TRIETHYLENE GLYCOL

CAS Number: 112-27-6

Synonyms: 2,2'-(Ethylenedioxy)diethanol; 2-[2-(2-hydroxyethoxy)ethoxy]ethanol; 2,2'-(Ethane-1,2-diylbis(oxy))diethanol; Triglycol

Molecular Formula: $C_6H_{14}O_4$

Chemical Structure[1]:

TLV®-TWA, 10 mg/m³, Inhalable fraction and vapor

TLV Recommendation

A TLV-TWA of 10 mg/m³, measured as inhalable fraction and vapor, is recommended for occupational exposure to triethylene glycol to protect against the potential for body weight effects and eye irritation.

The available human information for triethylene glycol is insufficient to characterize potential toxicity and dose-response effects, therefore the TLV-TWA is based on animal studies. Several clinical studies were reported for its use as an air sanitizer; however, the focus of these studies was on efficacy and not toxicity, the health status of the subjects was not specified, and the exposure information was limited.[2,3] (See Bigg et al., 1945; Krugman and Ward, 1951; and NMRU, 1952, in Ballantyne and Snellings[2]; and Hamburger et al., 1945; Harris and Stokes, 1945; Puck et al., 1945; Krugman and Ward, 1951; and NMRU, 1952, in STSC.[3]) A study of theater workers reported eye and upper respiratory symptoms, but their exposures were to fogs that included multiple substances, and hence these effects cannot be attributed solely to triethylene glycol.[4]

The toxic effects of oral exposure to triethylene glycol in laboratory animals have been thoroughly examined, with the results generally showing low toxicity; however, the information available on toxicity of repeated inhalation exposure is limited. Two well-designed and well-conducted repeated inhalation exposure studies were reported in rats, but testing included only 9 days of exposure. In the first study, rats were exposed in whole-body exposure chambers daily for 6 hours/day, with significant toxicity observed at the highest exposure concentration of 4,824 mg/m³ as indicated by deaths and clinical signs of systemic toxicity.[5] At both the lower concentrations, 494 and 2,011 mg/m³, there were clinical signs of toxicity (periocular swelling and perinasal encrustation) and changes in clinical chemistry (blood urea nitrogen and inorganic phosphorus). The study LOAEL for whole-body exposure was 494 mg/m³ based on clinical signs and clinical chemistry changes; however, the actual systemic exposures received by the rats cannot be determined because, in addition to inhalation exposure, the whole-body exposure route likely resulted in significant oral (through preening) and dermal exposures. The second study used daily 6-hour nose-only exposure.[6] The only finding that appeared to be related to triethylene glycol was a non–statistically significant decrease in body weight gains in the 517- and 1,036-mg/m³ females over exposure days 8 to 9 and 9 to 12. The effects of interest in these 2 studies were the ocular changes that were noted following 494 mg/m³ whole-body exposure (these effects were likely local effects and the possible systemic oral exposure issue in this study is not pertinent to local effects) and the body weight change that was noted following ≥517 mg/m³ nose-only exposure. No NOAEL was determined for the ocular effects as this concentration was the lowest studied in the whole-body exposure and the nose-only exposure study, although testing lower concentrations likely did not significantly expose the eyes of the rats. The NOEL for the body weight effects in the nose-only study was 102 mg/m³.These findings are

questionably adverse but no longer-term nose-only inhalation studies are available to further study this effect. Considering the body weight changes as evidence of general systemic toxicity and the eye effects as due to local ocular irritation, a TLV-TWA of 10 mg/m^3 for vapor and aerosol should be sufficient to protect against the toxic effects of triethylene glycol. Limiting aerosols to this concentration is also consistent with good industrial hygiene practice of improved housekeeping, avoiding a slippery material that can represent a safety concern (e.g., visual impairment, slips, and falls).

Sufficient data were not available to support a TLV-STEL. Although respiratory, nasal, and eye irritation have been reported in humans following exposure to theatrical fogs containing triethylene glycol,[4] exposure to other substances occurred, and to durations that may have been longer than 15 minutes; therefore, a STEL based on these effects is not warranted.

Results of a guinea pig sensitization study (see the Biodynamics study, 1990, in Ballantyne and Snellings[2]) and a human repeated patch test (see the TKL Research, Inc., 1989, study in OECD[7]) were negative, so a DSEN notation is not recommended.

Sufficient data were not available for triethylene glycol to recommend a TLV-SL, Skin, RSEN, OTO, or cancer notation.

TLV Basis

Body weight effects; eye irritation.

Chemical and Physical Properties

Triethylene glycol is an aliphatic alcohol that exists as a colorless, hygroscopic liquid (at room temperature).[1,8] It has been described as odorless, nearly odorless, or having a mild sweet odor.[1,2,8] No odor detection threshold was identified. This substance has very low volatility, and may exist as a vapor that is heavier than air, denser than water, and highly miscible with water. Select physicochemical properties are listed in Table 1.[1,2,7-10]

Table 1. Chemical and Physical Properties of Triethylene Glycol

Property	Triethylene Glycol
Molecular weight	150.17 g/mol
Specific gravity	1.1255 g/mL
Melting point	-4.3°C (24.3°F)
Boiling point	288°C (550°F)
Vapor pressure	1.32 × 10^{-3} mm Hg @ 25°C (77°F)
Saturated vapor concentration	1.7 ppm (10.4 mg/m^3) @ 25°C (77°F)
Flash point	177°C (351°F); Method: closed cup
Explosive limits	0.9% to 9.2% v/v in air
Autoignition temperature	371°C (700°F)
Solubility (water)	≥100 mg/mL
Octanol/water partition coefficients	Log K_{ow} −1.75 @ 25°C (77°F)
Vapor density	5.2 (air = 1)
Conversion factors at 25°C and 760 torr	1 ppm = 6.14 mg/m^3; 1 mg/m^3 = 0.16 ppm

Major Sources of Occupational Exposure

Triethylene glycol is prepared commercially by the hydration of ethylene oxide.[1,11] This process produces (mono)ethylene glycol, diethylene glycol, triethylene glycol, and tetraethylene glycols which are separated by distillation. This substance has not been reported to occur naturally. The US national aggregate production volume of triethylene glycol reported annually in 2016 through 2019 was 100,000,000 to <250,000,000 lbs.[12]

Triethylene glycol has industrial, professional, and consumer uses. Among its industrial uses are natural gas dehydration, in plastics to increase pliability, as a solvent and plasticizer in vinyl polyester and polyurethane resins, as a humectant, as an extraction solvent, and as an ingredient in brake fluids.[8] It has

regulated uses as a bacteriostat (against odor-causing bacteria for air sanitization and deodorization); in combination with other active agents, it is used as a fungicide, virucide, and miticide for disinfection of hard, nonporous surfaces; as an insecticide (against lice) to treat birds; as an inert ingredient in agricultural pesticide formulations; as a preservative for food packaging adhesives; and as a plasticizer in cellophane.[2,3,10] More recently, triethylene glycol has been used as an active ingredient in airborne antiviral products (treatment of SARS-CoV-2 virus).[13] A professional use of triethylene glycol is in formulations for the generation of smokes, mists, or fogs for theatrical purposes.[2] Consumer uses of triethylene glycol are in cosmetic products as a fragrance ingredient and a viscosity-decreasing agent.[8]

There is no current information on worker exposures to triethylene glycol. Given its downstream uses, significant exposures to workers and consumers are expected by inhalation and skin and eye contact.

Human Studies

Several clinical studies were reported that evaluated triethylene glycol use as an air sanitizer. These studies evaluated the ability of triethylene glycol administered into the air of dormitories and hospitals to control or reduce bacterial infections in military personnel and patients (see Bigg et al., 1945; Krugman and Ward, 1951; and NMRU, 1952, in Ballantyne and Snellings[2]; and Hamburger et al., 1945; Harris and Stokes, 1945; Puck et al., 1945; Krugman and Ward, 1951; and NMRU, 1952, in STSC[3]). Triethylene glycol exposures ranged from 1 to 13 mg/m^3 and were continuous for varying time lengths. The exposure metrics were not well-described and likely represented area samples and not personal exposures. Two studies reported finding no toxicologic effects (see Bigg et al., 1945, in Ballantyne and Snellings[2] and Hamburger et al., 1945, in STSC[3]), though the extent and timing of the examinations were not identified, and the other studies did not specifically report observing for toxicologic effects. The overall focus of these studies was on efficacy and not toxicity, and the health status of the subjects was not specified.

Health symptoms have been reported in workers exposed to triethylene and other glycol aerosols used in theatrical productions.[4] The complaints included nasal symptoms (sneezing, runny or stuffy nose), respiratory symptoms (cough, wheeze, breathlessness, chest tightness) and mucous membrane symptoms (sore throat, hoarseness, dry throat, itchy/burning eyes, dry eyes). The materials used to produce fogs were reported to contain propylene glycol, 2,3-butylene glycol, triethylene glycol, ethylene glycol, and diethylene glycol. Triethylene glycol found in one of the fog air samples was reported to be in the range of <0.04 to 3.7 mg/m^3. Other substances were also identified in the tested atmospheres, including C_9 to C_{12} aliphatic hydrocarbons, C_9H_{12} alkyl benzenes, 1,1,1-trichloroethane, acetaldehyde, acetone, isopropanol, toluene, limonene, siloxanes, and perchloroethylene. NIOSH concluded that there was no evidence that the theatrical smoke at the levels found in their study was a cause for occupational asthma among performers but noted that some of the constituents could have irritative or mucous membrane–drying properties in some individuals.

Skin reactions to triethylene glycol have been studied in human volunteers. In a primary skin irritation test, 103 subjects (12 males and 91 females; age range 18 to 74 years) received 0.2 mL of undiluted triethylene glycol that was applied to the infrascapular skin and maintained under occlusive dressing for 48 hours (see TKL Research, Inc., 1989, in OECD[7]). The primary irritation index calculated from the subject responses was 35.9 which was interpreted as minimal irritation. The skin sensitization potential of triethylene glycol was tested in a repeated insult patch test performed on 397 volunteers (37 males, 360 females; ages ranged from 18 to 85 years) (see TKL Research, Inc., 1989, in OECD[7]). This induction phase consisted of 9 consecutive applications of undiluted triethylene glycol (0.2 mL) to infrascapular skin and covered with occlusive or semiocclusive patches for 24 hours. After a 2-week rest phase, the challenge phase was initiated with the application of undiluted triethylene glycol (0.2 mL) that was also covered with patches for 24 hours. The skin sites were graded for irritation responses at 48 and 72 hours after removal of the challenge patches. No evidence of sensitization was reported in this study.

A single case of poisoning following supposed ingestion of triethylene glycol is reported (see Vassiliadis et al., 1999, in the final report on the safety assessment of triethylene glycol and PEG-4[8]). A 23-year-old woman who intentionally ingested one gulp (volume not specified) of a brake fluid product containing 99.9% triethylene glycol exhibited unconsciousness and metabolic acidosis. Treatment

consisted of sodium bicarbonate and ethanol (to act as a competitor for the metabolism by alcohol dehydrogenase), and her blood pH returned to normal after 8 hours. However, this product's content of triethylene glycol is questionable as the manufacturer's safety data sheet states that the major ingredient in this product was glycol ether borate ester.[2]

There are no epidemiologic studies that evaluated health effects in triethylene glycol–exposed workers.

Animal Studies

Triethylene glycol has low acute toxicity for oral, dermal, and inhalation exposures.

Acute/Subacute

Oral

Triethylene glycol has been evaluated for acute oral toxicity in rats, guinea pigs, mice, and rabbits. Oral LD_{50} values were reported to range from >18 to 22 g/kg in rats (see Smyth et al., 1941, in Ballantyne and Snellings,[2] and Bushy Run Research Center, 1990, in Ballantyne and Snellings[2] and ECHA[14]), 7.9 to 14.6 g/kg in guinea pigs (see Laug et al., 1959, in OECD,[7] and Smyth et al., 1941, in Ballantyne and Snellings[2]), >18.5 g/kg in mice (see Smyth et al., 1941, in Ballantine and Snellings[2]), and 8.4 to 9.5 g/kg in rabbits (see NIOSH, 2003, in Ballantine and Snellings[2]). In rats (Sprague-Dawley, 5 males and 5 females), the only clinical sign of toxicity observed after a dosage of 16 mL/kg (approximately equivalent to 18 g/kg) triethylene glycol (99.82% purity) was sluggishness and unsteady gait that appeared 30 minutes to 1 hour following dosing and resolved by 3 hours to 1 day after exposure (see Bushy Run Research Center, 1990, in Ballantyne and Snellings[2] and ECHA[14]). No deaths or gross pathology changes were observed.

Two subacute oral toxicity studies on triethylene glycol were reported. A subacute oral dietary study was conducted in rats to support dose selection for a subsequent 90-day study (see Van Miller and Ballantyne, 2001, in Ballantyne and Snellings[2]). Groups of 20 male and 20 female Fischer 344 rats had triethylene glycol (>99% purity) incorporated into their diets at concentrations of 0, 10,000, 20,000, and 50,000 ppm for 14 days. The daily estimated triethylene glycol consumption at these concentrations were 0, 1,132, 2,311, and 5,916 mg/kg per day, respectively, for males and 0, 1,177, 2,411, and 6,209 mg/kg per day for females. In this study no treatment-related effects on mortality, clinical signs, body weights, food consumption, clinical chemistry, organ weights, or pathology were observed. The only treatment-related effects were in urinalysis values, with a dose-related increase in urine volume identified at 20,000 and 50,000 ppm and a decrease in pH and triple phosphate crystals identified at 50,000 ppm. These changes were not associated with changes in serum chemistry or kidney histopathology and hence may have been related to the excretion of triethylene glycol or its metabolites. The NOAEL for this study was 50,000 ppm (5,916 and 6,209 mg/kg in males and females, respectively).

A subacute oral toxicity study conducted using drinking water exposure to triethylene glycol was also reported (see Bossert et al., 1992, in STSC[3]). This study was performed to aid dose selection for a mouse reproductive toxicity study of triethylene glycol. In this study, 8 male and 8 female CD-1 mice were administered triethylene glycol (97% purity) in the drinking water for 14 days at 0, 1%, 2.5%, 5%, 7.5%, or 10% (resulting in daily estimated triethylene glycol dosages of 0, 1,750, 4,375, 8,750, 13,125, and 17,500 mg/kg per day, respectively). Evaluations in this study were limited to mortality, morbidity, body weight, and water consumption. Treatment-related deaths included 2 males at 8,750 mg/kg per day, 1 female at 13,125 mg/kg per day, and 1 female at 17,500 mg/kg per day. In these dosage groups, clinical signs of toxicity included dehydration, lethargy, and piloerection. At ≥8,750 mg/kg per day, mean final body weight and body weight gain were also reduced by >10%. The NOAEL for this study was 4,375 mg/kg per day.

Dermal

A single rabbit acute dermal toxicity study was reported (see Bushy Run Research Center, 1990, in Ballantyne and Snellings[2]). This study applied a single application of 16 mL/kg (approximately equivalent to 18 g/kg) triethylene glycol (99.82% purity) to 5 male and 5 female New Zealand white rabbits under

occlusive dressing for 24 hours. One of the females died 6 days after exposure and exhibited gas-filled intestines. Clinical signs of systemic toxicity were limited to emaciation and abdominal distention in this female and only abdominal distention in another female. There were no local skin changes related to triethylene glycol exposure. The study LD_{50} was >18 g/kg.

Inhalation

Acute and subacute rodent inhalation toxicity studies were identified for triethylene glycol.

Triethylene glycol vapor and aerosol have been examined for acute inhalation toxicity in rats. A 6-hour exposure to dynamically generated saturated vapor (concentration not specified) of triethylene glycol did not lead to any deaths in rats (strain, sex, and numbers not specified) or cause any clinical signs of toxicity, body weight effects, or gross pathology changes (see Bushy Run Research Center, 1986, in Ballantyne and Snellings[2]). An LC_{50} value cannot be determined from this study.

Two acute aerosol exposure studies have been reported in rats. In the earliest study, rats (strain, sex, and numbers not specified) were exposed for 4 hours to triethylene glycol aerosol concentrations of 4,400 to 4,600 mg/m^3 (see Cascieri et al., 1991, in Ballantyne and Snellings[2]). The median mass aerodynamic diameter [MMAD] of these aerosols ranged from 1.6 to 3.1 µm, with 95% of the particles being <10 µm. No deaths occurred, but decreased activity was noted during exposure, which resolved after the animals were removed from the exposure chamber. Transient body weight loss, nasal discharge, and excessive lacrimation were noted in the first few days after the exposure. No gross pathology changes were identified at necropsy. This study supports an LC_{50} of >4,600 mg/m^3. The second study examined male and female Sprague-Dawley rats (6 males and 6 females per group) exposed to aerosols of triethylene glycol for 4 hours at concentrations of 2,620, 3,900, 5,020 and 6,730 mg/m^3 (see Ballantyne et al., 2006, in Ballantyne and Snellings[2]). The corresponding MMAD of the particles were 4.4 to 4.5 µm, 4.8 to 4.9 µm, 5.3 to 5.4 µm, and 7.1 to 7.2 µm. All females exposed to 5,520 mg/m^3 died but none of the males exposed to this concentration or the females or males exposed to 6,730 mg/m^3 died during the study. Clinical signs of toxicity found in animals exposed to both the high aerosol concentrations were limited to irritancy effects indicated by perioral/perinasal encrustation and blepharospasm. No gross pathology changes were identified in the deceased females or any of the animals that survived until the end of the 14-day exposure period. Given the observed deaths at 5,520 mg/m^3, a follow-up study was performed, which tested 2 additional aerosol concentrations of 4,967 mg/m^3 (females; MMAD 7.3 to 9.3 µm) and 5,230 mg/m^3 (males and females; MMAD 5.4 to 5.5 µm). There were no deaths in this study. Together, these studies support an LC_{50} of >6,730 mg/m^3.

An acute aerosol inhalation study in mice was performed to evaluate the sensory irritation potential of triethylene glycol.[15] Groups of 4 male Swiss Webster mice were exposed by nose-only for 30 minutes to triethylene glycol aerosol concentrations ranging from 3,601 to 5,099 mg/m^3 (MMAD ranged from 2.45 to 3.10 µm) and evaluated for respiratory rate depression using a method for assessing sensory irritation. Maximum decreases in respiratory rate were noted within 15 to 25 minutes of the exposure start and were sustained for the exposure period. From the exposure concentration-response relationship, the concentration causing a 50% decrease in breathing rate (RD_{50}) was identified as 5,140 mg/m^3.

Subacute inhalation toxicity of triethylene glycol aerosol was examined in rats in two 9-day studies (9 days of exposure over an 11-day period). The studies used different exposure apparatuses and found different results. The first study used whole-body exposure chambers.[5] Groups of 10 male and 10 female Sprague-Dawley rats were exposed to 99.9% pure triethylene glycol aerosol at concentrations of 0, 494, 2,011, or 4,824 mg/m^3 (MMAD values ranged from 1.9 to 2.9 µm) for 6 hours/day, 5 days/week, for 9 days over an 11-day period. None of the animals that received the 494 and 2,011 mg/m^3 exposures died, but all the rats that were exposed to 4,824 mg/m^3 died between study days 2 and 5. Clinical signs of toxicity in the rats that died during the study included ataxia, prostration, labored breathing, swollen periocular tissues, ocular discharge, perinasal and periocular encrustation, and involuntary spasms of the eyelid. At the 2 lower concentrations, the clinical signs were limited to periocular swelling and perinasal encrustation. Body weight and gain decreases occurred in the 4,824-mg/m^3 rats (both sexes) and 2,011-mg/m^3 males. In the rats that survived to study termination (all but the 4,824-mg/m^3 rats), there were no

treatment-related changes to hematology parameters, whereas increases in clinical chemistry parameters were found in alanine aminotransferase, at 2,011 mg/m^3; alkaline phosphatase, at 494 and 2,011 mg/m^3; and blood urea nitrogen and inorganic phosphorus, at 494 and 2,011 mg/m^3 (females only). The surviving female rats exposed to 2,011 mg/m^3 exhibited increases in liver and kidney weights. Pathology changes in the 4,824 mg/m^3 rats consisted of gross evidence of hyperinflated lungs, congestion, and hemorrhage of various organs and tissues, which was detected microscopically in the pituitary, nasal mucosa, brain, lungs, kidney (females only) and thymus (females only). No gross pathology changes were noted in the 494- and 2,011-mg/m^3 rats; however, the histopathologic examination found minimal to mild alveolar histiocytosis in the 2,011-mg/m^3 rats. No NOAEL was identified in this study. The study LOAEL was 494 mg/m^3 based on clinical signs and clinical chemistry changes, but the actual systemic exposures received by the rats cannot be determined. This is because, in addition to inhalation exposure, the whole-body exposure route likely resulted in significant oral (through preening) and dermal exposures.

A second similarly designed subacute study was performed as a follow-up to the first study. Nose-only exposure was used to understand the potential contributions to toxicity of oral and dermal exposures in the whole-body exposure study.[6] This study also tested groups of Sprague-Dawley rats (10 per sex per group) exposed to triethylene glycol aerosol for 6 hours/day, 5 days/week, for 9 days over an 11-day period, but at measured concentrations of 0, 102, 517 and 1,036 mg/m^3 (MMAD values ranged from 1.2 to 1.4 µm). Two animals in the 517-mg/m^3 group died, but these deaths were not considered to be due to treatment as there were no signs of toxicity or any other abnormalities in these animals, and no deaths occurred at the higher concentration. This study found no treatment-related effects on clinical signs, hematology or clinical chemistry parameters, or gross or histopathologic findings. The only finding that appeared to be related to triethylene glycol exposure was a non–statistically significant decrease in body weight gains in the 517- and 1,036-mg/m^3 females over exposure days 8 to 9 and 9 to 12. The NOEL for this study was 102 mg/m^3 based on slightly decreased weight gains detected in females exposed to ≥517 mg/m^3. These findings are questionably adverse (hence not assigned as the NOAEL) but no longer-term nose-only inhalation studies are available to further study this effect.

Sensitization

Triethylene glycol did not produce skin sensitization in a guinea pig study (strain, sex, and number not specified) (see Biodynamics, 1990, in Ballantyne and Snellings[2]). The maximization method was used to test induction exposures consisting of intradermal injections of triethylene glycol (dosage not specified), followed 7 days later with an epicutaneous application (dosage not specified). After 14 days, an epicutaneous challenge dose was administered (dosage not specified) and observations for skin responses were made 24 and 48 hours after the challenge exposure. This study found no skin reactions indicative of skin sensitization due to triethylene glycol dermal exposure.

Other Studies

Liquid triethylene glycol produced minimal to no skin and eye irritation and aerosol produced eye and respiratory irritation in experimental animal studies.

In an occluded patch test in 3 male and 3 female New Zealand white rabbits, 0.5 mL undiluted triethylene glycol (99.82% purity) applied to the skin and covered with an occluded patch for 4 hours did not produce any erythema, edema, or other dermal reactions (see Bushy Run Research Center, 1990, in ECHA[14]). To test for eye irritancy, 0.1 mL of undiluted triethylene glycol (99.82% purity) was applied to the eyes of 6 New Zealand white rabbits (sex not specified) (see Bushy Run Research Center, 1990, in ECHA[14]). Two of the rabbits exhibited minor conjunctival redness and chemosis, moderate to substantial conjunctival discharge, and minor iritis at the 1- and 4-hour readings, whereas no changes were detected in these rabbits at the 24-hour through 7-day readings; the remaining 4 rabbits exhibited no changes at any time.

A subacute inhalation toxicity study was conducted of whole-body exposures to triethylene glycol aerosol in rats(see Acute/Subacute Inhalation Toxicity section for details).[5] The study found periocular swelling and perinasal encrustations in the rats exposed to 494 and 2,011 mg/m^3, and swollen periocular

tissues, ocular discharge, perinasal and periocular encrustation, and involuntary spasms of the eyelid in the rats exposed to 4,824 mg/m^3.

Subchronic

One subchronic inhalation and 3 subchronic oral toxicity studies of triethylene glycol were identified.

An early inhalation study tested rats (strain, sex, and number not specified) exposed to supersaturated triethylene glycol vapor (purity not specified, reported approximate concentration 449 mg/m^3) continuously for 41 days, and reported no exposure-related effects (see Maassen, 1953, in STSC[3]). The concentration suggests that aerosols may have been present in the tested atmosphere. This report is not available in English and very limited information on the study design and results were identified, hence this information is insufficient for assessment.

Oral studies were conducted in rats using dietary, drinking water, and gavage exposures. The most comprehensive of these subchronic oral studies used triethylene glycol dietary exposures (see Van Miller and Ballantyne, 2001, in Ballantyne and Snellings[2] and STSC[3]). In this study, groups of Fischer 344 rats (20 males and 20 females in the low- and mid-dose groups and 30 males and 30 females in the control and high-dose groups) were fed diets containing 0, 10,000, 20,000, or 50,000 ppm triethylene glycol (>99.45% purity) for 90 days. The estimated daily dosages of these dietary concentrations were 0, 748, 1,522, and 3,849 mg/kg per day for males and 0, 848, 1,699, and 4,360 mg/kg per day for females, respectively. At the end of the exposure period, 20 rats per sex per treatment group were sacrificed for evaluation and the remaining 10 rats per sex in the control and high-dose groups were retained for a 6-week postexposure period. There were no treatment-related deaths, clinical signs of toxicity, or changes in clinical chemistry, gross pathology, or histopathology. Decreases in body weight and body weight gain that were generally <10% were found in the 50,000-ppm males and females during the exposure period but became comparable in the males during the postexposure period. There were slight decreases in erythrocyte count and hematocrit in 20,000- and 50,000-ppm males and an increase in mean corpuscular volume in the 50,000-ppm males at the end of the exposure period; these changes were not evident in the high-dose males at the end of the postexposure period. Urinalysis showed a dose-related decrease in pH in all males and females in the 20,000- and 50,000-ppm groups. The 50,000-ppm males also exhibited a decrease in urine volume. There were no effects on urinalysis evident at the end of the postexposure period. The only treatment-related organ weight change occurred in the kidneys. Absolute kidney weights were increased in the 50,000-ppm females at the end of the dosing period but not at the end of the postexposure period, and relative (to body weight) kidney weight was increased in all treated male groups and in the 20,000- and 50,000-ppm females at the end of the dosing period. These increases were dose-related but were <10%. There were no treatment-related changes noted on gross or histopathologic examination. The authors considered the urinary and kidney changes to be likely the result of excretion of the large oral doses of triethylene glycol and/or its metabolites, and the blood changes may have been caused by a hemodilution effect of the high loading of triethylene glycol. Overall, this study did not find that high oral doses of triethylene glycol produced toxicologically significant systemic effects. The absence of significant kidney toxicity is a key finding in this study relative to the kidney toxicity produced by ethylene and diethylene glycols.[11] As there were changes at all doses in this triethylene glycol study, no NOAEL is assigned; however, given the low magnitude of the changes and likely contribution to high dose load and excretion rather than target organ toxicity, the NOEL for this study is 50,000 ppm (3,849 mg/kg per day for males and 4,360 mg/kg per day for males).

Two earlier subchronic oral studies were reported for triethylene glycol, but given the limitations of the study designs, these studies are only briefly described herein. Both studies were performed in rats (see Lauter and Vrla, 1940, in STSC[3]). One study was an oral gavage study that administered daily doses of triethylene glycol (purity not specified) to 4 groups of 5 albino rats (sex not specified) for 30 days. The tested dosages were not reported but daily doses of aqueous solutions (0.1 mL/kg as a 5% solution and 3 mL/kg as a 30% solution) and undiluted triethylene glycol (10 or 20 mL/kg) were administered. The dosing period was 30 consecutive days followed by a 15-day postexposure period. There were no signs of toxicity or body weight changes observed in the rats that received the lower aqueous solution doses,

whereas all of the 20-mL/kg rats died within 3 days of the study start. The 10-mL/kg rats had diarrhea, hair loss, and decreased body weight gain during the first exposure week.

These same authors conducted a similarly designed study using drinking water exposure to test both mature and young albino rats (see Lauter and Vrla, 1940, in STSC[3]). In the mature animal study, groups of 5 rats (sex and age not specified) received triethylene glycol (purity not specified) in drinking water daily for 30 days at concentrations of 5% or 10% (volume) followed by a 15-day postexposure period. Severe signs of toxicity and deaths occurred in both groups of animals, with only 2 of the low-dose group surviving the postexposure period. Given the high water concentrations used in this study, the palatability and consumption of water may have been affected and contributed to the effects observed in this study. This study design was applied to groups of five 3-week-old albino rats (sex not specified) that received triethylene glycol concentrations in water of 3% and 5% (volume). This study found no signs of toxicity or deaths in the 3% group, whereas the 5% group had clinical signs of toxicity (not specified) and lower body weights during the first 2 weeks only and 1 death. The authors noted that 5% triethylene glycol produced higher mortality in adult rats than in young rats. The younger rats were reported to have consumed more water than the adult rats and hence likely received higher dosages; however, the lower water intake by the adult rats may have compromised their physiology, hence, interpretation of these results is difficult.

Chronic/Carcinogenic

There were no contemporary chronic studies identified for triethylene glycol. Early rat and monkey chronic inhalation and oral studies with limited study designs have been reported.

The rat and monkey inhalation studies tested supersaturated triethylene glycol vapor concentrations of approximately 4 mg/m^3 (see Robertson et al., 1947, in STSC[3]). It was not stated if this exposure concentration was nominal or analytically measured, and the purity of the test material was also unstated. In the rat study, 24 male and 12 females (strain not specified) were exposed continuously to the triethylene glycol atmosphere for 6 to 13 months. Controls consisted of 4 male and 2 female rats that were maintained in a chamber with air exposure. The animal numbers were noted to be increased to 60 and 14, respectively, for the triethylene glycol–treated and control animals due to breeding during the exposure period. Select rats were sacrificed at 3, 4, 5, and 6 months. There were no treatment-related effects on growth rates of adult and offspring rats or on general health, hematologic, or pathologic findings. The NOAEL for this study, 4 mg/m^3, was the only concentration tested. Two monkey studies were performed. In the first study, 17 Rhesus macaque monkeys (sex not specified) were exposed to the same concentration used for the rats, 4 mg/m^3, continuously from 1 to 10 months, and 8 monkeys were maintained in an air chamber for 5 to 8 months. There was high mortality or moribund sacrifices in both the treated and control monkeys (7 of 17 and 5 of 8, respectively). Blood parameters, clinical chemistry, and urinalysis findings were reported to be similar in the control and treated animals, but decreased body weight, browning of the facial skin, and crusting of the ears were noted in the treated animals. The results of this study suggest that 4 mg/m^3 was the study LOAEL. A second study continuously exposed 8 Rhesus macaque monkeys to approximately 2 to 3 mg/m^3 triethylene vapor from 2 weeks to 10 months with 8 controls exposed to air only. There were no treatment-related clinical effects or histopathologic changes (examined tissues not specified). The NOAEL for this study was 3 mg/m^3.

These authors also performed rat and mouse chronic oral studies for triethylene glycol (see Robertson et al., 1947, in STSC[3]). The rat study tested drinking water exposures of varying numbers of rats (strain and sex not specified, group sizes ranged from 7 to 24 rats) to triethylene glycol (noted as “purified” but purity not specified) water concentrations of 0, 0.14, 0.32, or 2.66 mL/kg per day for 13 months. Interim sacrifices were performed on select animals at 3 and 8 months. There were no treatment-related effects on body weight, blood or urine parameters, or pathology with these exposures. In the monkey study, triethylene glycol was orally administered in eggnog at daily concentrations of 0.25 or 0.5 mL/kg per day to 10 Rhesus macaque monkeys (sex not specified) for up to 12 months. This study included 2 animals in the 0.25 mL/kg per day group and 8 in the 0.5 mL/kg per day group (with sets of 2 animals receiving exposures for 3, 3.5, and 12 months). No separate control group was used, and the

treated animals served as their own controls. This study also found no treatment-related effects on body weight, blood or urine parameters, or pathologic findings in the monkeys.

A chronic oral dietary study was reported in rats (see Fitzhugh and Nelson, 1946, in STSC[3]). This study administered triethylene glycol (purity not specified) to groups of 12 male Osborne-Mendel rats at concentrations of 0, 1%, 2%, or 4% for 2 years. There were no treatment-related effects on mortality, food consumption, body weight gain, or pathologic changes. The histopathologic examination included review of 11 organ/tissues (lung, heart, spleen, pancreas, stomach, small intestine, colon, kidney, adrenal, testis) in all animals and other tissues (not specified) in some animals. Tumor incidences were not reported but increases were apparently not identified.

Overall, the available chronic exposure studies had limited experimental designs (e.g., small numbers of animals, single doses tested in some studies, uneven group sizes, few parameters examined), and were poorly reported. In the oral studies, the dosages tested (mg/kg per day) were not specifically identified by the authors and the lack of specific water and feed consumption data in these studies do not support calculation of study-specific dosages. These dosages can be estimated using average published body weights and food and water consumption rates for these animals but, as these studies have inherent uncertainty and are not used to support the TLV derivation for triethylene glycol, estimated dosages and NOAELs/LOAELs were not determined. These studies, however, are of qualitative value because high chronic exposures to triethylene glycol have not been demonstrated to produce nephrotoxicity, as seen with ethylene and diethylene glycol.[11]

Genotoxic

Triethylene glycol was nongenotoxic in *in vitro* tests.

Two bacterial mutagenicity studies have been reported, with both finding negative results. Triethylene glycol was evaluated in an Ames bacterial mutagenicity assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, in both the presence and absence of metabolic activation (see Bushy Run Research Center, 1986, in Ballantyne and Snellings[2]). Concentrations of 1 to 112.6 mg triethylene glycol per plate were not mutagenic in any of the strains tested. A second study tested triethylene glycol for mutagenic potential in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli WP2 uvrA* in the presence and absence of metabolic activation and concentrations of up to 5,000 µg per plate and found no increases in mutation frequencies.[14]

Mammalian cells have been tested for induction of mutations and chromosomal aberrations. In a forward gene mutation assay in Chinese hamster ovary cells (HGPRT locus), triethylene glycol concentrations in the range of 24 to 50 mg/mL tested with or without metabolic activation produced no treatment-related increases in the incidence of mutations (see Bushy Run Research Center, 1986, in Ballantyne and Snellings[2]). These same concentrations of triethylene glycol were tested for clastogenic potential in Chinese hamster ovary cells with and without metabolic activation, and no increases in the incidence of chromosomal aberrations were observed (see Bushy Run Research Center, 1986, in Ballantyne and Snellings[2]).

No *in vivo* genotoxicity studies were identified for triethylene glycol.

Reproductive and Developmental Toxicity

Reproductive toxicity for triethylene glycol has been examined in mice, and developmental toxicity has been examined in rats and mice, all by oral exposure.

The reproductive toxicity study used the continuous breeding study design and is detailed in 3 publications (see Bossert et al., 1992; Morrissey et al., 1989; and Lamb, 1997, in STSC[3]). Notably this study design differs from the multigenerational reproductive toxicity studies by providing multiple breedings and litters by the same pairs during the first-generation exposures. Groups of male and female CD-1 mice (20 breeding pairs for the treated groups and 40 pairs for the control group) received triethylene glycol (97% purity) in drinking water at concentrations of 0, 0.3%, 1.5%, and 3% (estimated dosages of 0, 590, 3,300, and 6,780 mg/kg per day, respectively) beginning 1 week before mating and continuing for 14 weeks. After 14 weeks, the breeding pairs were separated, and the dams were treated for an additional 21 days while delivering the last litter. The last litters for the control and 6,780-mg/kg per

day group were used as the second generation and received exposures for 21 days. These litters were maintained on the same triethylene glycol concentrations to assess second generation fertility. The parental animals were evaluated for mortality, clinical signs of toxicity, body weights, and water consumption. A comprehensive evaluation of reproductive and litter parameters was accessed in addition to a detailed assessment of male reproductive function (reproductive organ weights and histology, sperm motility, epididymal sperm concentration, abnormal sperm). There were no treatment-related effects on parental toxicity, male reproductive function, or litter parameters, except for a decrease in mean live pup weights in the 3,300- and 6,780-mg/kg per day groups. Although these changes may provide some indication of developmental toxicity, they were <5% and hence not considered to be biologically significant. The NOAEL for parental and reproductive toxicity in this study was 6,780 mg/kg per day.

Rat and mouse developmental toxicity studies used oral gavage exposures. In the rat study, pregnant CD rats (25 per group) were given daily gavage feedings of undiluted triethylene glycol (>99% purity) from gestation days 6 to 15 at dosages of 0, 1,126, 5,630, or 11,260 mg/kg per day (administered as 1, 5, and 10 mL/kg per day) (see Ballantyne and Snellings, 2005, in STSC[3]). The control rats received 10 mL/kg per day of distilled water. Standard maternal and fetal evaluations were made, with additional histologic examination performed on the maternal kidneys. The study found no treatment-related deaths or clinical signs of toxicity, and pregnancy rates were comparable across groups. There were minor (<10%) decreases in body weights in the 11,260-mg/kg per day dams from gestation days 9 to 18 and in the 5,630-mg/kg per day dams on gestation day 18. There was also a slight increase in relative kidney weight in the 11,260-mg/kg per day dams, but no pathologic changes were found, suggesting that this effect was related to renal excretion of triethylene glycol and/or its metabolites. No treatment-related effects were observed on the number of corpora lutea, pre- and postimplantation loss, live fetuses, or sex ratio. The male and female fetuses of the 11,260-mg/kg per day dams were significantly reduced relative to controls. All groups showed no treatment-related increases in the incidence of malformations (visceral or skeletal) by fetuses or by litter, nor were there increases in the incidence of external or visceral variations. There was, however, an increase in the incidence of bilobed thoracic centrum in the 11,260-mg/kg per day pups. The study NOAEL for maternal toxicity was 11,260 mg/kg per day and the NOAEL for developmental toxicity was 5,630 mg/kg per day.

In another similarly designed study, pregnant CD-1 mice (30 per group) were given 0, 563, 5,630, or 11,260 mg/kg per day triethylene glycol (0.5, 5.0, and 10.0 mL/kg per day) by gavage on gestational days 6 to 15 (see Ballantyne and Snellings, 2005, in STSC[3]). This study found no treatment-related deaths. Clinical signs of toxicity were observed in two 11,260-mg/kg per day dams as evidenced by hypoactivity and rapid breathing. There were no treatment effects on pregnancy rates. Maternal body weights were not affected, but there was a non–statistically significant dose-related decrease in gravid uterine weights, which was likely due to decreased fetal weights. The 11,260-mg/kg per day dams exhibited slight increases in relative kidney weights but no histologic evidence of kidney lesions was found. The gestational parameters, number of live fetuses per litter, or sex ratio were not affected by treatment. Triethylene glycol produced a dose-related decrease in fetal body weights per litter in the 5,630 and 11,260 mg/kg per day mice. There were no treatment-related increases in the incidence of visceral or skeletal malformations or in the incidence of total malformations by fetus or by litter, and no increases in the incidence of external or visceral variations were found. However, several individual fetal skeletal variation changes were seen that attained statistical significance. Mouse fetuses exhibited delayed ossification in the cervical region and hind-limb proximal phalanges, as well as reduced caudal segments, in the 11,260-mg/kg per day litters. Delayed ossification observed in the supraoccipital and frontal bones was statistically significant for both effects at 5,630 mg/kg per day. The patterns of both these delayed ossification findings were considered to be consistent with reduced fetal body weights. The NOAELs for this study were 5,630 mg/kg per day for maternal toxicity and 563 mg/kg per day for developmental toxicity.

An earlier screening developmental toxicity study was performed in pregnant CD-1 mice (50 per group) that received oral gavage dosages of undiluted triethylene glycol (99% purity) at a dosage of 11,270 mg/kg per day on gestational days 6 to 13. That study found increases in maternal deaths and

decreases in maternal body weight, but no evidence of developmental toxicity was seen (see Schuler et al., 1984, and Hardin et al., 1987, in STSC[3]).

Toxicokinetic/Toxicodynamic Studies

The disposition of triethylene glycol after oral exposures was examined in rats and rabbits (see Mckennis, 1962, in STSC[3]). Two female New Zealand white rabbits were administered single oral gavage dosages of 200 or 2,000 mg/kg of triethylene glycol, and their urine specimens were collected for 24 hours. Approximately 24% of the triethylene glycol dosage was found to be excreted unchanged and the urine of 1 rabbit contained 35.2% of the administered dose as a hydroxyacid form of triethylene glycol. In the rat study, 4 male albino rats received single oral gavage dosages of 11.5 mg ^{14}C-triethylene glycol. The animals were placed in a metabolic chamber in which urine, feces, and expired air were collected over a period of 5 days. The rats were found to eliminate 91% to 98% of the triethylene glycol over this period, with the major fraction being in urine (84% to 94%), small amounts in feces, and only trace amounts as expired $^{14}CO_2$. In urine, triethylene glycol was present in unchanged and oxidized forms. Chromatographic examination of urine suggested the presence of ethylenedioxydiacetic acid. Only negligible amounts of oxalic acid were found in urine. Another study also failed to detect oxalate stone formation following the chronic oral administration of triethylene glycol to rats (see Fitzhugh and Nelson, 1946, in STSC[3]). In reviews of poisoning treatment, the authors stated that triethylene glycol is believed to be metabolized in mammals by alcohol dehydrogenase to acidic products, causing metabolic acidosis (see Borron et al., 1997, and Vassiliadis, 1999, in the final report[8]).

No studies were identified that examined the disposition of triethylene glycol after dermal or inhalation exposures. Triethylene glycol uptake after inhalation exposure is suggested by the finding of (minimal) systemic effects after subacute inhalation exposure in rats but the available limited dermal toxicity studies did not show systemic effects, and hence uptake cannot be presumed.[6] Once triethylene glycol passes through the respiratory tract or skin, its disposition would be expected to be similar to that demonstrated for oral exposures.

Overall, the available disposition information indicates that triethylene glycol is well absorbed after oral exposure, distributed throughout the body but does not accumulate in tissues, metabolized likely by oxidation, and largely excreted by the kidney.

TLV Chronology

Table 2. TLV Chronology: *Triethylene Glycol*

Date	Action	Determinant	TLV
2024	*Proposed*	TLV-TWA	10 mg/m^3 IFV

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