MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Ethylene Glycol (CAS # 107-21-1)

FROM: Keisha Williams, Air Quality Division

DATE: October 17, 2017

SUBJECT: Screening Level Update for Ethylene Glycol

The initial threshold screening level (ITSL) for ethylene glycol is 4700 µg/m^3 (1-hour averaging time) based on Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) Rule 233[1]. Previously an acute ITSL was established on October 20, 1998, but is now being rescinded based on this updated review.

The following references and databases were searched to identify data for screening level derivation: United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances, the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, MDEQ Library, International Agency for Research on Cancer Monographs, National Library of Medicine, Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Status Report, EPA Toxic Substances Control Act Test Submissions database, EPA Superfund Provisional Peer Reviewed Toxicity Values, EPA Acute Exposure Guideline Levels for Airborne Chemicals, EPA High Production Volume Database, United States Department of Labor Occupational Safety and Health Administration Permissible Exposure Limits, Spacecraft Maximum Allowable Concentrations, Agency for Toxic Substances and Disease Registry's (ATSDR's) Toxicological Profiles, California Office of Environmental Health Hazard Assessment's Reference Exposure Levels, Texas Commission on Environmental Quality Effects Screening Levels, Maximum Workplace Concentrations (Maximale Arbeitsplatz-konzentrationen) for Germany, SciFinder, EPA School Air Toxics Benchmarks, EPA National Air Toxics Assessment Benchmarks, World Health Organization Air Quality Guidelines, and European Chemicals Agency Registered Substances Dossiers.

Background Information

Ethylene glycol (Figure 1) is used in several different applications including as a drying agent; as a solvent; and to make polyethylene terephthalate resins, antifreeze, polyester fibers, and polyester film (ATSDR, 2010). Chemical properties are listed in Table 1 and health benchmark values to protect against adverse effects from inhalation are listed in Table 2.

[1] 336.1233. Air Pollution Control Rules in Michigan Administrative Code promulgated pursuant to Article II Pollution Control, Part 55 (Sections 324.5501-324.5542), Air Pollution Control, of the Natural Resources and Environmental Protection Act, 1994.PA 451, as amended (NREPA).

Figure 1. Chemical structure for ethylene glycol

Table 1. Chemical and physical properties of ethylene glycol

Molecular weight: 62.068 grams/mole
Melting point: 9° F
Boiling point: 388° F
Vapor pressure: 0.06 mmHg at 68° F
Physical state: liquid
Color: colorless
Odor: odorless

Reference: National Center for Biotechnology Information, https://pubchem.ncbi.nlm.nih.gov/compound/174

Table 2. Health benchmark values for inhalation exposure to ethylene glycol

Agency	Benchmark Value
American Conference of Governmental Industrial Hygienists (ACGIH)	Threshold Limit Values (TLVs): 25 ppm for vapor phase, 8-hour time-weighted average 50 ppm for vapor phase, short-term exposure limit (STEL) 10 mg/m^3, STEL for inhalable particulate matter and aerosol only (ACGIH, 2017)
California Office of Environmental Health Hazard Assessment (OEHHA)	Reference Exposure Level (REL): 400 µg/m^3 for chronic inhalation (OEHHA, 2008)
Agency for Toxic Substances and Disease Registry (ATSDR)	Minimal Risk Level (MRL): 2 mg/m^3 for acute exposure (ATSDR, 2010)
National Research Council	Spacecraft Maximum Allowable Concentrations (SMACs): 64 mg/m^3, 1-hour and 24-hour averaging time 13 mg/m^3, 7-day, monthly and bi-annual averaging time (Wong, 1996)
Texas Commission on Environmental Quality (TCEQ)	Final Reference Values (ReVs): 1500 µg/m^3 for short-term exposure 15 µg/m^3 for long-term exposure (TCEQ, 2016)

Ethylene glycol is a known nephrotoxicant, hepatotoxicant, central nervous system toxicant, cardiopulmonary toxicant and developmental toxicant especially via the oral route of exposure (ATSDR, 2010; Corley et al., 2005; Environment Canada, 2010; NTP-CERHR, 2004). The metabolites, glycolic acid and oxalic acid, have been shown to play a major role in nephrotoxicity and developmental toxicity (NTP-CERHR, 2004; Snellings et al., 2013). However, portal of entry effects described by Wills et al. (1974) and Coon et al. (1970) show the respiratory tract to be the most sensitive organ affected by acute or chronic inhalation exposure. Furthermore, the NTP-CERHR report on the weight of the evidence of ethylene glycol-induced developmental toxicity and the physiologically based pharmacokinetic model developed by Corley et al. (2005) state that it is unlikely that developmental toxicity is possible via the

inhalation route of exposure. Because of potential portal of entry effects, it is not appropriate to use oral studies to derive an inhalation screening level for ethylene glycol.

Evaluation of Cancer Risk

There has been an epidemiological study investigating the association of increased kidney cancer with occupational exposures to ethylene glycol (ACGIH, 2017), but there were no significant associations found between exposure and increased cancer. There have also been animal studies conducted to look at tumor production after oral ingestion of ethylene glycol in rats and mice (ACGIH, 2017; NTP, 1993), and there was no evidence of increased cancer with lifetime exposures to up to 100 mg/kg per day. As a result, ethylene glycol is not classifiable as a human carcinogen.

Review of Relevant Studies for Non-Carcinogenic Effects

Controlled human studies provide some of the best information for acute screening level derivation. Three controlled human studies were identified with this review. In the more recent studies by Carstens et al. (2003) and Upadhyay et al. (2008), researchers investigated metabolism and toxicokinetics at concentrations that were expected to be no-observable-adverse-effect-levels (NOAELs). More specifically, in the Carstens et al. (2003) study and the Upadhyay et al. (2008) study, male volunteers (N=2 and 4, respectively) were exposed to approximately 25 to 30 mg/m^3 ethylene glycol for 4 hours. The original publications were not obtained, but based on a summary from TCEQ, no adverse effects were reported at these exposure concentrations (TCEQ, 2016). The 1974 Wills et al. study, however, was designed to reach concentrations that would produce adverse effects. In as much, the Wills et al. study has been used by all the agencies listed in Table 2 in their health benchmark derivations to protect against toxic effects from ethylene glycol inhalation. It is also important to note that the agencies above also use varying derivation methods, including different points of departure (PODs) based on concentrations referenced in the Wills et al. study.

In the Wills et al. study (1974), 19-20 male volunteers were exposed to ethylene glycol, while 14 other volunteers were kept under similar conditions but not exposed to ethylene glycol. The low, high, and weekly mean concentrations were reported for the first four weeks of exposure. For the last two days of exposure, the low, high and mean ethylene glycol concentrations were reported. Physical exams as well as psychological tests were reported to be performed before the exposure, 2 weeks after the exposure began, and at the end of the exposure. Blood samples were collected before the study began, and every 2-4 days during the exposure. Urine samples were collected daily. Wills et al. noted, “Considering each single test or all tests collectively…there was no difference between the control and the exposed groups.”

In the Wills et al. (1974) study, the concentrations of ethylene glycol varied. The authors initially hypothesized that:

> “[W]e felt we could begin to expose a few human volunteers for a short duration of almost continuous exposure to a concentration of aerosolized ethylene glycol of around 30 mg/m^3 without endangering them. If indeed, no ill effects were suffered, we would then increase gradually the level of exposure.”

Ethylene glycol concentrations were incrementally raised to concentrations as high as 308 mg/m^3 while the exposed group was taking a meal break. It was reported that at 140 mg/m^3, the irritation became significant; at 188 mg/m^3, ethylene glycol was irritating but tolerable for 15 minutes; at 244 mg/m^3, ethylene glycol was intolerable for more than 1-2

minutes; and at 308 mg/m^3, ethylene glycol was intolerable for more than 1-2 breaths (Wills et al., 1974).

There are noted limitations to this study. For one, the study was carried out in a prison with volunteer inmates, which brings up ethical questions and considerations. Furthermore, details about the results for the physical examinations were not provided, and it is unclear how similar this population is to the general population.

Derivation of Acute ITSL

The established health benchmarks from Table 2 were considered for ITSL derivation. In contrast to the occupational exposure limits (the TLV and the acute SMAC), the health benchmarks developed by the ATSDR, OEHHA, and TCEQ are designed to protect the general population, including sensitive populations. Since the adverse effect of irritation is considered a concentration-dependent response, not a duration-dependent response, the acute benchmarks were deemed more appropriate than the chronic health benchmark that had been derived by OEHHA. As a result, the ATSDR acute inhalation MRL and the TCEQ ReV were further evaluated for ITSL derivation.

ATSDR considered the exposure within the first 2 weeks, 23 mg/m^3 (average of 29 and 17 mg/m^3), to be the no-observed-adverse-effect-level (NOAEL), and derived the MRL from this POD. However, AQD does not consider the mean of daily exposures to be the best method to determine levels for acute acting sensory irritants. TCEQ used the LOAEL, 140 mg/m^3, as the POD; however, TCEQ also applied a database uncertainty factor that was deemed unnecessary given the robust research database on ethylene glycol. Taken together, it was decided that an acute ITSL would be derived based on the LOAEL measured during the Wills et al. (1974) study, 140 mg/m^3. It is unclear how long the volunteers would have been exposed to this concentration. However, AQD inferred that this concentration was probably not used for an extended period, and a 1-hr duration was considered as a likely time consistent with other time periods Wills et al. (1974) used as excursions for elevated concentration tests (e.g., 244 and 308 mg/m^3). Furthermore, it is unlikely that the duration was as long as 8 hours, the next higher available period used in AQD averaging times for screening levels. Using this point of departure, the following acute ITSL was obtained:

$$\text{Acute } ITSL = \frac{POD}{UF_H x\ UF_L} \times \frac{hours\ exposed}{averaging\ time}$$

Where:

-POD =LOAEL =140 mg/m^3

-UF_H=10 for human variability

-UF_L=3 for LOAEL to NOAEL extrapolation

-The hours exposed/averaging time adjustment to continuous exposure was deemed unnecessary because the irritation effects are expected to be concentration-related not duration-related.

$$\text{Acute } ITSL = \frac{140\frac{mg}{m^3}}{30} x \frac{10^3 \mu g}{mg} = 4666.67\frac{\mu g}{m^3} \approx 4700\frac{\mu g}{m^3}, 1-hour\ averaging\ time$$

Therefore, the acute ITSL is 4700 µg/m^3, 1-hour averaging time.

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MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

October 20, 1998

TO: File for Ethylene Glycol (CAS #107-21-1)

FROM: Michael Depa, Toxics Unit, Air Quality Division

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for ethylene glycol is 1000 $\mu g/m^3$ with a 1-hour averaging time. The principal adverse effect of inhalation exposure to ethylene glycol is respiratory irritation. The ITSL was derived from the ACGIH TLV-ceiling limit of 100 mg/m^3 which was based on a human clinical inhalation study (Wills et al., 1974).

The following references or databases were searched to identify data to determine the ITSL: IRIS, RTECS, ACGIH Threshold Limit Values, NIOSH Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, IARC Monographs, CAS On-line (1967 - March 19, 1994), and NTP Management Status Report. Review of these sources found that EPA has not established an RfC for ethylene glycol. An RfD was established by the EPA at 2 mg/kg/day based on kidney toxicity seen in a chronic rat feeding study. A Ceiling TLV of 100 mg/m^3 was established by ACGIH. NIOSH has not set an REL for ethylene glycol. The molecular weight of ethylene glycol is 62.08g and the vapor pressure at 20°C is 0.06 mmHg.

The Agency for Toxic Substance and Disease Registry (ATSDR) characterized the toxicological and adverse health effects information on ethylene glycol (ATSDR, 1993). Most of the human information summarized in the report is from acute oral exposure. Histopathological findings in humans show renal tubular necrosis and deposition of calcium oxalate crystals in the kidney after acute overdose concentrations (ATSDR, 1993). The ATSDR did not review all the inhalation studies available. These inhalation studies are described below.

Groups of male and female Sprague-Dawley or Long-Evans rats, male and female Princeton-derived guinea pigs, male New Zealand albino rabbits, male squirrel monkeys and purebred beagle dogs were exposed to 0, 10, or 57 mg/m^3 ethylene glycol for 8 hours/day, 5 days/week for a total of 30 exposures (Coon et. al., 1970). Different groups of the same species, strain, and numbers of animals were continuously exposed to 12 mg/m^3 ethylene glycol for 90 days. These results are presented in Table 1. There were no deaths during the repeated exposure to 10 mg/m^3. Mild conjunctivitis was noted in 1 eye of each of 2 rabbits during the fourth and fifth weeks, which persisted until the end of the exposure; each of these rabbits also developed a small lesion over the irritated eye. The authors stated that these signs were probably brought on by the accidental trauma which may have been aggravated by the exposure. The authors stated that

hematologic values of all the animals were within normal limits (data not reported). Histopathlogical examination of the animals in the 10 mg/m³ group revealed mild congestion in the spleens of both dogs; hepatic fatty changes in 2/8 guinea pigs and 1/8 rats. Focal necrosis of the liver was also seen in 1/3 control guinea pigs. There were no deaths during the repeated exposure to 57 mg/m³. All hematologic data and observations during necropsies compared favorably with the controls. Histopathologic examinations revealed nonspecific inflammatory changes in the lungs and occasionally the hearts of all species. The livers of 2 of the 3 monkeys and 1 of the 8 guinea pigs revealed areas of focal necrosis. Serum urea nitrogen concentrations in the experimental guinea pigs were not significantly different from the control values. The researchers stated that the focal necrosis in the monkey livers were not considered to be chemically induced. However, these changes were not reported in the control monkeys. The dose level of 57 mg/m³ was considered a LOAEL based on occasional inflammation of the hearts in all species and areas of focal necrosis in the livers of the monkeys.

Table 1. Mortality of Animals Exposed to Ethylene Glycol from Coon et al., 1970

Concentration	Type of Study	Number Died / Number exposed				
		Rat	Guinea Pig	Rabbit	Dog	Monkey
0 mg/m³	-	4/123	0/73	0/12	0/12	0/8
10 (±1) mg/m³	Repeated 8 hrs/day, 5 days/week, for 6 weeks	0/15	0/15	0/3	0/2	0/2
57 (±14) mg/m³	Repeated 8 hrs/day, 5 days/week, for 6 weeks	0/15	0/15	0/3	0/2	0/2
12 (±2) mg/m³	Continuous - 90 days	1/15	3/15	1/3	0/2	0/2

Continuous exposure to 12 mg/m³ for 90 days caused moderate to severe eye irritation in the rabbits and rats. Erythema, edema, and discharge began in the rabbits after 3 days of exposure. The edema was severe enough to result in virtual closure of the eyes. Two rats developed corneal opacity after 8 days and appeared to be blind for the remainder of the exposure. One rabbit, 3 guinea pigs and 1 rat died during exposure although they had not shown any specific signs of toxicity. All hematologic data were within limits. Observations during necropsy revealed normal organs and tissues. Histopathologic examination showed inflammatory changes in the lungs of all species and to a lesser degree in controls. Occasional foci of inflammatory cells were seen in kidneys from several guinea pigs and 1 rabbit had hamartomatosis in liver bile ducts. These were not interpreted as being specific chemically induced changes. Analysis of several serum enzymes showed no difference from control animals. Based on the occurrence of blindness in the rats (thought not to be reversible), this dose level was considered a Frank Effect Level (FEL) and could not be used directly to develop a screening level.

The Coon et al. (1970) study reported above was found to have small dose groups, several reporting discrepancies and to be deficient in statistical analysis. For example, in a table presented by the authors it was indicated that only 2 monkeys were exposed at 10 mg/m^3; however, in the text they indicated 3 monkeys were exposed. The same kind of discrepancy occurred with the guinea pigs. These discrepancies could not be resolved by reading the experimental methods section. It was deemed that this was a poor quality study; therefore, the conclusions that can be drawn from this study are limited. Still, some conclusions can be inferred. Focal necrosis was observed in the livers of 2 of 3 monkeys dosed at 57 mg/m^3 for 8 hrs/day, 5 days/week for 6 weeks (No mention of control monkey livers was offered by the researchers). However, because of the small dose groups it is difficult to say for sure if this is a chemical specific systemic effect. The effects reported at the 12 mg/m^3, 90-day continuous exposure indicate severe irritation. The 10 mg/m^3 was considered a no observed adverse effect level (NOAEL). A LOAEL of 57 mg/m^3 was identified based on occasional inflammation of the hearts of all animals.

In another report, groups of 6 timed-pregnant CD rats and 6 CD-1 mice were exposed to 0, 150, 1000, or 2500 mg/m^3 ethylene glycol aerosol on gestational days 6 through 15, six hours per day by inhalation (Bushy Run, 1985). The exposure was via whole body inhalation (as opposed to nose only). For mother rats, absolute and relative liver weight was significantly increased at 2500 mg/m^3. Food and water consumption, maternal body weights and weight gain, and maternal organ weight (other than liver) were unaffected by exposure. Reproductive parameters were unaffected by exposure, including pre- and postimplantation loss, live fetuses per litter, sex ratio and fetal body weight per litter. Some evidence of fetal toxicity, expressed as reduced ossification in the humerus, the zygomatic arch, and metatarsals and proximal phalanges of the hindlimb, was observed at 1000 and 2500 mg/m^3. The NOAEL for both the dams and conceptus was 150 mg/m^3.

For mice, all dams survived to scheduled sacrifice. Pregnancy rate was uniform across all groups; one dam at 2500 mg/m^3 was carrying a totally resorbed litter at sacrifice. Maternal toxicity was observed at 1000 and 2500 mg/m^3, expressed as reduced body weight and weight gain during the exposure and postexposure periods, and reduced body weight and gravid uterine weight at sacrifice. Embryo/fetal toxicity was also observed at 1000 and 2500 mg/m^3, expressed as an increase in non-viable implantations per litter, a reduction in viable implantation per litter, and reduced fetal body weights (male, female and total) per litter. The incidence of individual and total external visceral and skeletal malformations was elevated at 1000 and 2500 mg/m^3 as was the incidence of total malformations. Malformations were found in the head (exencephaly), face (cleft palate, foreshortened and abnormal face), and skeleton (vertebral fusions, fused, forked and missing ribs and abnormal facial bones). Fetal variations were also increased at 1000 and 2500 mg/m^3. The no observable effect level (NOAEL) for both the dam and conceptus was 150 mg/m^3. A major confounding factor in this study was the deposition of a detectable quantity of ethylene glycol upon the animals during exposure. The EPA (1997) reviewed this study and stated:

The animals could have received the chemical via the oral route by preening or by dermal absorption, although much less would be taken in via the skin. Analysis of the chemical on the fur of rats and mice after the exposure period at the highest concentration indicated that much of the chemical dose (65-95%) was potentially derived form ingestion after grooming.

In order to address the confounding of oral exposure due to grooming, a nose-only study was performed in 1988 and is described here. Groups of 30 timed-pregnant CD-1 mice were exposed to ethylene glycol aerosol (0, 500, 1000, or 2500 mg/m^3) on gestational days 6 through 15, six hours per day by nose-only procedures (Bushy Run, 1988). Control animals were exposed to 4200 mg/m^3 water vapor. Pregnancy rates were equivalent across all groups. Terminal body weight and gestational weight gain, and liver weights (absolute and relative) were unaffected by treatment. Absolute kidney weight for the dams were increased at 1000 and 2500 mg/m^3 but no treatment related histopathological lesions were observed. There was no difference among groups in the number of corpora lutea/dam or the number of total or viable implants/litter of in sex ratio. Fetal body weights per litter were reduced at 2500 mg/m^3. There was no increase in the incidence of individual, total external or visceral malformations of any group relative to the control. At 2500 mg/m^3 one skeletal malformation, fused ribs, was increased relative to control (there were no skeletal malformations in the control group). The NOAEL for maternal toxicity was 500 mg/m^3 based on absolute kidney weight. The developmental toxicity NOAEL was 1000 mg/m^3 based on reduced fetal body weight.

In a human study, volunteers inhaled ethylene glycol at a mean concentration of 31 mg/m^3 (range = 3 - 67 mg/m^3; standard deviation = 11) for 20-22 hours/day for 4 weeks (Wills et al., 1974). For relatively brief periods ($\leq$ 15 minutes) the concentration in the chamber was raised to very high concentrations. Samples of venous blood were collected on days 0, 1, 3, 5, 8, 12, 18, 22, 26, and 29. The blood samples were analyzed for hematocrit, hemoglobin, total and differential leukocyte counts, and using serum, for glucose urea nitrogen, creatinine, cholesterol (total and esters), sodium, potassium, chlorine, bicarbonate, bilirubin, glutamate-oxalacetate transferase, and alkaline phosphotase. Oxalated plasma was used for estimation of prothrombin time. Morning urine samples were examined daily, particular attention was paid to the possibility of occurrence of oxalate crystals and erythrocytes. Urine was measured for volume, specific gravity, color, clarity, pH, amino acid nitrogen and creatinine. No significant alterations in blood or urine were noted. Doses above 200 mg/m^3 were very irritating and were not tolerated for more than 1 minute. The irritative phenomena became common when the concentration of ethylene glycol in the ambient air was raised to about 140 mg/m^3. Responses to physiological tests, including reaction time, reaction time with discrimination, depth perception, visual motor coordination and mental ability (e.g. subtraction) showed no statistical differences from controls.

$ITSL = NOAEL/(UF_1 \times UF_2 \times UF_3) \times$ (ave. hours exposed per day/24 hour day)

$ITSL = (31\ mg/m^3)/(10 \times 3 \times 10) \times 21$ hours/24 hours

$ITSL = 0.09\ mg/m^3$

ITSL = 90 $\mu g/m^3$ (annual averaging time)

where, UF_1 is 10 to account for sensitive subpopulations
UF_2 is 3 to account for less than subchronic exposure duration in the study
UF_3 is 10 to convert the duration from subchronic to chronic

NTP performed a 2-year feed study in male and female B6C3F1 mice, and concluded that there was no evidence of carcinogenic activity (NTP, 1993). Administration of ethylene glycol resulted in statistically significant increase in the incidence ($p<0.01$) of hepatocellular hyaline degeneration in male mice fed diets containing 12,500 of 25,000 ppm (2,812 and 5,824 mg/kg respectively) and in female mice fed diets containing 50,000 ppm (13,097 mg/kg). Hepatocellular hyaline degeneration was characterized by intercytoplasmic accumulations of granular to globular, nonbirefringent, eosinophilic material with dimensions and tinctorial properties similar to those of erythrocytes. The incidence and severity of nephropathy were not influenced by ethylene glycol administration in either sex. Other treatment-related urinary system lesions occurred only in males. Small numbers of oxalate-like crystals and/or calculi were noted in kidneys, urethras, and/or urinary bladders in some high-dose male mice. An increased incidence of medial hyperplasia of small pulmonary arteries and arterioles occurred in female mice fed diets containing 12,500, 25,000, or 50,000 ppm ethylene glycol (3,015, 6,251, and 13,097 mg/kg respectively). A NOAEL of 6,250 ppm (1,352 mg/kg/day) was identified.

A subchronic reproductive toxicity study performed in the National Toxicology Program laboratory was identified. In this continuous breeding study groups of 20 male and female COBS Crl:CD-1 out bred Swiss albino mice were fed diets containing doses of 0.41, 0.84, and 1.65 g/kg/day of ethylene glycol (Morrissey, et al., 1989). The control groups consisted of 40 male and female mice. The male and female mice were exposed to the chemical for a 7 day premating period, and were then randomly grouped as mating pairs and cohabited and treated continuously for 98 days. Data were collected on all newborns during this period (body weight, proportion of males and females, number of litters per pair, number of live and dead pups) within 12 hours of birth, after which each litter was discarded. No other toxicological endpoints (e.g. organ weights) were examined. At the 1.65 g/kg dose the mean number of litters per pair and mean number of live pups per pair were significantly decreased ($p<0.05$). At this dose level mean live pup weight per litter was significantly decreased ($p<0.05$). At the 0.84 g/kg dose level mean live female pup weight per litter was significantly decreased ($p<0.05$) compared to control. A NOAEL of 0.41 g/kg ethylene glycol was identified.

In an chronic oral oncogenicity study CD-1 mice groups of 80 male and female mice received 0, 0.04, 0.2, or 1.0 g/kg/day ethylene glycol (DePass et al., 1986). A second control group of 80 male and female mice was used for comparison. Twenty mice per sex per group were sacrificed at 80 weeks (~18 months). A similar study in rats was reported in the same journal article. Complete necropsies were performed on all animals except when precluded by autolysis or cannibalism. No clinical chemistry or hematology measurements were performed. Weights of the liver, kidneys, spleen, heart, brain, lung, and testes were recorded. Microscopic examination

was performed on tissues from all major organs. There were no treatment related increases in nonneoplastic lesions. The only tumor type for which there was any evidence of a possible increased incidence was lymphosarcoma in female mice. Statistical analysis revealed no significant difference among groups when the unadjusted or time-adjusted proportions of animals with lymphosarcoma were compared. However, the time adjusted incidence of lymphosarcoma in female mice was significantly increased ($p<0.05$) according to one of three trend tests. Comparisons among groups for differences in tumor proportions indicated the observed results could easily have occurred by chance alone ($p>0.05$). The authors concluded that there was no evidence of an oncogenic effect of ethylene glycol in rodents.

Table 2. Summary of Possible Screening Levels for Ethylene Glycol

Reference	Route, Species, Effects, NOAEL/LOAEL	Possible ITSL (Averaging Time)
EPA RfD (IRIS, 1995)	Oral, Rat, Kidney, NOAEL = 200 mg/kg **[RfD = 2 mg/kg/day]**	7000 µg/m³ (24 hour)
ACGIH C-TLV (ACGIH, 1993)	Inhalation, Human, Irritation of the Throat and Upper Respiratory Tract, LOAEL = 31 mg/m³ **[TLV-Ceiling = 100 mg/m³]**	1000µg/m³ (1 hour)
Coon et al., 1970	Inhalation, Monkey, Occasional Inflammation of the Heart, Focal Necrosis of the Liver, NOAEL = 10 mg/m³	2 µg/m³ (annual)
Coon et al., 1970	Inhalation, Rat, Blindness, All Animals Tested had Inflammation of the Lungs, FEL = 12 mg/m³	No ITSL could be determined.
Bushy Run, 1988	Inhalation, Mice, Fetal Toxicity, NOAEL = 1000 mg/m³	Developmental ITSL = 2500 µg/m³ (24 hour)
Bushy Run, 1988	Inhalation, Mice, Maternal Toxicity, NOAEL = 500 mg/m³	36 µg/m³ (annual)
Wills et al., 1974	Inhalation, Human, Irritation of the Throat and Upper Respiratory Tract, NOAEL = 31 mg/m³	90 µg/m³ (annual)

The ACGIH ceiling TLV (100 mg/m³) was based on the Wills et al. (1974) study. In this study, irritation was noted at 140 mg/m³. The authors mentioned that a slight headache and low backache were noted occasionally, but it is not known if these occurred during the high exposures or during the lower mean exposure of 31 mg/m³. The occupational exposure limit for ethylene glycol has been in existence since 1971 and reports of ethylene glycol health effects below the TLV have not been noted in the literature. This provides some support for using the TLV for derivation of the ITSL. Furthermore, consider that a TLV based ITSL of 1000 µg/m³ (1 hour averaging time; or 13 µg/m³ annualized) would be roughly 2 orders of magnitude lower than the ITSL based on developmental effects (developmental ITSL = 2500 µg/m³ with a 24 hour averaging time, or 250 µg/m³ annualized). This would provide a certain degree of assurance that

the TLV based ITSL protects against adverse health effects such as irritation (seen at 140 mg/m^3) and decreased fetal body weight (seen at 2500 mg/m^3). The annualized ITSL of 13 µg/m^3 based on the TLV would also be below the ITSL based on the maternal toxicity seen in nose only exposure study performed by Bushy Run (1988). The RfD based ITSL of 7000 µg/m^3 (24 hour averaging time) would be inappropriate given that a surrogate ITSL for developmental effects is 2500 µg/m^3 and that the principal effects were respiratory irritation which cannot be assessed in oral dose studies. Furthermore, the EPA (1997) stated that:

> In general, the oral RfD should not be used to evaluate inhalation exposures to ethylene glycol because it appears that the metabolism via the two routes is different. Specifically, this is demonstrated by the lack of toxic metabolites of ethylene glycol found in the urine and plasma of animals dosed via inhalation. Additionally, it is believed that the proximate cause for the toxicity seen from ethylene glycol in not attributed to the chemical itself but rather to its metabolites. Therefore, use of the RfD would tend to be overly protective for inhalation effects from exposure to ethylene glycol.

Rule 232 hierarchy describes that the ITSL is to be based on an RfC when available (Rule 232(1)(a)). There was no RfC available for ethylene glycol. The RfD, next in line for the derivation of the ITSL, was determined to be inappropriate and inadequate to protect public health based on developmental and respiratory irritation effects mentioned above. There is no information available that indicates a TLV derived ITSL would be inappropriate. Therefore, the ITSL is based on the TLV according to Rule 232(1)(c). The ITSL for ethylene glycol is 1000 µg/m^3 based on a 1 hour averaging time (see page 1 and 2 for derivation).

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