in heat exchangers, antifreeze formulations, hydraulic fluids, and chemical intermediates. Glycols are also used as industrial solvents for nitrocellulose and cellulose acetate and as solvents for the pharmaceutical, food additives, cosmetics, inks, and lacquer industries. Due to their low volatility, glycols produce little vapor hazard at ordinary temperatures. However, when used in antifreeze, hydraulic fluids, and in heat exchangers they may be encountered in the vapor or mist form, particularly at high temperatures.[2]

The purpose of this report, as previously stated, is to search and review scientific literature regarding the safe inhalation exposure concentrations for the glycols that are listed. It is important to understand that workplace air contaminant standards in the United States are promulgated through the Occupational Safety and Health Administration (OSHA) and do not exist for every chemical manufactured. The standards for chemicals that OSHA promulgates are termed permissible exposure limits (PELs). OSHA standards are considered to be the legal minimum health protection required of employers and are designed to protect against a variety of toxic effects including irritation, target organ toxicity, chronic lung disease, and biochemical/metabolic effects.

In addition to OSHA, other organizations concerned with the health and well being of the worker have developed occupational exposure limits (OELs) for airborne contaminates. These groups include, the National Institute for Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygienists (ACGIH), and the American Industrial Hygiene Association (AIHA). ACGIH is an independent organization comprised of industrial hygienists and other health professionals from academia and govenment related institutions. The threshold limit values (TLVs) developed by ACGIH are exposure guidelines based on a belief that there is a threshold(s) of response, derived from an assessment of the available published scientific information including animal studies, human studies, and industrial experience and at exposures below these levels no adverse health effects will occur to workers. The ACGIH periodically publishes a documentation of TLVs in which it gives the data and information upon which the TLV for each substance is based. NIOSH has recommended a number of standards for chemicals, known as recommended exposure limits (RELs). RELs are usually set through the publishing of a criteria document. As part of the process of developing a criteria document, extensive research is done to review existing human and animal data. AIHA is a professional organization that develops workplace environmental exposure limits (WEELs) for chemical substances and physical stresses for which no TLV, PEL, or other limit exists. A committee utilizes all available information on epidemiology, toxicology, industrial hygiene, and workplace experience information to develop safe exposure guidelines. Most organizations that develop OELs, either in the United States or internationally, are attempting to protect a worker from excessive health risk based on an 8-hour day, 40-hour work week.

The OELs currently available in the United States or internationally for the selected glycols are not complete and vary to a great extent. Even when an OEL exists for a chosen substance, a health professional must consider whether the development of the OEL considered all of the applications or uses encountered when it was created.

When the application of an OEL does not apply or there are no OEL standards for a given material, toxicology data is considered. In the case of the glycols listed in this report, a literature search for the applicable toxicology information was necessary.

Toxicology is the study of the adverse effects of chemicals agents on biologic systems. Adverse or toxic effects in a biologic system are not produced by a chemical agent unless that agent or its biotransformation products reach the appropriate target within the biologic system at the right concentration and for a sufficient amount of time. Therefore, whether or not a toxic response occurs is dependent on the chemical and physical properties of that agent, the exposure situation, and the susceptibility of the biologic system or subject. Thus, to characterize a potential hazard or toxicity of a specific chemical agent the following information must be examined:

What is the agent of concern?
What type of effect does the chemical in question produce?
What dose or amount is required to produce the effect?
What are the exposure conditions?
Who are the subjects exposed?

In this report, we will be discussing what type of effects the glycols and glycerol listed produce on the human or animal system.

III. KEY OBSERVATIONS AND ASSUMPTIONS

In order to remain focused on the information requested in the report, the following key observations and assumptions were made:

A. *Occupational Exposure Limits vs Toxicology Data*

Thoroughly research occupational exposure limits for the substances listed. Since this area was expected to be limited, the applicable toxicology data was researched.

B. *Inhalation Toxicology Takes Precedence*

Since the application of the glycol based fluids are through vaporization, the potential exposure route is by inhalation. Therefore, the priority area of interest in identifying potential effects was inhalation toxicology literature. If inhalation toxicology information was not available or was limited, oral toxicity literature was considered. In addition, any literature regarding skin or eye irritation was examined and considered in this report as relevant to potential exposures.

C. *Pure materials vs mixtures*

The fog fluids are generally composed of a mixture of various glycols and water. It is only possible in this report to consider one compound of interest at a time.

IV. INDIVIDUAL COMPONENTS OF CONCERN

A. Propylene Glycol (PG)

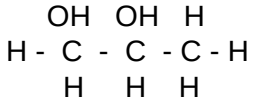
1.0 Physical and Chemical Properties [1, 3, 6, 11, 12]

Identification: CAS # 57-55-6

Common names: Sirlene®, PG12

Synonyms: 1,2-Propanediol; 1,2-dihydroxypropane; methyl ethylene glycol; methyl glycol; propane-1,2-diol

Structure:



Molecular Formula: $C_3H_8O_2$

Propylene glycol (PG) is a stable, viscous, hygroscopic liquid (hygroscopic pertains to a material that absorbs moisture readily). It is colorless and has a sight odor and a slight acrid taste. It is completely miscible with water and alcohols. It will also dissolve in a number of resins, dyes, essential oils, ether and benzene.[3, 6] Under ordinary conditions PG is considered stable, but can react with oxidizing materials.

Molecular Weight: 76.09 (1 ppm (v/v) = 3.1 mg/m^3
Boiling Point: 188 deg C (370 deg F)
Density: 1.038 @ 25 deg C (77 deg F)
Vapor Pressure: 0.05mm Hg @ 20 deg C (68 deg F)
% in Saturated Air: Approximately 0.038 @ 20 deg
Odor Threshold: Practically odorless
Flash point: 107 deg C (225 deg F)

1 ppm is approximately 3.11 mg/m^3 @ 25 Deg C, 760 mm Hg

2.0 Background

2.1 *Sources and Uses*

PG is manufactured in a number of different ways. One way PG is produced commercially is by hydrolysis of propylene oxide.[14] PG is used in many applications including use in various foods, cosmetics, and pharmaceutical products. The Food and Drug Administration (FDA) has classified PG as a Generally Recognized as Safe (GRAS) additive. GRAS additives are materials which are virtually indistinguishable from foods. Such substances are regulated in the Code of Federal Regulations. These substances may be added in relatively substantial amounts to food, in some instances at levels representing more than 1 percent of dietary intake.[2] The FDA considers an average daily dietary intake of 23 mg/kg of body weight of PG to be safe for

persons 2 to 65 years of age.[11] For an average 70 kg person, this is approximately 1.6 grams or approximately 1.6 mls. As a solvent and surfactant in food colors and flavors as well as in food products, the concentrations can range from <0.001% in eggs and soups to 15% in some seasonings and flavorings. It is also used as a humectant or moistening agent in foods, such as shredded coconut, tobacco, and pet foods.

In industry, it is used as a lubricant or heat-transfer fluid where leakage might lead to food contact, in antifreeze and coolant applications and deicing fluids for aircraft. The largest amounts used are in the textile industry where it used as an intermediate in polyester fiber and urethane production.[6, 11]

2.2 *Industrial Exposure*

Industrial exposures to PG are from direct contact or from inhalation of vapors and of mists where the material is heated or violently agitated. Other exposure is by ingestion resulting from its use in foods and drugs. Although exposures created by operations producing hot vapors, or fogs have not been studied, it is felt that the inhalation of atmospheres containing PG presents no hazard to health since the systemic toxicity is so low.[12]

OELs have been established for PG by a number of organizations. Based on its low toxicity by all routes of exposure and a NOEL (no observable effect level) of 1000 mg/m^3 in rats, the United Kingdom (UK), Health and Safety Executive (HES) has set an 8-hour time-weighted average occupational exposure standard (OES) of 150 ppm (470 mg/m^3) for total vapor (a vapor is the gaseous form of substances which are normally found in a solid or liquid state and which can be changed to these states either by increasing the pressure or decreasing the temperature[45]) and particulates, and 10 mg/m^3 for particulates only in 1991. The latter level being set to avoid uncomfortable or visibility impairing conditions if the material were present as a fog. The AIHA has also set an 8-hour time-weighted WEEL guide of 50 ppm (155 mg/m^3) for total vapor and aerosol (an aerosol is an assemblage of small particles, solid or liquid, suspended in air, e.g., dust, fog, smoke[45]), and 10 mg/m^3 for aerosol only. The Ontario Ministry of Labour's Health and Safety Support Services Branch (HSSSB) had issued a working exposure guideline time weighted average (WEG-TWA) of 100 ppm for PG in 1984. However, more recently in 1991, the HSSSB issued a WEG-TWA of 50 ppm for total vapor and aerosol over an 8-hour work day or a 40-hour work week. The HSSSB further recommends a WEG-TWA of 10 mg/m^3 for assessing the visibility in a work environment where aerosol is present.[18]

3.0 Toxicology Review

3.1 *Summary*

PG has been well studied. Its systemic toxicity is very low and it has been used extensively in food and pharmaceuticals compared to other dihydric glycols. The hazards to health in the industrial handling and use of PG seem to be negligible. Symptoms of acute PG intoxication are those of CNS depression or narcosis (unconscious state). No system or organ has been established as a target for the acute lethal effects of PG. The explanation for the low toxicity of PG lies in its metabolism. PG is metabolized by alcohol dehydrogenase to lactic acid and ultimately to pyruvic acid. Both lactic and pyruvic acid are normal constituents of carbohydrate metabolism and are ultimately broken down to carbon dioxide and water.[2]

3.2 *Inhalation Exposure*

Studies have been done in hospital wards using PG in an air-sterilization application. In these studies, humans were exposed to saturated and super saturated atmospheres for prolonged periods without adverse effects.[12] In 1971, the uptake of PG mist by humans was studied using a 10% solution in labeled deionized water which was nebulized into a mist tent. Less then 5% of the mist entered the body, and of this 5%, 90% lodged in the nasopharynx and rapidly disappeared into the stomach. Very little PG was found in the lungs. [12]

Robertson and coworkers (1947) exposed monkeys and rats to atmospheres saturated with PG vapor and found no adverse effects in animals after periods of 12 to 18 months.[30] Rats exposed to a 90-day inhalation study using PG aerosol at concentrations up to 2,200 mg/m^3 (160, 1000 and 2200 mg/m^3), for 6 hours/day, 5 days/week did not demonstrate systemic toxicity. However, it was reported that there was a significant increase in the number of goblet cells (a type of secretory cell found in the top layer of the intestinal and respiratory tract that secretes mucus) and/or an increase in the mucin content of the existing goblet cells in the nasal passages of rats exposed to the high and medium doses. In addition, the PG concentration in this study caused nasal hemorrhage and ocular discharge in a high proportion of animals, all of these reversible effects are considered to be the result of dehydration of the nares and eyes.[23] The dehydration would be expected with PG, as it is a hydroscopic material and can cause irritation simply by removing excess water from the eyes and nasal passages.

Minute changes in cilia cell structures were observed after rabbits had been exposed to 10% PG for 20 minutes by inhalation. It was reported that the goblet cells were discharging mucous or were completely exhausted. [3]

3.3 *Oral Toxicity*

A report of a case where PG was used as a vehicle in a vitamin preparation for a 15 month-old youngster, caused adverse signs characterized by hypoglycemia (low blood sugar) and central nervous system (CNS) depression. Recovery was prompt upon cessation of treatment. [17] It should be noted that, PG is given orally (1-1.5g/kg) to humans therapeutically to reduce intraoccular pressure by raising the osmotic pressure of the blood.[6]

PG has been investigated by numerous studies under acute conditions. Reports of acute administration of lethal and sublethal doses of PG to rats, mice, rabbits, guinea pigs and dogs resulted in CNS depression. PG produced lack of muscular coordination, loss of equilibrium, analgesia (sleep like state), muscle tremors, and occasionally, convulsions. Additional consequences included increase and/or decrease in respiration rates, hypotension, irritation of the digestive tract, hemolysis (destruction of red blood cells) and diuresis (secretion of large amounts of urine).[14]

More specifically, acute oral administration 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.[14] When comparing acute oral toxicity, the LD 50s or the Lethal Dose to kill 50% of the animal test population, in rats, rabbits, and dogs were approximately 30, 18 and 19 g/kg body weight, respectively.[12] As the LD 50 values are generally used as a method to compare toxicity of various compounds, PG, relatively, is considered nontoxic.[2]

When chronic and subchronic doses of PG were administered in the drinking water (1-10%) of rats for up to 234 days or when given by gavage to rabbits for 50 days, no effects where found, other than at the higher doses, a transient inhibition of growth at the beginning of the experiment was experienced. No gross or microscopic evidence of pathology was observed.[14] In addition, no effects were found in rats fed up to 50,000 ppm in the diet for 2 years.[22] However, other long term feeding studies showed hemopoietic (blood) changes in dogs.[21]

3.4 *Eye and Skin Irritation*

A single drop in the human eye causes immediate stinging, blinking and lacrimation. This discomfort lasts until the eye tears enough to dilute the material. This is followed by mild transient conjunctival redness, but no residual discomfort or injury.[13]

Skin reactions due to PG are generally rare. Irritation of the skin may occur, especially under occlusive (covered) conditions. Hypersensitivity type reactions (allergic) have been reported.[25] Undiluted PG has been applied to human volunteers in various patch test studies. On average 15% of the test subjects demonstrated a reaction, of these
15 %, 60 - 70% had irritant type reactions and 30-40% had allergic type reactions. Most of the irritation is expected to be due to the dehydration effect of the PG (being a hygroscopic material). [3] Work by Willis et al. suggested that the dehydration effect was due to osmotic hydration of corneal cells, however, the patterns of cell damage observed in the epidermis (top cell layer of the skin) was dependent on the amount tested (dose) as well as time left on the skin.[22] Because PG has a very low systemic toxicity, no problem is expected from any possible percutaneous absorption.[12]

B. Dipropylene Glycol (DPG)

1.0 Physical and Chemical Properties [1, 8, 12, 14]

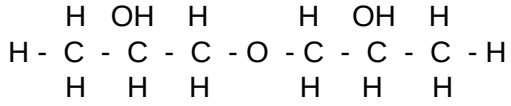
Identification: CAS # 110-98-5

Note: DPG when manufactured commercially is a mixture of three isomers (CAS # 25265-71-8). In the literature reviewed, the authors did not specify the identity or isomer composition of the DPG reported. In most instances, it appears to have been the commercial product containing all 3 isomers. The percentages are as follows:

1) 108-61-2 4%
2) 110-98-5 43%
3) 106-62-7 53%

Synonyms for CAS # 110-98-5: 1,1'-Oxybis-2-Propanol, Bis(2-Hydroxypropyl) Ether, 2,2' - Dihydroxy Dipropyl Ether

Structure for CAS # 110-98-5:



Molecular Formula: $C_6H_{14}O_2$

Dipropylene glycol (DPG) is a colorless, slightly viscous liquid, which is practically odorless. It is soluble in water, alcohols, toluene, and ether. It is considered stable.[8]

Molecular Weight: 134.17
Boiling Point: 233 DEG C
Density: 1.0252 @ 20 deg C
Vapor Pressure: 0.03 mm Hg @ 25 deg C
% in Saturated Air: > 0.0013 @ 20 deg
Odor Threshold: Practically odorless
Flash point: 280 Deg F (Open Cup)

1 ppm is approximately 5.49 mg/m^3 @ 25 Deg C, 760 mm Hg

2.0 Background

2.1 *Sources and Uses*

DPG is prepared commercially as a by-product of propylene glycol production.[12] There are three isomers of Dipropylene glycol. The commercially produced DPG is composed of all three isomers. DPG is used for many of the same purposes as other glycols, but most commonly as a solvent since it is more soluble in hydrocarbons then the other glycols and has low volatility. It is used in the manufacture of printing inks, resins, plastics and antifreezes.[8] It is not used in drugs, pharmaceuticals, or food applications because its toxicologic characteristics have not been clearly defined.[12]

2.2 *Industrial Exposure*

Industrial exposure is most likely expected to be from direct contact and possible inhalation of mist from heated or violently agitated material. Currently, there are no recognized occupational health standards set for DPG. Although there is no occupational exposure data available for DPG, based on its low oral toxicity and low vapor pressure, exposures at ordinary temperatures are not expected to represent a significant hazard. Under conditions of heated or violently agitated material, however, it would be prudent to use respiratory protection until more experimental data becomes available.

3.0 Toxicology Review

3.1 *Summary*

Based on the information available, DPG exhibits low acute oral toxicity when tested in animals, is not irritating to the skin and is not absorbed in toxic amounts though intact skin.[8] However, DPG does cause more CNS depression in high acute doses than diethylene and propylene glycol when tested in animal studies.

3.2 *Inhalation Toxicity*

There is currently no experimental information available in the scientific literature.

3.3 *Oral Toxicity*

The acute oral LD50 in rats has been reported as 14.8 g/kg and 15.0 g/kg. A dose which places this substance in the slightly toxic rating when compared by LD50 to other compounds. In a subacute study, Yoshida et al. feed chicks 5% DPG for up to 27 days without adverse effects. The chicks, unlike propylene glycol, were unable to utilize this substance as an energy source.[12] Dogs given 4 to 6 repeated oral doses of DPG (1.53, 2.04, and 5.04 g/kg) showed no outward signs of toxicity, had a minimal amount of liver damage and an insignificant to moderate amount of degeneration of the renal convoluted tubules.[14]

Under more long-term conditions, DPG given to rats subchronicly (77 days) as a 5% solution in their drinking water, produced no detectable effects. According to the authors, the organs of the treatment group appeared no different from the control group. When the concentration was increased to 10% in the drinking water, renal lesions in almost half the 25 rats tested occurred, many of which died.[14]

3.4 *Eye and Skin Irritation*

DPG has been shown to cause no significant eye irritation or injury when tested in the eyes of rabbits. [12]

DPG was nonirritating in a 48-hour closed patch test on human subjects, nor did this preparation produce sensitization reaction in a maximization test.[14] Ten applications of DPG to the skin of rabbits in 12 days produced negligible irritation. No signs of systemic toxicity was observed.[14]

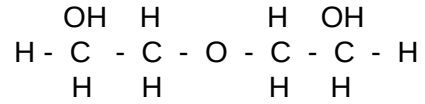
C. Diethylene Glycol (DEG)

1.0 Chemical and Physical Properties [1, 2, 4, 9, 12]

Identification: CAS #: 111-46-6

Synonyms: DEG, Diglycol, Ethylene diglycol, 2,2'-oxydiethanol, 2-(2-hydroxyethyl) ethanol

Structure:



Molecular Formula: $C_4H_{10}O_3$

DEG is a colorless, hygroscopic, practically odorless liquid with a sharply sweet taste. DEG is miscible in water, alcohol, ether, acetone, ethylene glycol; and is insoluble in benzene, and carbon tetrachloride. It is considered stable.

Molecular Weight: 106.12
Boiling Point: 245 Deg C @ 760 mm Hg
Flash Point: 290 Deg F (Open Cup)
Density: 1.118 @ 20 Deg C
Vapor Pressure: <0.01 mm Hg @ 25 Deg C
Odor Threshold: Odorless

1 ppm is approximately 4.35 mg/m^3 @ 25 Deg C and 760 mm Hg

2.0 Background

2.1 *Sources and Uses* [4, 9, 12]

DEG is produced commercially as a by-product of ethylene glycol production. It can also be produced directly by reaction between ethylene glycol and ethylene oxide. It is used in gas conditioning and in permanent antifreeze formulations; as a constituent of brake fluids, lubricants, mold release agents, adhesives, paper, packaging materials, coatings and inks; as a softening agent for textiles; as a plasticizer for cork; as an intermediate in the production of explosive diethylene glycol dinitrate; as an intermediate in the production of certain resins; and in diethylene glycol esters and ethers.

2.2 *Industrial Exposure*

Although the occupational exposure information available for DEG is limited,[28] it is felt that DEG presents practically no hazard from the standpoint of industrial handling, except, possibly where it is being used at elevated temperatures. It is low in acute oral toxicity, not irritating to the eyes or skin, not readily absorbed through the skin, and its vapor pressure is sufficiently low enough that toxic concentrations of vapor can not occur at room temperatures. [12]

The AIHA has established a WEEL for DEG of 50 ppm (156 mg/m^3) as an eight hour time-weighted average. The rationale behind this standard is that DEG is of lower acute toxicity than ethylene glycol (a compound which has been studied extensively in humans, particularly by inhalation). DEG's vapor pressure is sufficiently low enough that high concentrations of vapor are not likely to occur in the environment. However, when the conditions of use involve higher ambient or process temperature, a level of 10 mg/m^3 for aerosol exposure was established.[4]

3.0 Toxicology Review

3.1 *Summary*

Diethylene glycol is of low acute lethal toxicity to animals by way of oral, intraperitoneal (injection into the abdomen), intravenous, and subcutaneous (under the skin) routes of administration. DEG is not irritating to the skin or eyes of animals and is considered a low skin absorption hazard. However, similar to ethylene glycol, man appears more susceptible to DEG than laboratory animals by the oral route.[4] Prior to 1937, the human toxicology information of DEG and other glycols was rather incomplete. In 1937, more than 100 deaths were caused by the ingestion of an elixir containing sulfanilamide and DEG in man.[12] Although, this compound appears to be of low toxicity to animals, the long term and chronic studies demonstrate questionable results when compared to other glycols that have been tested more extensively.

3.2 *Inhalation Toxicity*

Although there is data in the literature available regarding inhalation toxicity, reviews of this literature cautioned against the purity of the DEG when the studies were performed. Rats and mice developed mammary tumors when exposed by inhalation to 4 and 5 mg/m^3 (about 1 ppm) DEG for 2 hr/day for 6 to 7 months. A similar experiment exposing rats and mice to 4 and 5 mg/m^3 for 3 to 7 months found structural changes in the central nervous system, endocrine, and other pathological effects. [12]

3.3 *Oral Toxicity*

The major hazards involved from diethylene glycol exposure occurs following the ingestion of relatively large single acute doses in man. One hundred and five fatalities have occurred out of 353 people who ingested a solution of 10 % sulfanilamide in an aqueous mixture containing 72% DEG.[27] Subsequent animal studies confirmed that the DEG was the toxicant. Symptoms included nausea, dizziness, and pain in the kidney region. This was followed in a few days by oliguria (diminished amount of urine formation) and anuria (absence of urine formation) with death resulting in uremic (kidney) poisoning. It has been estimated based on this data, that 1 ml/kg (approximately 1.18 g/kg) is the lethal single oral dose in man.[2] Other estimates include ranges between 0.5 - 5 g/kg; that is between 1 ounce and 1 pint for a 70 kg person (150 lb).[9, 17] This is <10 fold lower than the acute LD50 values determined in animal studies. Additional deaths due to acute renal failure have occurred as recently as 1990 in Bangladesh, from the ingestion of Paracetamol elixirs made with DEG as a diluent.[26] DEG in large doses appears to be a central nervous system depressant. Death from large single doses which occur within 24 hours are believed to result from this action. Acute toxic doses, not always immediately fatal, may exert their effect primarily on the kidney and, to a lesser extent, on the liver. [12]

Findings of Laug reports the acute oral LD50 values for rats, guinea-pigs, and mice to be 16.6, 8.7 and 26.5g/kg, respectively. Smyth et al. reported similar values of 20.8g/kg for rats and 13.2g/kg for guinea pigs.[12] Symptoms reported were similar across the species. Thirst was noted first, diuresis, roughened coat and refusal of food, followed by suppression of urine, protein in urine, difficulty in breathing, a bloated appearance, coma, decrease in body temperature, followed by death. [12]

Weil et al. fed DEG to rats at 2 and 4% for up to 2 years. The conclusions reported that DEG, which was considered substantially free of ethylene glycol, does not cause bladder stones, suggesting that it is not metabolized to any great degree to ethylene glycol.[12] Additional long-term feeding studies showed that 1% DEG in the diet of rats for a 2 year period resulted in slight growth depression, some oxalate bladder stones, minimal kidney damage, and occasional liver damage in rats. At 4%, these findings were enhanced.[12]

3.4 *Eye and Skin Irritation*

DEG was reported as failing to cause appreciable irritation when introduced into the eyes of rabbits.[12]

Although DEG produces no significant skin irritation, if prolonged contact over an extended period of time occurs, a macerating (softening of the skin) action can be produced. [12] Studies using undiluted commercial DEG of unknown purities reported absorption of toxic amounts through the skin of rabbits. Similar studies performed on rats by applying 2.8mg/kg/day for 2 months to the skin produced edema of the brain, plethora (overfullness of blood vessels), and minute brain hemorrhages.[12]

A mixture of DEG and propylene glycol produced slight thickening of the stratum granulosum and proliferation in the stratum basale after occluded topical application for 100 days with 0.5ml/day. [4]

D. Triethylene Glycol (TEG)

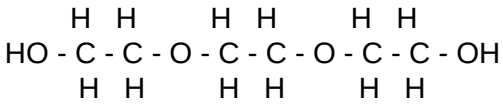
1.0 Chemical and Physical Properties [1, 7, 12]

Identification: CAS # 112-27-6

Common names**:** Trigen, TEG

Synonyms**:** Triglycol, Glycol BIS(hydroxyethyl) ether

Structure:



Molecular Formula: $C_6H_{14}O_4$

TEG is a colorless to pale straw-colored liquid, which is practically odorless, has a slight taste, is viscous, and hygroscopic. It is miscible with water, alcohol, benzene, toluene, but sparingly soluble in ether, and practically insoluble in petroleum ether or aliphatic hydrocarbons and fats. It is considered stable.

Molecular Weight: 150.17
Boiling Point: 285 Deg C
Density: 1.1274 @ 15 Deg C
Vapor Pressure: 1.32×10^{-3} mm Hg @ 25 Deg C
% in Saturated Air: Approximately 0.00013 @ 25 Deg C
Odor Threshold: Practically odorless
Flash Point: 350 Deg F (Open Cup)

1 ppm is approximately 6.14 mg/m^3 @ 25 Deg C, 760 mm Hg

2.0 Background [1, 7, 12]

2.1 *Sources and Uses*

TEG , like diethylene glycol, is produced commercially as a by-product of ethylene glycol production.[12] TEG is used for many of the same applications as diethylene glycol, but differs as it is less volatile and less toxic. TEG has been in public use since the 1940's. Around this time it was discovered that the vapors of certain glycols were highly germicidal for air-borne bacteria and virus. It was at this time that TEG was tested as an aerial disinfection agent in hospitals. Since this time, it has been used in soap, detergent, creams, lotions and in fragrances. The amounts used in fragrances alone are approximately 10,000 lb/yr in the USA. TEG is not listed by the Food and Drug Administration (FDA), the Council of Europe (1974), or in the Food Chemicals Codex (1972). [29]

TEG is currently used as an intermediate in the manufacture of plasticizers, resins, emulsifiers, demulsifiers, lubricants and explosives. It is also used as a solvent and plasticizer in vinyl, polyester, and polyurethane resins. It is used in various plastics to increase pliability, and as a solvent and lubricant in textile dyeing and printing industries. TEG's hygroscopic properties are used in the natural gas industry as a dehydration agent, and as a humectant in tobacco and in printing inks.[7]

2.2 *Industrial Exposure*

In the industrial setting, handling and use of TEG has not presented any significant problems due to ingestion, skin contact or vapor inhalation. It is felt that the low oral acute and chronic toxicity indicates that TEG is safe for applications where intake is limited. TEG is well noted for its negligible skin irritation and low absorption properties. Currently, there are no occupational health standards established for TEG in the United States, as under normal industrial conditions they are not recognized as necessary.[12] The Deutsche Forschungsgemeinschaft (DFG), Federal Republic of German, Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, has established an occupational health limit. The German limits are called MAKs, or Maximum Concentration Values in the Workplace. The MAK for TEG is 44 mg/m^3 .[46]

3.0 Toxicology Review

3.1 *Summary*

Triethylene glycol is very low both in acute and chronic oral toxicity, it is not irritating to eyes or skin, and under normal industrial conditions the inhalation of amounts that conceivably could cause injury does not seem likely. Even under conditions of exposure to mist or vapor, TEG seems to have very low toxicity as repeated in a number of human and animal studies.

3.2 *Inhalation Toxicity*

The use of TEG as an inhaled material was initiated by the observation of Robertson et al.. The testing began in 1943 through 1947[30, 31, 32] and demonstrated that TEG was an effective air sterilizer.[31] Patients were exposed to TEG vapor at concentrations of 0.003 to 0.012 mg/l in air for a period up to 25 days. This concentration of vapor was reported as creating a slight to moderate fog and no harmful or irritating effects were observed in the patients exposed. Other hospital studies using concentrations between 0.0044+/ - 0.0021 mg/l and 0.0091+/- 0.0029 mg/l also concluded that the TEG treatments were in no way harmful to the patients.[32] Studies have also been done in infant hospital wards. There was no evidence of toxic effects on the respiratory tract or skin of infants who lived on the test ward from a few days to several weeks. In addition, there were no major complaints from the attendants, nurses, or doctors who worked on the ward from a few days to several months, with the exception of two nurses who complained of headaches as a result of working on the ward when a visible glycol vapor fog was present. [33]

Preliminary data from Roberston showed that intratracheal injections in the rat with as little as 0.25ml of undiluted propylene glycol (PG) caused marked pulmonary irritation, acute edema and later fibrosis and abscess formation, in 1947, Robertson et al. set out to test the effect of prolonged inhalation of PG and TEG on the lungs of monkey and rats. The very low vapor pressures of PG and TEG at room temperatures
as well as the fact that both glycols are very soluble in the body fluids, made it seem unlikely that the amounts of glycols used in air sterilization could accumulate enough to cause irritation of the respiratory tract.

Rats and Monkeys were exposed to PG and TEG vapor for a period of 3 to 18 months at concentrations of 60 to 75% of saturated conditions (60% PG = 0.10 - 0.22 mg/l; 65-75% TG = 0.002-0.003 mg/l), and super saturated conditions. It should be noted that electrical heating of the glycols was necessary to maintain the saturated conditions. A method for producing atmospheres saturated and super saturated was achieved for TEG by regulating a shallow dish on a hot plate and keeping the temperature of the glycol at 100 Deg C. Temperatures above 100 Deg C were expected to decompose. A hot plate method of heating the PG was used initially, however, it was found that this method caused a yellow discoloration of the coats of the rats in the glycol chamber observed. This was found to be due to decomposition of the PG by an excessively high temperature (220 Deg C) of the hot plate surface. When the method of vaporization was changed so to keep the heated PG to below 95 Deg C, the yellow tint of the coat disappeared. [30]

The study concluded that rats and monkeys exposed to TEG and PG by inhalation had no evidence of generalized pulmonary irritation, or localized disturbances, no difference between growth rates, blood counts, urine, kidney function tests, or fertility of either group when compared to the controls. The only exception was that rats exposed to the glycols exhibited consistently high weight gains. In addition, some drying of the skin of the monkey's faces occurred after several months of continuous exposure to a heavy fog of TEG. This effect was controlled when the concentration of TEG was maintained just below saturation. [30]

3.3 *Oral Toxicity*

Additional toxicity data for TEG was reviewed by Opdyke (1979). Acute oral LD 50 toxicity was reported as follows:

Author	Rat	Mice	Rabbit	Guinea-pigs	Humans
Smyth et al. 1941	22g/kg			4.66g/kg	
1941					
Laug et al. 1939	16.8 ml/kg	18.7 ml/kg	8.4 ml/kg	7.9 ml/kg	
Stenger et al. 1968	15-22 g/kg	21 g/kg	9.5 g/kg	9-15 g/kg	
NIOSH, 1977	18.7 g/kg		8.4 g/kg	7.9 g/kg	
Gosselin et al., 1976					5-15 g/kg
NIOSH, 1977					"

When the Oral LD 50 of TEG is compared with the list of glycols present in this report, TEG is more toxic then PG, and Glycerol, but less toxic when compared to DG, DPG, and BG.

The most comprehensive study for repeated-dose (chronic) oral toxicity of TEG is that reported by Fitzhugh and Nelson.[34] These investigators fed the material at concentrations of 1, 2 and 4 percent in the diet of rats for 2 years. These dose levels represent 3 to 4 g/kg/day.[12] No adverse effects were detected. From these
findings, it is apparent that TEG is very low in repeated-dose oral toxicity, far less then ethylene glycol or DEG. Conclusions drawn from this study suggested that chronic oral toxicity to rats decreases with an increase in molecular weight of glycols.

3.4 *Eye and Skin Irritation*

When introduced into the eyes of rabbits, 100% TEG failed to cause appreciable irritation.[29] TEG has also been reported as causing immediate pain when applied to rabbit eyes, but no injury was detectable 24 hours later. Splash contamination in eyes of man has been reported as causing acute pain. It was also reported that splashes to the eye may be followed by transitory disturbances of the corneal epithelium with gradual diminishing sensation and signs of irritation, but no persistent injury is expected.[13] Its prolonged contact with skin may result in a macerating action (cause softening of the skin by steeping or as if soaked in water). When applied to intact or abraded rabbit skin for 24 hours under occlusion (covered) it was slightly irritating, but when a concentration of less then 20% was used, it produced no irritation after a 48 hour closed-patch test on human subjects. No sensitization reactions (allergic) were produced when 25 volunteers were tested using 20% TEG in petrolatum using a common allergy test method. [29]

Although it is possible that under conditions of very prolonged severe exposures some of the material maybe absorbed through the skin, it is extremely doubtful that a quantity sufficient to produce an appreciable systemic injury would be absorbed.[12]

E. 1,4-Butylene Glycol (BG)

1.0 Chemical and Physical Properties [1, 5, 12]

Identification: [1, 5, 12] CAS# 110-63-4

Common name**:** 1,4-Butanediol

Synonyms**:** Butane-1,4-diol, Sucol B, 1,4-Dihydroxybutane

Structure:

```
      H   H   H   H
HO - C - C - C - C - OH
      H   H   H   H
```

Molecular Formula: $C_4H_{10}O_2$

BG is a colorless, viscous, and nearly odorless liquid. It is soluble in water, alcohol, esters, and ketones and is insoluble in alphatic hydrocarbons. It is considered stable under normal conditions.

Molecular Weight: 90.12
Boiling Point: 230 Deg C @ 760 mm Hg
Flash Point: 247 Deg F (Open Cup)
Density: 1.0171 @ 20 Deg C
Vapor Pressure: 0.0105 mm Hg @ 25 Deg C
Odor Threshold: Practically odorless
Flash Point: 350 F (Open Cup)

1 ppm is approx. 3.68 mg/m^3 @ 25 Deg C, 760 mm Hg

2.0 Background [5, 12, 35]

2.1 *Sources and Uses*

1,4-Butylene glycol (BG) is one of 4 isomers (isomers are chemical which have the same molecular weight and chemical composition, however, are structurally distinct) which is produced on a large industrial scale by hydrogenation of 2-butyne-1,4-diol over a modified nickel catalyst. BG is used as a humectant, and an intermediate in polyester resins, tetrahydrofuran and other acetylenic chemicals. It is also used in the production of polyester glycols and polyurethanes. The first U.S. plant to manufacture BG was GAF in the 1950's.[5] The 1,3 isomer, because of its low toxicity, has been proposed for cosmetic and pharmaceutical applications. The 1,4 isomer, however, is approximately 10 times as toxic when administered to animals as is the 1,2 or 1,3 isomer in single and repeated doses.

2.2 *Industrial Exposure*

During the production and use of BG, the possibility for aerosol exposure exists in the workplace.[35] However, human data regarding industrial exposure could not be identified in the scientific literature at this time. Currently no recognized occupational health standards exist for BG.

3.0 Toxicology Review

3.1 *Summary*

When BG is compared to its isomers, it is considered more toxic. However, data on the 1,4-BG isomer indicates that when it is studied in animals, it has a low acute oral and inhalation toxicity, is not significantly irritating to the eyes, skin or mucous membranes and is not expected to absorb through the skin in hazardous amounts. Keeping in mind that animal studies often involve very high doses, it was found that when a dose high enough to cause death in rats (2-40 g/kg) was given, rapid narcosis, constriction of the pupils, and loss of reflexes was produced. The cause of death in this case is attributed to central nervous system (CNS) paralysis.[35]

There is very limited information on human exposure. Seven cases of poisoning were reported from its use internally as a substitute for glycerin. Damage to the kidneys was observed.[5] One report involves a dose of 15 grams rectally, which was followed by miosis (constriction of the pupils), unconsciousness, and coma.[12]

Although this is beyond the scope of this report, BG seems to be unique among the glycols in it metabolism. Maxwell and Roth found that slices of rat brain, kidney, liver, and heart were able to metabolize BG to Gamma-hydroxybutyrate (GHB). They postulated that the CNS depressing action of BG is due primarily to the presence of gamma-hydroxybutyrate.[12] Behavioral, electrical, and biochemical studies in rats suggest that the effects of BG are mediated by GHB. This information suggests that BG has unique pharmacologic properties among the glycols.[36] It has been found that BG is rapidly metabolized to 4-hydroxybutyric acid in humans and in monkeys.[5]

3.2 *Inhalation Toxicology*

Based on short term (4 hour) inhalation studies in which BG was generated as an aerosol of respirable particle size at concentrations of 4.6, 9.4 and 15 mg / l, BG was considered to be at worst case, only slightly toxic following acute inhalation. At these concentrations (4600, 9400 and 15000 mg/m^3 respectively), a dense mist was present in the test chambers and it was reported that observation of the rats was not possible. Red discharge was seen in the perineal area of rats exposed to the highest dose at 15.0 mg/l, as well as weight loss for a 24 hour period following the exposure. Even under repeated exposures (0.20, and 1.1 mg/l) for a total of 10 days, 6 hour a day, no observable effects were produced. Rats exposed to these same repeat conditions but at a higher dose (5.2 mg/l) initially loss weight over 3 days, but gained weight back over time at a lower rates compared to the controls. In the highest dose group, atrophy of the thymic tissue in 3 of 5 rats exposed, slight changes in hematocrit values, as well as a decrease in serum cholesterol concentrations was observed. The significance of these findings were not considered relevant as concentrations in the industrial setting are not expected to reach such high concentrations. The low degree of toxicity seen with most glycols appears to be true of BG as well. Inhalation of aerosol concentrations by rats of up to 5.2 mg/l were toler-

ated well. These inhalation studies concluded that no significant inhalation hazards would be expected under normal industrial conditions.[35]

3.3 *Oral Toxicity*

This isomer is about 10 times as toxic when administered to animals as the 1,2 or the 1,3 isomer of BG. The oral LD50 has been found to be 2.18 g/kg for mice, 1.78 g/kg for rats, 1.2 g/kg for guinea pigs and 2.53 g/kg for the rabbit.[12]

Guinea pigs and rats fed diets of BG containing 25 to 30 mg/kg/day for 6 months demonstrated no observable effect at 25 mg/kg/day. At 30 mg/kg/day levels, the animals showed signs of blood cholinesterase depression, changes in the protein fraction of the serum, and a decrease in the sulfhydryl groups of the blood.[12]

3.4 *Eye and Skin Irritation*

When BG was applied to the eyes of rabbits it caused slight irritation of the conjunctiva, but no corneal injury. Repeated application to the rabbits' skin, both intact and abraded (scraped or broken to allow passage thought the skin), resulted in no appreciable irritation and no evidence of absorption of acutely toxic amounts. Additional skin studies have reported finding the material highly toxic, however, it has been suggested that the discrepancy can be attributed to the quality of the test material.[12]

F. Glycerol

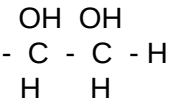
1.0 Chemical and Physical Properties[1, 10, 15, 37]

Identification: CAS# 56-81-5

Common Names**:** Glycerin

Synonyms**:** Glycerin, Glycerine, 1,2,3-Propanetriol, Trihydroxypropane

Structure:



Molecular Formula**:** $C_3 H_{14} O_4$

Chemically, glycerol is a trihydric (polyhydric) alcohol, meaning it has three hydroxyl groups (-OH) in it's structure. Physically glycerol is a clear, syrupy liquid with a warm, sweet taste. Glycerol is very hygroscopic, can be volatilized in steam, and can absorb half its weight in water. It is miscible in water and alcohol; insoluble in ether, benzene, and chloroform and in fixed and volatile oils. Under normal circumstances glycerol is considered stable, however, it can produce violent or explosive reactions when it comes in contact with many solid oxidants. This is due to its unique properties of having three centers of reactivity (OH groups).[10]

Molecular Weight: 92.09
Boiling Point: 290 Deg C
Density: 1.260 @ 20 Deg C
Vapor Pressure: 0.000158 mm Hg @ 25 Deg C
Odor Threshold: Odorless
Flash Point: 176 Deg C (Open Cup)

1 ppm is approximately 3.76 mg/m^3 @ 25 Deg C, 760 mm Hg

2.0 Backgound[10, 15]

2.1 *Sources and Uses*

Documentation on glycerol goes back as early as the 1870's. Over the years glycerol has been used in many different applications. Glycerol can be manufactured synthetically, by fermentation of sugars, or by hydrolysis of fats and oils or as a by-product of soap manufacture. They are used in the manufacture of alkyd resins, dynamite, ester gums, pharmaceuticals, perfume, plasticizers for regenerated cellulose, cosmetics, foodstuffs including confectioneries, conditioning tobacco, liquors, solvent, printer's ink rolls, polyurethane polyols, emulsifying agents, rubber stamp and copying inks, binders for cements and mixes, special soaps, lubricants and softeners, bacteriostats, penetrants, hydraulic fluids, humectants, fermentation nutrients, and anti-freeze mixtures to name a few. [10]

The chief end markets for glycerol are drugs, toothpaste, cosmetics and personal care products and food. Glycerol is used as a multiple purpose GRAS (Generally Recognized as Safe) food additive in food for human consumption, animal feeds, and drug applications, and related products when used in accordance with good manufacturing pratice. [10, 43]

Glycerol is used in many applications in the pharmaceutical industry. It is probably used more frequently in prescriptions than any other substance besides water.[37] Therapeutically glycerin is added to humidifying inhalants. It is added as a hygroscopic agent, used to draw more water into bronchial secretions and reduce viscosity. Glycerol is used in suppositories, and works by forcing water into the intestinal lumen through osmotic forces. Given orally, glycerol reduces intraocular pressure and cerebral edema, especially in patients with acute angle-closure glaucoma and after ophthalmic surgery.[10]

As of 1992 there were not appropriate studies on the relationship of age to the effects of oral glycerol performed in the pediatric population.

2.2 *Industrial Exposure*

Glycerol mist is considered a “nuisance” particulate. It seems to have little adverse effect on the lung and does not produce significant organic disease or toxic effects when exposures are kept under reasonable control. The OSHA PEL for glycerol mist is 15 mg/m^3 as total dust and 5 mg/m^3 as a respirable fraction. Total dust generally refers to all airborne particulate independent of size, whereas the respirable fraction represents particles of 10 microns or less in size. OSHA feels that this limit will provide protection against the risk of kidney damage, and testicular effects which have been recently examined in the scientific literature.[43]

NIOSH states that at high concentrations, exposure may cause hemolysis, hemoglobinuria, and renal failure.[43] However, NIOSH has not recommended an occupational exposure limit to date. ACGIH has established a TLV of 10 mg/m^3 , as a total particulate, until additional toxicology data and industrial hygiene experience becomes available.[15] ACGIH has reported that glycerin mist is easily metabolized and excreted. In the adult human of average weight, 2 grams of glycerol can be metabolized and excreted in an 8 hour work day. At this metabolic and elimination rate, the ACGIH believes that no ill effects are likely to occur as a result of exposure at or below 10 mg/m^3 as an 8 hour TWA. [15] Additional international standards include, 10 mg/m^3 for Australia and the United Kingdom.[15]

3.0 Toxicology

3.1 *Summary*

Glycerol has been safely used in many industrial and pharmaceutical applications for over 100 years and is generally recognized for its low risk health effects. The majority of the toxicologic information on this material is from human data. Toxic doses of glycerol, as with all chemicals, can be obtained when administered in sufficient
quantities. However, healthy individuals can easily tolerate doses of up to 1.5 g/kg or less with only slight diuresis (passage of large amounts of urine) occurring. [10] Glycerol is absorbed from the intestinal tract and is metabolized to carbon dioxide and glycogen in the liver. Glycerol is considered a nuisance particulate which seems to have little effects on the lung and does not produce significant disease or toxic effects when exposures are kept under reasonable

control.[15] Appropriate studies on the relationship of age to the effects of oral glycerol have not been performed in children or geriatric populations. [10, 41]

3.2 *Inhalation Toxicity*

There is very little data regarding the inhalation toxicity of glycerol in both animal species or humans. However, glycerol is used therapeutically to increase the efficiency of inhalants. Due to its hydroscopic properties it is added in an attempt to draw more water into bronchial secretions and thus reduce their viscosity.[10]

3.3 *Oral Toxicity*

Adverse effects in humans following oral administration of glycerol include mild headache, dizziness, nausea, vomiting, thirst, and diarrhea. The quantity necessary to cause death varies with the mode of administration. In both human and animal studies, oral administration requires the highest dose of all routes to produce lethality. Lethal oral doses produce death ultimately due to the combine effect of failing circulation and respiration. Oral administered glycerol also produces increases in the degree of irritability of muscle, causes relaxation of the sphincter of the gall bladder, and appears to increase the force and amplitude of intestinal contractions. No significant blood changes have been reported after oral administration.[37]

One fatal and one non-fatal oral poisoning case has been reported in children. One case, of unknown amounts, caused death. The second child, a 2 1/2 year old took 300 grams orally, loss consciousness and recovered after its stomach was pumped. [37, 39] Another report of an adult patient who took repeated oral and rectal doses of glycerol over a 2 week period, suffered from debility, vomiting, diarrhea, and muscular cramps which disappeared promptly after discontinuation. This paper stated that this reaction is possible due to the irritant effects of glycerol, however, it is more likely that the patient was using contaminated product.[39] Ingestion of 30 ml of glycerol 3X daily for a period of 50 days by normal human subjects was found to be harmless.[37]

3.4 *Eye and Skin Irritation*

Glycerol is regularly used as an ophthalmic solution to reduce superficial corneal edema resulting from disease or trauma. Adverse effects reported when used as a pharmaceutical application suggest pain and or irritation may occur following topical application to the eye.[41] Specular microscopy has shown that repeated application of
100% glycerol to the surface of the human eye causes extensive changes in the appearance of the endothelium, but most of these changes disappear within 90 minutes after exposure is ended.[10] When applied to unbroken skin, pure glycerol apparently is not appreciably absorbed and systemic effects do not occur.[10]

V. Conclusions and Recommendations

Overall, the toxicity data for glycerol and the glycols of concern examined in this report are fairly low. When comparing the order of toxicity for each compound based on the LD50 in rats, the least toxic material is propylene glycol (PG), followed by glycerol (G), triethylene glycol (TEG), diethylene glycol (DEG), dipropylene glycol (DPG), and the most toxic being 1,4-butylene glycol (BG). This information is consistent with the acute and chronic toxicities for PG, G, and TEG.

PG, G, and TEG's toxicity data appears to be well studied and demonstrates low occupational hazards. Although DPG appears to have low toxicity based on its effects in acute and chronic studies, more data is necessary for an adequate review, particularly in the area of inhalation. Similarly, BG showed very low inhalation toxicity when dosed at extremely high levels in rats, however, there are currently not enough data to predict long term effects over time, particularly in humans.

DEG demonstrates low acute toxicity, however, when compared to the other materials in this report, the literature suggests questionable long-term effects at levels that other materials (TEG) had no effects. When DEG is compared to ethylene glycol (EG), a well studied glycol which shares DEG's toxicological properties, a similar lethal oral doses in humans (1.4 ml/kg) is reported. It has been found that both materials, EG and DEG, appear to be less toxic in animal studies than in humans. It is important to note that EG is considered a relatively nontoxic chemical to humans under normal working conditions, unless ingested. EG is not readily absorbed through the skin, has a low vapor pressure and significant air concentrations are not achieved unless heated or sprayed. Human volunteers were able to tolerate 3 to 67 mg/m^3 continuously for 20 to 22 hr/day for 1 month. No significant effects were reported except for some irritation of the nose, and throat, an occasional slight headache, as well as a low backache.[12] It is based on this comparison that DEG is considered relatively low in toxicity.

The objective of this report is to identify safe inhalation exposure levels for the materials of interest. Occupational exposure limits (OELs) for 4 out of 6 of the compounds were identified (see Table 1, page 28). These OELs, for the most part, are intended to suggest levels of exposure to which most workers may be exposed for 8 hours per day, 40 hours per week, for a working lifetime without experiencing adverse health effects. It is, however, important to note that not all workers will be protected from adverse health effects if their exposures are maintained below these levels. A small percentage may experience adverse health effects because of individual susceptibility, a preexisting medical condition, and/or a hypersensitivity (allergy). OELs are determined from toxicology studies using animal models, human exposure data and are often based on the industrial environment in which they are used.

When evaluating OELs, it is necessary to understand the scientific data or documentation used in their development. While the documentation for AIHA, ACGIH and OSHA OELs are available, international OEL documentation was not readily available and therefore not evaluated at this time.

Table 1. United States and International Occupational Exposure Limits for Glycerol and Glycols

Glycol	OSHA PEL	ACGIH TLV	AIHA WEEL	Russian OEL	UK OES	Ontario WEG	German MAKs	Australian OEL
Triethylene Glycol							44 mg/m^3 Peak II,2	
Propylene Glycol			156 mg/m^3 (total) 10 mg/m^3 (aerosol)		470 mg/m^3 (total) 10 mg/m^3 (particulate, for visibility)	155 mg/m^3 (total vapor and aerosol) 10 mg/m^3 (aerosol visibility)		
Diethylene Glycol			217 mg/m^3 (total) 10 mg/m^3 (aerosol)	10 mg/m^3	100 mg/m^3			
Glycerin	15 mg/m^3 (total) 5 mg/m^3 (respirable)	10 mg/m^3			10 mg/m^3			10 mg/m^3
Dipropylene Glycol								
Butylene Glycol								

The OELs for aerosols of G (5 mg/m^3) and for PG and DEG (10 mg/m^3) appear to be sound guidelines based on the review of the toxicology information in this report and the available documentation.

The glycols and glycerol reported herein are used as components in theatrical fog fluids. These fluids are commonly composed of multiple glycols and water. The application of these mixtures is used to create a visible fog. This is commonly accomplished by heating the fluid to a vapor, where it then cools to form an aerosol fog. With consideration to the NIOSH report[44] evaluating the health risks associated with theatrical fog applications and the toxicology information regarding the compounds of interest, the following recommendations are made:

No information regarding the glycols applied as a mixture are currently represented in the literature. Although these fog fluids are mostly water and the chemical and physical properties of the glycols as a group are similar, I believe it is necessary to test the individual fog fluid brands as used under their normal conditions, in their respective fog making equipment. These tests should be performed by a qualified toxicology laboratory.

Consideration must be given to the study performed by NIOSH and the fact that various fog making equipment is designed to be operated at different temperature ranges and can potentially cause changes in the physical and chemical properties of the fog fluid components. NIOSH investigated the possibility of decomposition of the fog fluid components in a laboratory setting and in the work environment and found no decomposition products in their final report. However, it was cautioned in this report that heating fog fluids to the lowest temperature possible was prudent.

Additional considerations should involve monitoring the various environments where theatrical fogs are used in order to better characterize their concentrations, how they are used and in what type of applications they are applied.

VI. Bibliography

(1) Hawley's Condensed Chemical Dictionary, 12th ed. R.J. Lewis, Sr. editor. Van Nostrand Reinhold Co., New York. 1993.
(2) Cassarett and Doull's Toxicology, The Basic Science of Poisons, 5th ed. C.D. Kaassen editor. McGraw Hill, New York, NY 1996.
(3) American Industrial Hygiene Association, Workplace Environmental Exposure Level Guide for Propylene Glycol, 1985.
(4) American Industrial Hygiene Association, Workplace Environmental Exposure Level Guide for Diethylene Glycol, 1985.
(5) Hazardous Substances Data Bank [data base]: National Library of Medicine. Monograph title/HSN #:1112 for 1,4-Butanediol, Latest revision: 970225.
(6) Hazardous Substances Data Bank [data base]: National Library of Medicine. Monograph title/HSN #:174 for Propylene glycol. Latest revision: 970311.
(7) Hazardous Substances Data Bank [data base]: National Library of Medicine. Monograph title/HSN #:898 for Triethylene glycol, Latest revision: 970124.
(8) Hazardous Substances Data Bank [data base]: National Library of Medicine. Monograph title/HSN #:2854 for Dipropylene glycol. Latest revision: 960124.
(9) Hazardous Substances Data Bank [data base]: National Library of Medicine. Monograph title/HSN #:69 for Diethylene glycol, Latest revision: 970324.
(10) Hazardous Substances Data Bank [data base]: National Library of Medicine. Monograph title/HSN #: 492 for Glycerol, Latest revision: 960722.
(11) Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services. G. Pasternak and L. Goldfrank editors. Case Studies in Environmental Medicine for Ethylene and Propylene Glycol Toxicity # 30. September 1993.
(12) Patty's Industrial Hygiene and Toxicology, volume 2F, 4th edition. G.D. and F.E. Clayton, editors. John Wiley & Sons, New York, NY (1994) p:4645-4719.
(13) Toxicology of the Eye, 4th edition. W.M. Grant and JS. Schuman editiors. Charles C. Thomas, Springfield, IL, 1993 p: 551, 1209 and 1460.
(14) Center for Chemical Hazard Assessment, Syracuse Research Corporation. Information on Potential Occupational Hazards: Glycols. Prepared for NIOSH. Contract No. 210-79-0030. February 1982.
(15) American Conference of Governmental Industrial Hygienist, Documentation of Threshold Limit Values and Biological Exposure Indices for Glycerin Mist. 6th edition, (1992) 705-706.
(16) Contact and Occupational Dermatology, 2nd edition, Marks, J.G. Jr., and DeLeo, V.A. (1996) 156-157.
(17) Clinical Toxicology of Commercial Products, 5th edition, Gosselin, R., Smith, R., and Hodge, H. (1984) II-178-179.
(18) Circular for 1,2-Propylene Glycol, Ontario Ministry of Labour, Health and Safety Support Services Branch, Issue: 5-9-84, Updated: 5-29-91.
(19) Hanzlik, P.J., Newman, H.W., Van Winkle, W., Jr., Lehman, A.J., and Kennedy, N.K. Toxicity, Fats and Excretion of Propylene Glycol and Some other Glycols.
(20) Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 9th edition. Hardman,J.G. and Limbird, L.E. editors, (1996) McGraw-Hill 1682-83.
(21) Weil, G.S., Woodside, M.D., Smyth, H.F., and Carpenter, C.P. Results of Feeding Propylene Glycol in the Diet to Dogs for Two Years. (1971) Food and Cosmetic Toxicology. 9: 479-490.

(22) Gaunt, I.F., and Carpanini, F.M.B. Long-term Toxicity of Propylene Glycol in Rats. (1972) Food and Cosmetic Toxicology. 10: 151-162.
(23) Suber, R.L., Deskin, R., Nikiforov, I. Fouillet, X. and Goggins, C.R.E. Subchronic Nose-Only Inhalation Study of Propylene Glycol in Sprague-Dawley Rats. (1989) Food and Cosmetic Toxicology. 27: No. 9. 573-583.
(24) Willis, C.M., Stephens, C.J.M., and Wilkinson, J.D. Epidermal Damage Induced by Irritants in Man: A Light and Electron Microscopic Study. (1989) Investigative Dermatology 93: 695-699.
(25) Martindale's, The Extra Pharmacopeia, 30th edition. Reynolds, J.E.F. (1993).
(26) Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning. Ellenhorn, M.J. Editor. (1997). Williams and Wilkins. 1157-59.
(27) Wikinson, D.P. Diethylene Glycol Poisoning. Medical Journal of Australia. August 26, 1967. page 463-464.
(28) U.S. Department of Health and Human Services, Center for Disease Control, NIOSH. Health Hazard Evaluation Determination. Report No. MHETA 82-006-9002. Patil, A., Corwell, R.J. August 1992.
(29) Opdyke, D.L.J. (1979) Triethylene Glycol. Food and Cosmetic Toxicology. 17, 913-16.
(30) Robertson, O.H., Loosli, C.G. Loosli, Puck, T.T., Wise, H., Lemon, H.M., and Lester, W., Jr., (1947). Tests for the Chronic Toxicity of Propylene glycol and Triethylene glycol on Monkeys and Rats by Vapor Inhalation and Oral Administration. J of Pharmaceutical and Experimental Therapeutics. 91: 52-76.
(31) Hamburger, M, Jr., Puck, T.T., Theodore, T., and Robertson, O.H. (1945) The Effect of Triethylene Glycol Vapor on Air-borne Beta Hemolytic Streptococci in Hospital Wards. I. J of Infectious Diseases. 76: 208-215.
(32) Puck, T.T., Hamburger, M. Jr., Robertson, O.H., and Hurst, V. (1945). The Effect of Triethylene glycol Vapor on Airborne Beta Hemolytic Streptococci in Hospital Wards. J of Infectious Disease. 76: 217-26.
(33) Loosli, C.G., Smith, M.H.D., Gauld, R.L., Robertson, O.H., and Puck, T.T. (1947) Control of Cross-Infections in Infants' Wards by the Use of Triethylene glycol Vapor. American Journal of Public Health. 37: 1383-98.
(34) Fitzhugh, O.G. and Nelson, A.A. Comparison of the Chronic Toxicity of Triethylene glycol with that of Diethylene Glycol. (1946) 28: 40-43.
(35) Kinney, L.A., Burgess, B.A., Stula, E.F., and Kennedy, G.L., Jr. (1991) Inhalation Toxicology of 1,4-Butanediol. Inhalation Toxicology, 3: 379-388.
(36) Poldrugo, F. and Snead, O.C..(1984) 1,4 Butanediol, Gamma-Hydroxybutyric Acid and Ethanol: Relationships and Interactions. Neuropharmacology, 23, No. 1, 109-113.
(37) Deichmann, W. Glycerol — Behavior in the Animal Organism (A review of the Literature) (1940) Industrial Medicine (Industrial Hygiene Section). 9: 58-67.
(38) Medical Toxicology, Edited by Ellenhorn, M.J. & Barceloux, D.G., 1st edition (1988). Elsevier, New York, NY.
(39) Von-Oettingen, W.F. The Aliphatic Alcohols: Their Toxicity and Potential Dangers in Relation to Their Chemical Constitution and Their Fate in Metabolism. (1943) Public Health Bulletin, No. 281, 253 pages.
(40) Wiebe, J.P., Barr, K.J., and Buckingham, K.D.. Sustained Azoospermia in Squirrel Monkey, Salmir Schureus Resulting from a Single Intratesticular Glycerol Injection. (1989) Contraception. 39, no. 4, 447-457.
(41) AHFS Drug Information 1997 McEvoy, G.K. editor.
(42) Glycerin Mist, Federal Register, 54, No. 12, Thursday, January 19, 1989, Rules and Regulations, page 2593.

(43) 21 Code of Federal Register (4-1-96 edition), Part 182-Substances Generally Recognized as Safe, Subpart B.
(44) Burr, G.A., Driscoll, R., and Wilcox, T.G. Health Hazard Evaluation Report No. HETA-90-0355-2449. Hazard Evaluations and Technical Assistance Branch, NIOSH, U.S. Department of Health and Human Services. (1994) 59 pages.
(45) Industrial Ventialtion, A Manual of Recommended Practice. 21st edition. American Conference of Governmental Industrial Hygienists. ACGIH, Cincinnati, Ohio, 1992.
(46) List of MAK and BAT Values 1996. Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Report No. 32. Deutsche Forschungsgemeinschaft. VCH Publishers, Inc., New York, NY, 1996.
(47) Sax's Dangerous Properties of Industrial Materials, 9th Edition. Richard J. Lewis, Sr. Van Nostrand Reinhold. 1996.

VII. Appendix

Electronic Databases Used

Pub Med, National Library of Medicine (Run by HSE Consulting and Sampling, Inc.)

Hazardous Substance Data Bank, National Library of Medicine (Performed by University of Nebraska, Medical Center, McGoogan Libray)

Registry of Toxic Effects of Chemicals, National Library of Medicine (Performed by University of Nebraska, Medical Center, McGoogan Library)

NIOSHTIC is a computerized, bibiliographic database maintained by the NIOSH (Performed by NIOSH)