Development Support Document
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Ethylene Glycol

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Prepared by
Jessica L. Myers, Ph.D.
Heather Reddick, DrPH
Toxicology Division

Office of the Executive Director

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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Acronyms and Abbreviations

Acronyms and Abbreviations	Definitions
ADH	alcohol dehydrogenase
AMCV	Air Monitoring Comparison Value
°C	degrees Celsius
CNS	central nervous system
d	day(s)
DSD	development support document
EG	ethylene glycol
ESL	Effects Screening Level
$^{acute}ESL$	acute health-based Effects Screening Level for chemicals meeting minimum database requirements
$^{acute}ESL_{generic}$	acute health-based Effects Screening Level for chemicals not meeting minimum database requirements
$^{acute}ESL_{odor}$	acute odor-based Effects Screening Level
$^{acute}ESL_{veg}$	acute vegetation-based Effects Screening Level
$^{chronic}ESL_{nonthreshold(c)}$	chronic health-based Effects Screening Level for nonthreshold dose response cancer effect
$^{chronic}ESL_{nonthreshold(nc)}$	chronic health-based Effects Screening Level for nonthreshold dose response noncancer effects
$^{chronic}ESL_{threshold(c)}$	chronic health-based Effects Screening Level for threshold dose response cancer effects
$^{chronic}ESL_{threshold(nc)}$	chronic health-based Effects Screening Level for threshold dose response noncancer effects
$^{chronic}ESL_{veg}$	chronic vegetation-based Effects Screening Level
GA	glycolic acid/glycolate
GAl	glycoaldehyde
GD	gestational day
h	hour(s)

Acronyms and Abbreviations	Definitions
H	humans
$H_{b/g}$	blood:gas partition coefficient
$(H_{b/g})_A$	blood:gas partition coefficient, animal
$(H_{b/g})_H$	blood:gas partition coefficient, human
Hg	mercury
HEC	human equivalent concentration
HQ	hazard quotient
kg	kilogram(s)
LOAEL	lowest-observed-adverse-effect-level
MW	molecular weight
µg	microgram(s)
$\mu g/m^3$	micrograms per cubic meter
mg	milligram(s)
mg/m^3	milligrams per cubic meter
min	minute(s)
MOA	mode of action
NOAEL	no-observed-adverse-effect-level
POD	point of departure
POD_{ADJ}	point of departure adjusted for exposure duration
POD_{HEC}	point of departure adjusted for human equivalent concentration
ppb	parts per billion
ppm	parts per million
PG	propylene glycol
ReV	reference value
RGDR	regional gas dose ratio
SD	Sprague-Dawley

Acronyms and Abbreviations	Definitions
TCEQ	Texas Commission on Environmental Quality
TD	Toxicology Division
UF	uncertainty factor
UF_H	interindividual or intraspecies human uncertainty factor
UF_A	animal to human uncertainty factor
UF_{Sub}	subchronic to chronic exposure uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_D	incomplete database uncertainty factor
USEPA	United States Environmental Protection Agency
wk	week(s)
yr	year(s)

Chapter 1 Summary Tables

Table 1 for air monitoring and Table 2 for air permitting provide a summary of health- and welfare-based values resulting from an acute and chronic evaluation of ethylene glycol (EG). Please refer to Section 1.6.2 of the TCEQ Toxicity Factor Guidelines (2015) for an explanation of values used for review of ambient air monitoring data and air permitting. Table 3 provides summary information on EG's physical/chemical properties.

Table 1. Air Monitoring Comparison Values (AMCVs) for Ambient Air [a]

Short-Term Values	**Concentration**	**Notes**
Acute ReV	1500 µg/m^3 (590 ppb) **Short-Term Health**	**Critical Effect(s):** Respiratory irritation in human volunteers
$^{acute}ESL_{odor}$	---	Odorless
$^{acute}ESL_{veg}$	---	No data on vegetation effects found
Long-Term Values	**Concentration**	**Notes**
Chronic ReV	15 µg/m^3 (5.9 ppb) **Long-Term Health**	**Critical Effect(s):** Ocular irritation and nonspecific inflammatory changes in the lungs of laboratory animals
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	--- ---	Data are inadequate for an assessment of human carcinogenic potential via the inhalation route
$^{chronic}ESL_{veg}$	---	No data on vegetation effects found

[a] EG is not monitored for by the TCEQ's ambient air monitoring program.

Abbreviations for Tables 1 and 2: **ppb**, parts per billion; **µg/m^3**, micrograms per cubic meter; h, hour; **ESL**, Effects Screening Level; **AMCV**, Air Monitoring Comparison Value; **HQ**, hazard quotient; **ReV**, Reference Value; **^{acute}ESL**, acute health-based ESL; **$^{acute}ESL_{odor}$**, acute odor-based ESL; **$^{acute}ESL_{veg}$**, acute vegetation-based ESL; **$^{chronic}ESL_{nonthreshold(c)}$**, chronic health-based ESL for nonthreshold dose-response cancer effect; **$^{chronic}ESL_{threshold(nc)}$**, chronic health-based ESL for threshold dose-response noncancer effects; and **$^{chronic}ESL_{veg}$**, chronic vegetation-based ESL

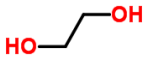
Table 2. Air Permitting Effects Screening Levels (ESLs)

Short-Term Values	Concentration	Notes
$^{acute}ESL$ [1 h] (HQ = 0.3)	450 µg/m^3 (180 ppb)[a] **Short-Term ESL for Air Permit Reviews**	**Critical Effect:** Respiratory irritation in human volunteers
$^{acute}ESL_{odor}$	---	Odorless
$^{acute}ESL_{veg}$	---	No data on vegetation effects found
Long-Term Values	**Concentration**	**Notes**
$^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3)	4.5 µg/m^3 (1.8 ppb)[b] **Long-Term ESL for Air Permit Reviews**	**Critical Effect:** Ocular irritation and nonspecific inflammatory changes in the lungs of laboratory animals
$^{chronic}ESL_{nonthreshold(c)}$ $^{chronic}ESL_{threshold(c)}$	--- ---	Data are inadequate for an assessment of human carcinogenic potential via the inhalation route
$^{chronic}ESL_{veg}$	---	No data on vegetation effects found

[a] Based on the acute ReV of 1500 µg/m^3 (590 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

[b] Based on the chronic ReV of 15 µg/m^3 (5.9 ppb) multiplied by 0.3 to account for cumulative and aggregate risk during the air permit review.

Table 3. Chemical and Physical Data

Parameter	Value	Reference
Molecular Formula	$C_2H_6O_2$	ATSDR 2010
Chemical Structure		ChemSpider 2015
Molecular Weight	62.07	ATSDR 2010
Physical State at 25°C	liquid	ATSDR 2010
Color	Clear, colorless	ATSDR 2010
Odor	Odorless	ATSDR 2010
CAS Registry Number	107-21-1	ATSDR 2010
Synonyms	1,2-Dihydroxyethane; 1,2-ethandiol; 1,2-ethane-diol; 2-hydroxyethanol; ethylene alcohol; ethylene dihydrate; glycol; monoethylene glycol; MEG; EG	ATSDR 2010
Solubility in water	Miscible with water	ATSDR 2010
Log K_{ow}	-1.36	ATSDR 2010
Vapor Pressure	0.089 mm Hg at 25°C	ATSDR 2010
Relative Vapor Density (air = 1)	2.14	ATSDR 2010
Melting Point	-12.69°C	ATSDR 2010
Boiling Point	197.3°C	ATSDR 2010
Conversion Factors	1 μg/m^3 = 0.39 ppb 1 ppb = 2.58 μg/m^3 at 25°C	ATSDR 2010

Chapter 2 Major Sources and Uses

EG is a colorless, odorless liquid with a sweet flavor. EG is used primarily in the production of polyethylene terephthalate for polyester fibers, containers, and films (Carney 1994), and is the primary ingredient in most automobile antifreeze reagents and airport de-icing solutions (ATSDR 2010). Other uses for EG include: electrolyte for electrolytic condensers, solvent for dye, component of skin lotions, and solvent for certain pharmaceutical preparations and food extracts (Troisi 1950). Environmental exposure is limited to industrial emissions and areas that use and dispose of antifreeze and de-icing reagents. ATSDR (2010) reports that measured EG vapor concentrations at airports during de-icing procedures ranged from 0.05 to 22 mg/m^3. The

most common route of exposure in humans is through dermal contact with EG-containing antifreeze (ATSDR 2010). Other routes of exposure include inhalation to EG vapors and dermal contact with contaminated soil and water, typically around or near industrial sites.

Chapter 3 Acute Evaluation

The Development Support Document (DSD) is a summary of the key and supporting studies and procedures used by the TCEQ to derive inhalation toxicity values. This section is based on a review of current literature as well as background readings in ATSDR (2010), which describes the acute toxicity of EG in detail. A systematic review was conducted and is detailed in Appendix 1.

3.1 Health-Based Acute ReV and ^{acute}ESL

The most commonly studied route of EG exposure is ingestion, and the majority of toxicity data stems from studies on accidental or intentional ingestion of automobile antifreeze. Oral exposure to high levels of EG can lead to central nervous system (CNS) depression, metabolic acidosis and associated cardiopulmonary symptoms, and ultimately nephrotoxicity and renal failure, possibly leading to death (ATSDR 2010). Exposure via inhalation or dermal uptake, however, is far more common and appears to be much less significant toxicologically than exposure through ingestion. Fewer studies have examined the effects of inhalation to EG, although data suggest that absorption through the respiratory tract does occur, albeit less effectively than through oral exposure (Carney 1994).

3.1.1 Physical/Chemical Properties

EG is a colorless, odorless liquid that is completely miscible with water. EG has a very low log K_{ow}, suggesting that it has a low chance of bioaccumulating. EG also has a low vapor pressure, so it tends to stay in liquid form, although it can form both vapors and aerosols once in the air. The other primary physical and chemical properties of EG are summarized in Table 3.

3.1.2 Key and Supporting Studies

Much of the available literature focuses on the acute high dose effects of EG following accidental or intentional ingestion. Studies have shown differences in the severity of effects depending on the route of exposure, with oral exposure being more severe than both inhalation and dermal (Carney 1994). This review will focus on the available inhalation data, as the purpose of the DSD is to derive inhalation (as opposed to oral) toxicity factors.

3.1.2.1 Human Studies

3.1.2.1.1 Key Human Study – Wills et al. (1974)

Wills et al. (1974) exposed 24 volunteer male prisoners to aerosolized EG with droplet diameters estimated to be 1-5 µm. An unused room in the prison was turned into an exposure chamber by

sealing the windows and placing aerosol devices in the air conditioners. Prisoners remained in the room throughout the duration of the experiment, approximately 20 hours (h)/day (d), but were allowed out for meals and bathroom breaks. Moderate smoking was allowed in the chamber. An additional 14 volunteers were used as a control group and housed in a separate room in the prison. The main 30 d study involving 20 volunteers was preceded by an initial 7 d study with 4 volunteers, and this group of 4 volunteers was later used as controls. Blood and urine samples were collected from all of the volunteers and tested for EG and metabolite concentrations, and various hematological and urological parameters. Air concentrations of EG, measured five times each day, varied throughout the exposure and were reported as high, low, and mean weekly concentrations (Table 4). Biological measurements were taken throughout the study and during a two-week follow up period. No significant alterations were found in any of the hematologic, clinically chemical, or clinically pathologic parameters that were examined. Several psychological tests were also performed to test the effects of EG on the CNS. However, no significant differences between exposed and control groups were observed, and none of the volunteers in either group reported any eye or respiratory irritation. The authors concluded that absorption of EG aerosols via inhalation is poor.

Table 4. EG chamber concentrations measured throughout the Wills et al. (1974) study

		EG Concentration mg/m^3		
Days	**# Volunteers**	**Low**	**High**	**Mean**
1 – 7 [a]	4	3.6	75.0	37
8 - 14	20	18.8	44.8	29
15 – 21	20	0.8	41.6	17
22 – 28	20	3.5	49.2	23
29 – 35	20	20.6	66.8	49
36 - 37	20	14.4	39.0	31

[a] Days 1-7 represent the initial 7-d study, the main study began on day 8

During the 30 d study, the authors assessed for respiratory irritation by increasing the EG concentrations in the chamber while the volunteers were at a meal. At a concentration of 188 mg/m^3, volunteers could only tolerate being in the chamber for 15 minutes (min). A second test involved a chamber concentration of 244 mg/m^3, which could not be tolerated for more than 1-2 min. Finally, an air concentration of 308 mg/m^3 was tested, and the authors stated that one or two breaths at this level sent the volunteers running from the room. In the primary chamber study (Table 4), concentrations reached as high as 75 mg/m^3 without complaints of irritation. The authors concluded that irritation to EG occurs when air concentrations reach 140 mg/m^3, although there was no mention of testing at this specific concentration.

For respiratory irritation, the lowest observed adverse effect level (LOAEL) was 188 mg/m^3 EG, and volunteers could not tolerate this level for more than 15 min. The authors noted that respiratory irritation became common at 140 mg/m^3 (no duration specified), and this concentration was used by ATSDR (2010) to develop the inhalation MRL for acute durations. No complaints of irritation were noted in chamber concentrations as high as 75 mg/m^3, although the time spent at this concentration was not detailed. While respiratory irritation may be more dependent on concentration rather than exposure duration (TCEQ 2015), the lack of exposure duration information at 75 mg/m^3 makes this high concentration less than suitable for use as a NOAEL. Similarly, no complaints of irritation occurred at the mean concentration of 37 mg/m^3 during the initial 7 d study, although the exposure concentration varied, only 4 volunteers were exposed, and a 7 d study is of limited utility for derivation of a 1-h ReV (TCEQ 2015). Therefore, consistent with ATSDR (2010), the LOAEL of 140 mg/m^3 for common complaints of respiratory irritation will be used as the POD for the development of the acute 1-h ReV.

3.1.2.1.2 Supporting Human Studies

Several other studies have looked at the short-term effects of EG inhalation in humans. However, they tend to show negative results or have confounding factors such as multiple chemical exposure or unknown exposure concentrations. These studies are informative, though, as supporting studies in the derivation of the 1-h acute ReV and ESL.

3.1.2.1.2.1 Carstens et al. (2003)

Two male volunteers were exposed to 1.34 and 1.43 mmol (86.07 and 92.16 mg) of vaporous 13C-labeled EG over a 4-h period. Based on a standard breathing rate of 20 m^3/d, these doses are equivalent to breathing air concentrations of approximately 25 to 28 mg/m^3. The main purpose of this study was to determine the correlation between EG concentrations in air and the concentrations of EG and its metabolites in urine. Although no specific health effects were evaluated, the authors stated that the volunteers did not report any effects related to the exposure. This supports the reported lack of complaints at 75 mg/m^3 in Wills et al. (1974).

3.1.2.1.2.2 Upadhyay et al. (2008)

Four male volunteers were exposed to vaporous 13C-labeled EG between 1.34 and 1.61 mmol (83 and 100 mg, respectively) over a 4-h period. Based on a standard breathing rate of 20 m^3/d, these doses are equivalent to breathing air concentrations of approximately 25 to 30 mg/m^3. In a separate experiment, three subjects were also exposed dermally to EG for up to 6 h. This was an extension of the Carstens et al. (2003) study, where the authors' focus was to determine the correlation between EG concentrations in air and the concentrations of EG and its metabolites in blood and urine. Although no specific health effects were assessed, the authors stated that the volunteers did not report any effects related to the exposure. This supports the reported lack of complaints at 75 mg/m^3 in Wills et al. (1974).

3.1.2.2 Animal Studies

Similar to the available human studies, animal studies tend to focus on the effects of high dose, oral exposures to EG. However, several inhalation studies are available.

3.1.2.2.1 Coon et al. (1970)

Groups of male and female Sprague-Dawley (SD) and Long-Evans rats (15 animals/group), male and female Princeton-derived guinea pigs (15 animals/group), male New Zealand albino rabbits (3 animals/group), male squirrel monkeys (3 animals/group), and male beagle dogs (2 animals/group) were exposed to measured vaporous EG concentrations of 10 ± 1 and 57 ± 14 mg/m^3 for 8 h/d, 5 d/week (wk) for 6 wk, or to 12 ± 2 mg/m^3 continuously for 90 d. The total number of control animals used in the study was 123 rats (number of each strain not specified), 73 guinea pigs, 12 rabbits, 12 dogs, and 8 monkeys, although multiple chemicals were tested and it was not specified how many controls were used for each study.

Repeated 6-wk exposure – no deaths were noted in either the 10 or 57 mg/m^3 exposure groups. At 10 mg/m^3, mild conjunctivitis along with a small lesion was observed in 2/3 rabbits during the 4^{th} and 5^{th} weeks, although the authors attributed it to accidental trauma. Hematologic analysis revealed no exposure-related changes, while a histopathological examination revealed mild congestion in the spleens of 2/2 dogs, hepatic fatty changes in 2/8 guinea pigs and 1/8 rats, and focal necrosis in the liver of 1/8 guinea pigs and 1/8 rats. Focal necrosis of the liver was also observed in 1/3 control guinea pigs. At 57 mg/m^3, hematological analyses were normal, and histopathology revealed nonspecific inflammatory changes in the heart and lungs of all the species. Focal necrosis of the liver was observed in 2/3 monkeys and 1/8 guinea pigs, although the authors determined it was not exposure related. For the repeated exposure study, the LOAEL for mild congestion in the spleens of dogs and fatty changes in the liver of guinea pigs and rats was 10 mg/m^3 following 6 wks of exposure. However, a 6-wk LOAEL is of limited utility for derivation of a 1-h ReV (TCEQ 2015).

Continuous 90 d exposure – 1/15 rats, 3/15 guinea pigs, and 1/3 rabbits died at 12 mg/m^3. Moderate to severe eye irritation was observed in the rabbits beginning 3 d after continuous exposure, suggesting that these effects were both concentration- and duration-dependent. Erythema, edema, and eye discharge began in the rabbits after 3 d of exposure, with the edema being severe enough to cause closure of the eyes. Rats (2/15) developed corneal opacity after 8 d of exposure and appeared blind for the remainder of the study. Hematological analyses were normal, and histopathology revealed nonspecific inflammatory changes in the lungs of all the species, and mildly in some controls. For the continuous exposure study, the LOAEL for eye irritation in rabbits was continuous 3 d exposure at 12 mg/m^3. However, a 72-h LOAEL is of limited utility for derivation of a 1-h ReV (TCEQ 2015).

3.1.2.2.1 Marshall and Cheng (1983)

Male and female 13-17 week old Fischer-344 rats (15/sex/exposure) were exposed through nose-only inhalation to either 32 ± 9 mg/m^3 vaporous EG for 30 min or 184 ± 64 mg/m^3 aerosolized EG for 17 min (analytical concentrations). For the EG aerosol, 31 ± 4 mg/m^3 was found in vapor form, and particles had a mass mean aerodynamic diameter (MMAD) of 2.3 µm and a geometric standard deviation (GSD) of 1.8. Deposition and absorption of EG was measured using radioactive gallium. No differences were observed between male and female rats. The highest concentration of EG deposition was found in the nostrils of the rats. The authors noted that deposition appeared to be the same between the vapor and aerosol EG, although some assumptions were made on the variations of breathing patterns of the rats. Urinary excretion was slightly higher following exposure to vaporous EG compared to the aerosol, although the authors state that the difference was insignificant compared to the amount of EG excreted following a bolus intravenous injection. No health effects were directly measured or specifically reported in the study.

3.1.2.3 Reproductive and Developmental Studies

EG has been reported to be a developmental toxicant in animal studies following administration of high oral doses. Species differences in metabolism and/or distribution following oral exposure have been observed in developmental studies. Carney et al. (2008) found a ten-fold difference between rats and rabbits in the embryonic exposure to the toxic metabolite glycolic acid (GA) following equivalent doses. The authors attributed this difference to differences in the rate of metabolism of EG and differences in disposition of GA to the embryo. Carney et al. (2008) suggest that humans are closer in EG toxicokinetics to rabbits, which are less sensitive than mice and rats.

A thorough review of the developmental toxicity of EG by various routes of exposure was published by Carney (1994). Carney states that developmental toxicity resulting from EG exposure requires blood concentration of 7-8 mM, and single oral gavage dose of 1000 mg/kg in rats can result in peak plasma concentrations of 28 mM. However, given that humans exposed continuously for 27 days to EG aerosol concentrations ranging from 17 – 49 mg/m^3 had little to no detectable EG in their blood (Wills et al. 1974), and only about 60% of inhaled EG is absorbed, the plasma concentrations needed to result in developmental toxicity are unlikely to result from inhalation exposure.

No studies were available regarding the reproductive and/or developmental effects of EG in humans following inhalation exposure. Two animal inhalation studies were conducted by the same group in order to determine any differences between whole-body and nose-only inhalation exposure routes. The authors concluded that there was a significant oral exposure in the whole-body inhalation chamber experiment due to grooming behaviors of the animals, making the nose-only study results much more relevant.

3.1.2.3.1 Tyl et al. (1995a)

Timed-pregnant female CD rats and CD-1 mice were exposed to whole-body EG aerosol concentrations of 0, 150, 1000, and 2500 mg/m^3 (analytical concentrations of 0, 119 ± 13, 888 ± 149, and 2090 ± 244 mg/m^3, respectively) for 6 h/d on gestational days (GD) 6-15 (25 animals/species/exposure). Animals were sacrificed on GD 21 (rats) and GD 18 (mice) and both maternal toxicity and fetal toxicity were examined. The maternal toxicity tests included food and water consumption, clinical observations, body and organ weights, and implantation sites. Fetal toxicity tests included body weights, number and sex of pups, and examination of external, visceral, and skeletal malformations. In the rat study, maternal relative and absolute liver weights were increased at 2500 mg/m^3, but no other signs of toxicity were observed. During the fetal examination, indications of treatment-related reductions in skeletal ossification were observed at 1000 and 2500 mg/m^3, but no statistically significant changes were observed. In the mouse study, maternal body weight and gravid uterine weight were reduced at 1000 and 2500 mg/m^3. There was a significant increase in late resorptions, an increase in nonviable implants/litter, and a decrease in viable implants/litter, and a reduction in fetal body weight at 1000 and 2500 mg/m^3. A significant increase in the incidence of several external, visceral, and skeletal malformations was also observed at 1000 and 2500 mg/m^3. The authors noted that the no observed adverse effect level (NOAEL) for maternal toxicity was 1000 mg/m^3 in rats and 150 mg/m^3 in mice, and the NOAEL for fetal toxicity was 150 mg/m^3 in rats and below 150 mg/m^3 in mice, making mice the more sensitive species. In addition to health effects, the amount of EG deposited on the animal's fur was measured in order to determine the proportion of the exposure that resulted from ingestion following grooming behaviors. The study determined that at 10% retention of the inhaled EG aerosol, ingestion contributed to 94-95% of the total dose for both species, while at 90% retention of the inhaled EG aerosol, ingestion contributed to 64-65% of the total dose. Significant oral exposure precludes this study as particularly informative for the inhalation route of interest.

3.1.2.3.2 Tyl et al. (1995b)

Timed-pregnant female CD-1 mice were exposed to nose-only EG aerosol concentrations of 0, 500, 1000, and 2500 mg/m^3 [analytical concentrations of 0, 360, 779, and 2505 mg/m^3 (exhaust side) and 250, 570, and 969 mg/m^3 (intake side), respectively] for 6 h/d on GD 6-15 (30 animals/exposure). A second group of animals was exposed by whole-body inhalation to 0 or 2100 mg/m^3 EG aerosol as a positive control. Animals were sacrificed on GD 18 and both maternal toxicity and fetal toxicity were examined. The maternal toxicity tests included food and water consumption, clinical observations, body and organ weights, and implantation sites. Fetal toxicity tests included body weights, number and sex of pups, and examination of external, visceral, and skeletal malformations. Maternal body weights were decreased in all of the nose-only inhalation groups, but were not affected by the exposure concentration (i.e., there was no dose-response). Maternal absolute kidney weights were increased at 1000 and 2500 mg/m^3, while relative kidney weights were increased only at 2500 mg/m^3. The incidences of 16 skeletal variations were increased in the 2500 mg/m^3 nose-only exposure group, including reduced ossification in cervical, thoracic, and lumbar centra, in sternebrae, extra bilateral 14th rib, and extra ossification in the sagittal suture of the skull. The authors concluded that the NOAEL for

maternal toxicity was 500 mg/m^3 and the NOAEL for fetal toxicity was 1000 mg/m^3, which is reversed from what was seen in the whole-exposure study, suggesting that the ingestion route for whole-body animal exposure plays a larger role in toxicity. The authors noted that the restraints used for the nose-only exposure could result in skeletal malformations in the absence of chemical exposure, making it a possible confounding factor. Relevant (i.e., nose-only) inhalation results from this study support respiratory irritation as a more sensitive effect than developmental effects.

3.1.2.4 Summary of the Available Studies Examined in the Acute Evaluation

The available acute EG inhalation studies are summarized in Table 5.

Coon et al. (1970) observed effects in several species following inhalation exposure to EG. For the continuous exposure study, the LOAEL for eye irritation in rabbits was continuous 3 d exposure at 12 mg/m^3. However, a 72-h LOAEL is of limited utility for derivation of a 1-hour ReV (TCEQ 2015).

Wills et al. (1974) observed that at a concentration of 188 mg/m^3, human volunteers could only tolerate being in the exposure chamber for 15 min. The authors stated that this irritation became common at 140 mg/m^3, although no duration was provided. No health effects were reported during longer exposure durations to concentrations of up to 75 mg/m^3. Varying chamber concentrations, however, make it difficult to determine how long the volunteers were exposed to the maximum reported concentrations. Although respiratory irritation is not considered duration dependent, measured chamber concentrations could reflect instantaneous events, with volunteers possibly being exposed to these high concentrations (75 mg/m^3) for only a few seconds. This makes these high concentrations less than suitable for use as a NOAEL.

Although the Coon et al. (1970) study had a lower LOAEL, the Wills et al. (1974) study used human subjects and exposure durations more applicable to the derivation of a 1-h acute ReV. Therefore, the Wills et al. (1974) study and the LOAEL of 140 mg/m^3 for respiratory irritation will be used as the point of departure (POD).

Table 5. Acute Inhalation Studies

Reference	Species	Exposure Concentration	Exposure Duration	NOAEL	LOAEL	Notes
Carstens et al. (2003)	Humans	25, 28 mg/m^3 (vapor)	4 h	28 mg/m^3	--	Health effects not measured or reported
Upadhyay et al. 2008)	Humans	25, 30 mg/m^3 (vapor)	4 h	30 mg/m^3	--	Health effects not measured or reported
Wills et al. (1974)	Humans	0.8-75 mg/m^3, 188, 244, 308 mg/m^3 (aerosol)	Varied	34 mg/m^3 (mean 7 d), 75 mg/m^3 (high)	140 mg/m^3 (duration not reported)	Respiratory irritation after 15 min at 188 mg/m^3, no changes in urinary markers
Coon et al. (1970)	Rats, guinea pigs, rabbits, monkeys, dogs	10 and 57 mg/m^3 repeatedly or 12 mg/m^3 continuously (vapor)	8 h/d, 5 d/wk for 6 wk (repeated) or 90 d (continuous)	--	12 mg/m^3 (3 d of continuous exposure)	Moderate to severe eye irritation in rabbits and rats
Marshall and Cheng (1983)	Rat	32 mg/m^3 (vapor), 184 (aerosol) mg/m^3	30 min (vapor), 17 min (aerosol)	32 mg/m^3 (vapor), 184 (aerosol) mg/m^3	--	Health effects not measured or reported
Tyl et al. (1995a)	Rats and mice	0, 150, 1000, and 2500 mg/m^3 (aerosol, whole body)	6 h/d on GD 6-15	150 mg/m^3 (mice, maternal) 150 mg/m^3 (fetal)	2500 mg/m^3 (maternal) 1000 mg/m^3 (fetal)	Increased resorptions, decreased fetal body weight, possible oral exposure
Tyl et al. (1995b)	Mice	0, 500, 1000, and 2500 mg/m^3 (aerosol, nose-only)	6 h/d on GD 6-15	500 mg/m^3 (maternal) 1000 mg/m^3 (fetal)	1000 mg/m^3 (maternal) 2500 mg/m^3 (fetal)	Increased maternal kidney weights, fetal skeletal variations

3.1.3 Mode-of-Action (MOA) Analysis and Dose Metric

The MOA responsible for the respiratory irritation that occurs following acute high dose inhalation exposure is unknown.

The majority of the metabolism and MOA data have come from studies examining single, high dose oral exposures to EG. Although research has shown that inhalation exposures do not follow the same toxicokinetics or reach the same high internal doses as oral exposures, the breakdown of EG is thought to proceed through a similar metabolic process as observed following oral exposure and in various species. A detailed description of the metabolism and MOA of EG can be found in the review by Carney et al. (1994). Briefly, EG is first metabolized to glycoaldehyde (GAl) by alcohol dehydrogenase (ADH) (Figure 1). ADH then oxidizes GAl to glycolate/glycolic acid (GA). This oxidation is the rate limiting step in the metabolism of EG, and the GA intermediate is thought to be responsible for the observed developmental toxicity following oral exposure to EG (Carney et al. 1996).

In vitro studies have shown that EG alone has little effect on the developing embryo, and that developmental effects are only observed at concentrations when GA is saturated (Carney et al. 2008). GA is also responsible for the metabolic acidosis that is often observed after EG poisoning (Guo et al. 2007). GA is further metabolized and the ultimate metabolic end product of EG is oxalic acid (OA), which is responsible for the renal effects observed following ingestion of high doses of EG. OA precipitates urinary calcium and inhibits cytochrome oxidase activity in renal mitochondria (Laitinen et al. 1995). These calcium crystals deposit in the brain and kidneys, so although OA is a minor metabolite, it can cause significant damage to these systems (Carney et al. 1994). Metabolic acidosis, developmental effects, and renal toxicity are often not observed following inhalation exposure to EG, due to the fact that air concentrations become saturated long before the active metabolites become saturated in blood and plasma. Although metabolism may play a role in respiratory irritation, the only available dose metric is the concentration of the parent compound, EG.

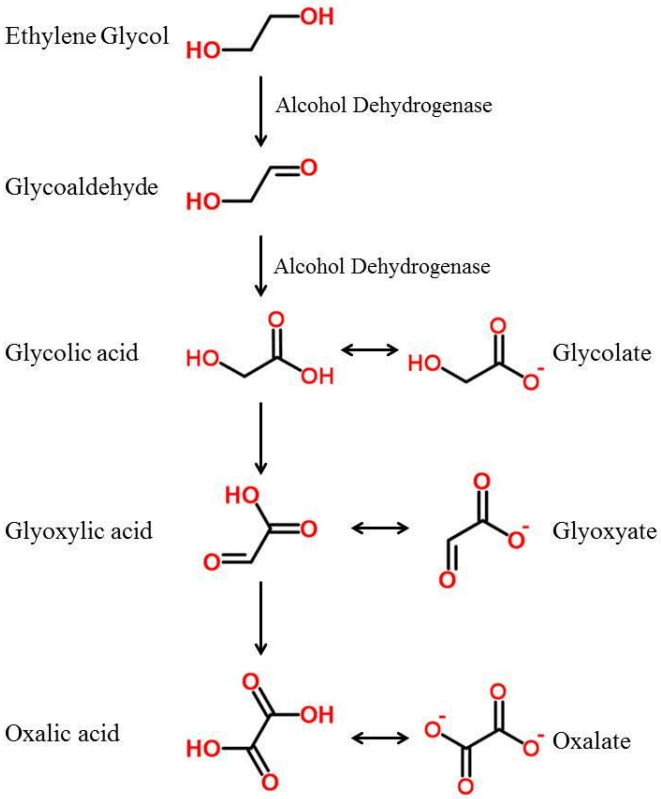


Figure 1. Metabolism of EG.

3.1.4 Point of Departure for Key Study and Critical Effects

Wills et al. (1974) observed that at a concentration of 188 mg/m^3, human volunteers could only tolerate being in the exposure chamber for 15 min. The authors stated that this irritation became apparent at 140 mg/m^3, although no duration was provided. No health effects were reported during longer exposure durations to concentrations of up to 75 mg/m^3. Varying chamber concentrations, however, make it difficult to determine how long the volunteers were exposed to the maximum reported concentrations. Although respiratory irritation may be more dependent on exposure concentration than duration (TCEQ 2015), the lack of information about the exposure duration at 75 mg/m^3 makes this concentration less than suitable for use as a NOAEL. Therefore, the Wills et al. (1974) study and the LOAEL of 140 mg/m3 for respiratory irritation will be used as the point of departure (POD), which is more conservative (i.e., considering that a LOAEL-to-NOAEL uncertainty factor will be applied).

3.1.5 Dosimetric Adjustments

3.1.5.1 Default Exposure Duration Adjustments

Since the critical effect is respiratory irritation, which is primarily concentration dependent, an exposure duration adjustment was not used, which is consistent with TCEQ guidelines (TCEQ 2015). Therefore, the POD_{ADJ} is 140 mg/m^3.

3.1.5.1 Default Dosimetry Adjustments from Animal-to-Human Exposure

An LOAEL of 140 mg/m^3 was identified in the Wills et al. (1974) study based on respiratory irritation in human volunteers and will be used as the human POD (POD_{HEC}) in further calculations of the acute ReV and ^{acute}ESL.

3.1.6 Adjustments of the POD_{HEC}

The POD_{HEC} based on a LOAEL from the Wills et al. (1974) study was used and UFs were applied to derive the acute ReV (i.e., assume a threshold MOA for a noncarcinogenic endpoint). The following uncertainty factors (UFs) were applied to the POD_{HEC} of 140 mg/m^3: 10 for intraspecies variability (UF_H), 3 for LOAEL-to-NOAEL uncertainty (UF_L), and 3 for database uncertainty (UF_D).

- A full UF_H of 10 was used to account for potential variation in sensitivity among the members of the human population (e.g., children, those with pre-existing medical conditions).
- An UF_L of 3 was used because the exposure concentration was a LOAEL, and while the authors noted that effects were common at this concentration, no other supporting data was given. A higher value was not used since no adverse effects were reported in the same chamber study at concentrations up to 75 mg/m^3 (e.g., 140 mg/m^3 / UF_L of 3 = 47 mg/m^3) or at a mean 7 d concentration of 34 mg/m^3, and two other human studies (Carstens et al. 2003 and Upadhyay et al. 2008) reported no health effects at approximate 4-h concentrations up to 30 mg/m^3. Therefore, an UF_L of 3 is considered sufficient to account for the difference between the LOAEL and NOAEL for respiratory irritation effects.
- An UF_D of 3 was used because there are several acute studies in multiple species available for EG, including reproductive and developmental studies. There is also some uncertainty associated with using an aerosol study rather than one that examined exposure to EG vapor. The quality of the study used as the POD is considered medium, and the confidence in the acute database is medium-high.

$$\text{acute ReV} = POD_{HEC} / (UF_H \times UF_L \times UF_D)$$
$$= 140\ mg/m^3 / (10 \times 3 \times 3)$$
$$= 140\ mg/m^3 / 90$$
$$= 1.5556\ mg/m^3$$
$$= 1555.6\ \mu g/m^3 \text{ or } 1500\ \mu g/m^3 \text{ (rounded to two significant digits)}$$

3.1.7 Health-Based Acute ReV and ^{acute}ESL

In deriving the acute ReV for EG, no numbers were rounded between equations until the ReV was calculated. Once the ReV was calculated, it was rounded to two significant figures. The resulting 1-h acute ReV is 1500 µg/m^3 (590 ppb) based on the Wills et al. (1974) study. The rounded acute ReV was then used to calculate the ^{acute}ESL. At the target hazard quotient (HQ) of 0.3, the ^{acute}ESL is 450 µg/m^3 (180 ppb) (Table 6).

Table 6. Derivation of the Acute ReV and ^{acute}ESL

Parameter	**Values and Descriptions**
Study	Wills et al. 1974
Study Population	24 human volunteers at a prison
Study Quality	Medium
Exposure Concentrations	Inhalation at 0.8-75 mg/m^3, 188, 244, 308 mg/m^3 (aerosol)
POD	140 mg/m^3
Critical Effects	Respiratory irritation
POD_{HEC}	140 mg/m^3
POD_{ADJ}	140 mg/m^3
Total UF	90
Interspecies UF	10
Intraspecies UF	1
LOAEL to NOAEL UF	3
Incomplete Database UF *Database Quality*	3 Medium-high
acute ReV [1 h] (HQ = 1)	**1500 µg/m^3 (590 ppb)**
^{acute}ESL [1 h] (HQ = 0.3)	**450 µg/m^3 (180 ppb)**

3.2 Welfare-Based Acute ESLs

3.2.1 Odor Perception

EG is a colorless, odorless liquid with a sweet taste (ATSDR 2010). Therefore, no odor values were derived.

3.2.2 Vegetation Effects

After a literature review, there was no data found on any adverse effects of EG on vegetation.

3.3 Short-Term ESL and Values for Air Monitoring Evaluation

The acute evaluation resulted in the derivation of the following values:

- acute ReV = 1500 µg/m^3 (590 ppb)
- ^{acute}ESL = 450 µg/m^3 (180 ppb)

Although we do not currently monitor for EG, the acute ReV of 1500 µg/m^3 (590 ppb) may be used in the evaluation of ambient air monitoring data in the future (Table 1). The short-term ESL used for air permit reviews is the health-based ^{acute}ESL of 450 µg/m^3 (180 ppb) (Table 2).

3.4 Acute Inhalation Observed Adverse Effect Level

Risk assessors, and the general public, often ask to have information on the levels in air where health effects would be expected to occur. So, when possible, the TCEQ provides chemical-specific observed adverse effects levels in DSDs (TCEQ 2015). As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose. Regarding critical effects due to acute EG exposure, the study by Wills et al. (1974) found a human LOAEL of 140 mg/m^3 for respiratory irritation. This LOAEL was used as the acute inhalation observed adverse effect level. No duration adjustment was made (TCEQ 2015).

This LOAEL represents a concentration at which it is possible that similar effects could occur in some individuals exposed to this level over a similar duration or longer. Importantly, effects are not a certainty due to potential intraspecies differences in sensitivity. As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose. The acute inhalation observed adverse effect level of 140 mg/m^3 (55 ppm) is provided for informational purposes only (TCEQ 2015).

The margin of exposure between the estimated acute inhalation observed adverse effect level of 140 mg/m^3 (55 ppm) and the acute ReV of 1.5 mg/m^3 is a factor of 93.

Chapter 4 Chronic Evaluation

4.1 Noncarcinogenic Potential

Studies examining chronic exposure to inhaled EG are limited compared to acute exposure. A systematic review was conducted and is detailed in Appendix 1.

4.1.2 Physical/Chemical Properties

The primary physical and chemical properties of EG are discussed in Chapter 3 and summarized in Table 3.

4.1.3 Key and Supporting Studies

Since much of the available literature focuses on the acute high dose effects of EG following accidental or intentional ingestion, very few studies are available on the chronic, long-term effects of inhalation exposure. This review will focus on the available inhalation data.

4.1.3.1 Human Studies

Several occupational studies have looked at workers exposed to EG vapor, but unfortunately these data are not useable due to either co-exposures to other hazardous chemicals, insufficient data on exposure, significant exposure by routes other than inhalation (i.e., dermal), and/or lack of a dose-response relationship.

4.1.3.1.1 Bond et al (1985)

A case-control study of workers in a chemical plant in Texas reported an increased incidence of mortality due to renal cancer than expected based on U.S. mortality rates, which is considered relatively uncommon. The chemical plant produced a number of chemicals, including EG. This study looked at cases of former employees deceased after 1940 with renal cancer listed as the cause of death and compared their work history to control groups without renal cancer. Two groups were used as controls; one that excluded any other type of cancer cases and one that did not. Twenty-six cases of renal cancer were identified in the population, most of which were designated as renal cell carcinoma cases. Smoking history was not available for most of the cases, although smoking has been identified as a moderate risk factor. Elevated, but not statistically significant, odds ratios were identified for a number of work areas, including EG production. A statistically significant elevated odds ratio was identified for workers in the cell maintenance area of chlorine production.

4.1.3.1.2 Gérin et al. (1997)

EG mist and vapor air concentrations (154 samples) were measured in the breathing zones of 33 aviation workers exposed to de-icing fluid during 42 working days over a 2-month period at a Montreal airport (employment years not provided). Urine samples were also collected and analyzed for EG concentrations and biomarkers for early kidney damage, including β-*N*-acetyl-glucosaminidase, albumin, β-2-microglobulin, and retinol-binding protein. For EG vapor, 88% of the samples were below the 22 mg/m^3 quantification limit. For EG mist, only 3 out of 154 samples had measurable concentrations over the 17 mg/m^3 quantification limit, ranging from 76 to 190 mg/m^3. The authors concluded that in most cases the exposure to EG vapor and mist was relatively low, and that the levels of the examined biomarkers for nephrotoxicity do not suggest overt kidney effects related to this occupational study.

4.1.3.1.3 Laitinen et al. (1995)

Air concentrations of EG and propylene glycol (PG) were measured in the workspace of 10 car mechanics frequently exposed to glycol-based cooling products. Urine samples were also collected and analyzed for EG, PG, and some common metabolites, along with succinate dehydrogenase activity and glycosaminoglycans as a measure of kidney function. These workers often did not wear gloves, so both inhalation and dermal exposure were plausible routes. Air sampling found that neither EG nor PG vapors were detected in the workers' breathing zones (detection limit for EG was 1.9 ppm), although urinary excretions from exposed workers were 3.8-fold higher than non-exposed controls. Excretion of glycosaminoglycans was significantly decreased, while succinate dehydrogenase activity was marginally decreased in exposed workers. The authors concluded that the primary route of exposure was most likely dermal; therefore, air monitoring does not reflect the total exposure. The authors also suggested that the differences in urinary markers may be an early indicator of metabolic effects in the kidneys.

4.1.3.1.4 Troisi (1950)

EG inhalation exposure was examined in 38 female workers at an electrolytic condenser factory (duration of employment/exposure not reported). Their duties involved spreading a high temperature mixture containing 40% EG by hand using paint brushes. Nine of the women reported episodes of losing consciousness on a frequent basis, at least two or three times a week. Urinary examination revealed no abnormalities, and the only other observable symptom was involuntary eye movements. Two of the women were permanently removed from the work area, and this alleviated the symptoms.

4.1.3.2 Key Animal Study – Coon et al. (1970)

Only a single animal study examined the effects of chronic inhalation exposure to EG, although several species were included in this study.

The Coon et al. (1970) study is detailed in Section 3.1.2.2. Briefly, groups of male and female SD and Long-Evans rats (15 animals/group), male and female Princeton-derived guinea pigs (15 animals/group), male New Zealand albino rabbits (3 animals/group), male squirrel monkeys (3 animals/group) and male beagle dogs (2 animals/group) were exposed to measured vaporous EG concentrations of 10 ± 1 and 57 ± 14 mg/m^3 for 8 h/d, 5 d/wk for 6 wk, or to 12 ± 2 mg/m^3 continuously for 90 d.

Repeated 6-wk exposure – no deaths were noted in either the 10 or 57 mg/m^3 exposure group. At 10 mg/m^3, hematologic analysis revealed no exposure related changes, while a histopathological examination revealed mild congestion in the spleens of 2/2 dogs, hepatic fatty changes in 2/8 guinea pigs and 1/8 rats, and focal necrosis in the liver of 1/8 guinea pigs and 1/8 rats. Focal necrosis of the liver was also observed in 1/3 control guinea pigs. At 57 mg/m^3, hematological analyses were normal, and histopathology revealed nonspecific inflammatory changes in the heart and lungs of all the species. Focal necrosis of the liver was observed in 2/3 monkeys and

1/8 guinea pigs, although the authors determined it was not exposure-related. For the repeated exposure study, the LOAEL for mild congestion in the spleens of dogs and fatty changes in the liver of guinea pigs and rats was 10 mg/m^3, and nonspecific inflammatory changes in the heart and lungs of all the species was 57 mg/m^3, following 6 wks of exposure.

Continuous 90-d exposure – 1/15 rats, 3/15 guinea pigs, and 1/3 rabbits died following continuous exposure at 12 mg/m^3. Moderate to severe eye irritation was observed in the rabbits beginning 3 d after continuous exposure, suggesting that these effects were duration-dependent. Erythema, edema, and eye discharge began in the rabbits after 3 d of exposure, with the edema being severe enough to cause closure of the eyes. Rats (2/15) developed corneal opacity after 8 d of exposure and appeared blind for the remainder of the study. Hematological analyses were normal, and histopathology revealed nonspecific inflammatory changes in the lungs of all the species, and mildly in some controls. For the continuous exposure study, the LOAEL for eye irritation in rats and rabbits and for nonspecific inflammatory changes in the lungs of all species was continuous 90 d exposure at 12 mg/m^3.

4.1.3.3 Reproductive and Developmental Studies

Previous studies examining the reproductive and developmental toxicity of EG are detailed in Section 3.1.2.3. No long-term reproductive or developmental studies following inhalation of EG were available. Several studies have been conducted using other routes of exposure, mainly oral, but data suggest that dose received orally is significantly higher than can be achieved via inhalation. Therefore, while available inhalation study results are summarized in Section 3.1.2.3, studies by other routes (e.g., oral) are not considered particularly relevant.

4.1.3.4 Summary of the Available Studies Examined in the Chronic Evaluation

The available chronic EG inhalation studies are summarized in Table 7. The Coon et al. (1970) study found mild congestion in the spleens of dogs and hepatic fatty changes in guinea pigs and rats following a 6-wk repeated exposure to 10 mg/m^3, but not in a similar repeated exposure study using 57 mg/m^3. Because these effects were inconsistent and did not appear to have a dose-response relationship, they will not be used as the critical effect.

During the continuous exposure, rats and rabbits experienced moderate to severe eye irritation that initially began at 3 and 8 d, respectively. This irritation lasted throughout the 90 d exposure. Coon et al. (1970) also found nonspecific inflammatory changes in the lungs of all animals following a 90-d continuous exposure to 12 mg/m^3. These nonspecific histopathological changes were also observed following repeated exposure to 57 mg/m^3 for 6 wks, which is a similar continuous dose following a duration adjustment (POD_{ADJ} = 57 mg/m^3 x 8 h/24 h x 5 d/7 d = 13.57 mg/m^3). No statistical analyses were provided, and therefore this response was conservatively assumed to be adverse.

As these two responses both occurred at the same concentration, ocular irritation in rats and rabbits and nonspecific inflammatory changes in the lungs of all animals following exposure to

12 mg/m^3 continuously for 90 d will be used at the critical effects and POD for the derivation of a chronic ReV.

Table 7. Chronic Inhalation Studies

Reference	Species	Exposure Concentration	Exposure Duration	NOAEL	LOAEL	Notes
Bond et al. (1985)	Humans	Unknown	Varied	--	--	Case-control study of chemical plant workers
Gérin et al. (1997)	Humans	Varied	Sampled 42 working days over 2 months	<22 mg/m^3 (vapor), 190 mg/m^3 (aerosol)	--	No changes in measured biomarkers for kidney effects
Laitinen et al. (1995)	Humans	<1.9 ppm (vapor)	Varied	--	--	Changes in urinary markers, possible dermal exposure
Troisi et al. (1950)	Humans	Unknown	Varied	--	--	Noted symptoms in chemical plant workers
Coon et al. (1970)	Rats, guinea pigs, rabbits, monkeys, dogs	10 and 57 mg/m^3 repeated or 12 mg/m^3 continuous (vapor)	8 h/d, 5 d/wk for 6 wk (repeated) or 90 d (continuous)	--	12 mg/m^3 (continuous)	Ocular irritation and nonspecific inflammatory changes in the lungs of all the species

4.1.4 MOA Analysis and Dose Metric

Available information on the metabolism and MOA of EG can be found in Section 3.1.3. The specific MOA for the ocular irritation and nonspecific inflammatory changes in the lungs identified in the Coon et al. (1970) study is unknown. The only available dose metric is the concentration of EG.

4.1.5 PODs for Key Study, Critical Effects and Dosimetric Adjustments

Based on the key study presented above (Coon et al. 1970), the TCEQ identifies 12 mg/m^3 as the free-standing LOAEL and subchronic POD based on ocular irritation and nonspecific inflammatory changes in the lungs.

4.1.5.1 Default Exposure Duration Adjustments

The 90-d exposure duration used in the key study was a continuous exposure protocol. Therefore, no adjustment to continuous exposure is needed.

4.1.5.2 Default Dosimetry Adjustments from Animal-to-Human Exposure

EG is miscible in water and causes ocular irritation and nonspecific changes in the lungs. However, while EG acts as a point-of-entry (POE) irritant (Category 1 gas), it also acts systemically (i.e., as a Category 3 gas) following inhalation (focal necrosis of the liver observed in Coon et al. 1970) and oral (metabolic acidosis, renal failure, CNS effects) exposure. For ocular irritation, no dosimetric adjustment is needed. For nonspecific changes in the lungs, EG would be treated as a Category 1 gas (USEPA 2012). No information was provided about the average ages or weights of any of the animals used in this study, which makes it difficult to calculate a species-specific regional gas dose ratio ($RGDR_r$). However, the nonspecific changes in the lungs were observed in all the species examined, including monkeys and dogs, which have similar respiratory systems as humans and may not require a dosimetric adjustment. Considering both the ocular irritation and the nonspecific changes observation in the lungs of all the species including monkeys and dogs, these data support not conducting an animal-to-human dosimetric adjustment. Therefore, the POD_{HEC} is equal to the POD_{ADJ} of 12 mg/m^3.

4.1.6 Adjustments of the POD_{HEC}

For the noncarcinogenic effects of EG, UFs are applied to a POD to derive a ReV (i.e., assume a nonlinear MOA for a noncarcinogenic endpoint). The following UFs were considered appropriate for application to the POD_{HEC} of 12 mg/m^3: 10 for UF_H, 3 for UF_A, 3 for subchronic to chronic uncertainty (UF_{Sub}), 3 for UF_L, and 3 for UF_D.

- A full UF_H of 10 was used to account for potential variation in sensitivity among the members of the human population (e.g., children, those with pre-existing medical conditions).
- An UF_A of 3 was used to account for potential interspecies toxicodynamic differences since a dosimetric adjustment for toxicokinetic differences was not needed.
- An UF_{Sub} of 3 was used to account for the use of a subchronic study due to some of the specific properties of EG, such as a relatively rapid elimination half-life of 2.5-8.4 h (ATSDR 2010) and a log K_{ow} well below 4 (Table 3), leading to reduced concerns about bioaccumulation and chronic effects differing significantly from subchronic effects.
- An UF_L of 3 was used because the exposure concentration of 12 mg/m^3 was a free-standing LOAEL. Ocular irritation was only observed in rabbits and rats, while nonspecific inflammatory changes suggest a mild effect. No changes in urinary markers were observed in humans exposed to an average weekly concentration of 30 mg/m^3 for 30 d, and no other respiratory effects were reported (Wills et al. 1974).
- An UF_D of 3 was used because only one subchronic animal and one subacute human study were available, and no long-term reproductive or developmental studies have been conducted

using the inhalation route. The quality of the study used as the POD is considered medium, and the confidence in the chronic database is medium to low.

chronic ReV = POD_{HEC} / (UF_H x UF_A x UF_{Sub} x UF_L x UF_D)
= 12 mg/m^3 / (10 x 3 x 3 x 3 x 3)
= 12 mg/m^3 / 810
= 0.0148 mg/m^3
= 14.8 µg/m^3 or 15 µg/m^3 (rounded to two significant digits)

4.1.7 Health-Based Chronic ReV and $^{chronic}ESL_{threshold(nc)}$

In deriving the chronic ReV, no numbers were rounded between equations until the ReV was calculated. The chronic ReV was rounded to two significant figures, resulting in a value of 15 µg/m^3 (5.9 ppb), and then used to calculate the $^{chronic}ESL_{threshold(nc).}$ At the target hazard quotient of 0.3, the $^{chronic}ESL_{threshold(nc)}$ is 4.5 µg/m^3 (1.8 ppb) (Table 8).

Table 8. Derivation of the Chronic ReV and ^{chronic}ESL

Parameter	Values and Descriptions
Study	Coon et al. 1970
Study Population	Male and female SD and Long-Evans rats (15 animals/group), male and female Princeton-derived guinea pigs (15 animals/group), male New Zealand albino rabbits (3 animals/group), male squirrel monkeys (3 animals/group) and male beagle dogs
Exposure Concentrations	10 and 57 mg/m^3 8 h/d, 5 d/wk for 6 wk or 12 mg/m^3 continuously for 90 d
Critical Effects	Ocular irritation and nonspecific inflammatory changes in the lungs of all species
POD	12 mg/m^3
Exposure Duration	90 d
POD_{ADJ}	12 mg/m^3
POD_{HEC}	12 mg/m^3
Total UF	810
Intraspecies UF	10
Interspecies UF	3
Subchronic to chronic UF	3
LOAEL UF	3
Incomplete Database UF *Database Quality*	3 Medium-Low
Chronic ReV (HQ = 1)	**15 µg/m^3 (5.9 ppb)**
$^{chronic}ESL_{nonlinear(nc)}$ (HQ = 0.3)	**4.5 µg/m^3 (1.8 ppb)**

4.2 Carcinogenic Potential

To date, there are no human or animal inhalation studies indicating that EG in particular is carcinogenic. More specifically, there is not a well-conducted chronic inhalation carcinogenicity study that could be used to conduct dose-response modeling. Consequently, a chronic carcinogenic inhalation value cannot be and was not developed.

4.3 Welfare-Based Chronic ESL

No data were found regarding long-term vegetation effects.

4.4 Long-Term ESL and Values for Air Monitoring Evaluation

The chronic evaluation resulted in the derivation of the following values:

- Chronic ReV = 15 µg/m^3 (5.9 ppb)
- $^{chronic}ESL_{threshold(nc)}$ = 4.5 µg/m^3 (1.8 ppb)

The long-term ESL for air permit reviews is the $^{chronic}ESL_{threshold(nc)}$ of 15 µg/m^3 (5.9 ppb) (Table 2). Although we do not currently monitor for EG, the chronic ReV of 4.5 µg/m^3 (1.8 ppb) could be used for the evaluation of ambient air monitoring data in the future (Table 1). The $^{chronic}ESL_{threshold(nc)}$ (HQ = 0.3) would not be used to evaluate ambient air monitoring data.

4.5 Chronic Inhalation Observed Adverse Effect Level

Observed inhalation adverse effect levels are described in more detail in Section 3.4 and in TCEQ 2015. The subchronic POD of 12 mg/m^3 determined from the Coon et al. 1970 study was based on ocular irritation and nonspecific inflammatory changes in the lung observed in all species following EG inhalation exposure.

The free-standing LOAEL of 12 mg/m^3, where effects occurred in some animals, represents a concentration at which similar effects could possibly occur in some individuals exposed over the same duration (90 d) or longer. Based on the TCEQ guidelines (2015), no duration adjustment is needed; however an animal-to-human dosimetric adjustment is used to calculate the $LOAEL_{HEC}$. Since the effects were ocular irritation and nonspecific inflammatory changes in the lungs, which was observed in monkeys, a dosimetric adjustment was not conducted (Section 4.1.5.2), and the $LOAEL_{HEC}$ is equal to the LOAEL of 12 mg/m^3. Effects are not a certainty as there may be inter- and intraspecies differences in sensitivity. The chronic inhalation observed adverse effect level of 12 mg/m^3 is provided for informational purposes only (TCEQ 2015). As the basis for development of inhalation observed adverse effect levels is limited to available data, future studies could possibly identify a lower POD for this purpose.

The margin of exposure between the observed adverse effect level (12 mg/m^3) and the chronic ReV (0.0045 mg/m^3) is a factor of approximately 2700.

Chapter 5 References

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Appendix 1 Systematic Review and Evidence Integration

A.1 Problem Formulation and Protocol

Problem formulation identifies and defines the causal questions and describes the extent of the evaluation. These questions structured the systematic review for EG:

- What are the physical and chemical properties of EG?
- What is the critical effect following exposure to EG?
- Are the doses that cause the critical effect environmentally relevant?
- Are there sensitive subpopulations?
- What is the mode of action (MOA)?
- Does route of exposure play a role?
- Is EG carcinogenic, and if so, is it carcinogenic by a specific route of exposure?
- Is EG a reproductive or developmental toxicant?

Protocol development is another important aspect in the initial process. A protocol is typically developed around a PECO statement: Populations, Exposure, Comparator/Control, and Outcomes. These identifiers are used to lay out the framework for the literature search and inclusion/exclusion criteria. The PECO statement for EG followed these criteria:

Table 9. PECO statement used by the TCEQ to develop toxicity factors for EG

Population	General human population and any relevant sensitive subpopulations, animals, and vegetation
Exposure	Exposure to EG, surrogates with demonstrated similar MOAs, and any identified metabolites
Comparator/ Control	Populations exposed to concentrations below the concentration that causes the most sensitive critical effect
Outcome(s)	The most sensitive critical effect directly related to EG exposure

The protocol used for the systematic review and the development of toxicity factors for EG is as follows:

1. Identify the chemical of interest and define the causal questions
2. Conduct a systematic review
    a. Conduct a systematic literature search
    b. Identify the inclusion/exclusion criteria
    c. Extract the relevant data from each data stream (human, animal, mechanistic)
    d. Assess the study quality and conduct a risk of bias analysis

e. Weigh the evidence in each data stream and then integrate the evidence across the data streams
f. Rate the confidence in the evidence

3. Derive toxicity factors (TCEQ 2015)
   a. Review the essential data, including chemical/physical properties and selected key studies from the systematic review
   b. Conduct MOA analysis
   c. Choose the appropriate dose metric considering toxicokinetics and MOA
   d. Select critical effect, based on human equivalent exposure considering each key study
   e. Extrapolate from the adjusted POD to lower exposures based on MOA analysis

A.2 Systematic Literature Review and Study Selection

As a first step, publically available databases were searched using explicitly stated search criteria. Please see TCEQ (2015) for a list of available databases that were searched. The search terms used in literature review for EG, along with the number of results from PubMed, are found in Table 10. Additional references were also identified using the reference sections from some of the selected studies. This literature review was conducted in June, 2015, and therefore studies published after this date were not available at the time of the review.

Table 10. Search strings used in the literature review of EG

Search Term/String	PubMed Results
ethylene glycol	20205
“ethylene glycol”	18895
“ethylene glycol” [mesh]	2093
“ethylene glycol” [mesh] NOT “ethylene oxide”	2077
“ethylene glycol” [mesh] NOT “ethylene oxide” AND (inhal* OR air OR carc* OR onco* OR oral)	168
“ethylene glycol” [mesh] NOT “ethylene oxide” AND (inhal* OR air OR carc* OR onco*)	106

An additional PubMed search was conducted using the search terms “ethylene glycol” AND inhalation, which resulted in 105 references. These references were compared to the list generated above and added as needed. The selected studies were imported into the Health Assessment Workspace Collaborative (HAWC) systematic literature review tool. Each title and abstract was reviewed for relevance and tagged for either inclusion (human, animal, or mechanistic) or exclusion (not a relevant/applicable study). For EG, a number of studies

involving cryopreservation and chemical synthesis were excluded due to the lack of relevance in a health-based risk assessment. Other reasons for this initial exclusion included studies using chemicals other than EG (di- or triethylene glycol, ethylene glycol ethers, etc.), studies that did not look at toxic effects (bactericidal or solvent effects), and unrelated mechanistic studies.

Additionally, several governmental and private sector organizations were searched for published literature and toxicity values for EG, and the available documents along with their relevant references were added to the pool of selected material.

Table 11. Available reviews and toxicity values for EG

Organization	Year	Toxicity Value
Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profiles	2010	Acute MRL*
Integrated Risk Information System (IRIS) USEPA	1989	Oral RfD*
Office of Environmental Health Hazard Assessment (OEHHA) CalEPA	2000	Chronic REL*
Health Canada	2000	NA
International Programme on Chemical Safety (IPCS)	2002	NA

MRL – minimal risk level, RfD – reference dose, REL – reference exposure level

Following this initial review, which produced a pool of ~170 articles and documents, specific inclusion and exclusion criteria were used to narrow down the pool of available data. The criteria along with examples of the kinds of studies that were excluded can be found in Table 12.

Table 12. Inclusion/exclusion criteria used in the review of EG

Study Type	Inclusion Criteria	Exclusion Criteria
General	Complete study available for review	- Only abstract is available - Study in a language other than English - Unpublished report/unable to retrieve
	Exposure concentration is environmentally relevant	- Significantly high concentrations used - Study focused on overdose/poisoning or mortality - Exposure concentration unknown
	Study contains original data	- Study is a review article
	Study examines effects related to chemical exposure	- Study measures concentration in products, etc. - Study does not examine health effects
	Study focused on the chemical of concern or active metabolites	- Study examined mixture effects (i.e. antifreeze) - Study on treatment following EG exposure
Animal	Route of exposure is relevant to environmental exposure and to toxicity factor development	- Exposure through i.v., i.p., or subcutaneous injection - Study examining dermal exposure - Study examining oral exposure*
	Relevant animal model and endpoints examined	- Study used non-mammalian animal models - Endpoint studied not relevant to human health - Endpoint not applicable to toxicity factor development
Human/Epi	Route of exposure is relevant to toxicity factor development	- Study examining dermal exposure - Study examining oral exposure* - Multiple routes possible/unknown route of exposure
	Relevant endpoints examined	- Study focused on mortality/intentional ingestion

i.v. – intravenous, i.p. – intraperitoneal
* Studies using the oral route of exposure were initially excluded from the key study selection due to the inhalation route being more applicable to the development of a ReV/ESL. Oral data may be used to fill gaps in the inhalation data as needed.

Using these inclusion/exclusion criteria, the pool of available data was narrowed down to 24 included studies: 7 human studies, 6 animal studies, 5 mechanistic/*in vitro* studies, and 5 government reports. These studies were collected and reviewed in detail by each of the authors.

A.3 Data Extraction

Each of the identified studies was reviewed in detail and the primary data was extracted for potential use in this DSD. Data from the studies can be found in Table 13 (human studies), Table

14 (animal studies), and Table 15 (in vitro studies). Data that was applicable to the development of the acute and chronic ReVs and ESLs are also in sections 3.1.2 and 4.1.2, respectively.

Table 13. Data extraction from human studies

Reference	Exposure Concentration	Exposure Duration	NOAEL	LOAEL	Notes
Bond et al. (1985)	Unknown	Varied	--	--	Case-control study of chemical plant workers
Carstens et al. (2003)	25, 28 mg/m^3 (vapor)	4 h	28 mg/m^3	--	Health effects not measured or reported
Gérin et al. (1997)	Varied	Sampled 42 working days over 2 months	<22 mg/m^3 (vapor), 190 mg/m^3 (aerosol)	--	No changes in measured biomarkers for kidney effects
Laitinen et al. (1995)	<1.9 ppm (vapor)	Varied	--	--	Changes in urinary markers, possible dermal exposure
Troisi et al. (1950)	Unknown	Varied	--	--	Noted symptoms in chemical plant workers
Upadhyay et al. (2008)	25, 30 mg/m^3 (vapor)	4 h	30 mg/m^3	--	Health effects not measured or reported
Wills et al. (1974)	0.8-75 mg/m^3, 188, 244, 308 mg/m^3 (aerosol)	Varied	34 mg/m^3 (mean 7 d), 75 mg/m^3 (high)	140 mg/m^3 (duration not reported)	Respiratory irritation occurred after 140 mg/m^3, no changes in urinary markers

Table 14. Data extraction from animal studies

Reference	Species	Exposure Concentration	Exposure Duration	NOAEL	LOAEL	Notes
Coon et al. (1970)	Rats, guinea pigs, rabbits, monkeys, dogs	10 and 57 mg/m^3 repeatedly or 12 mg/m^3 continuously (vapor)	8 h/d, 5 d/wk for 6 wk (repeated) or 90 d (continuously)	--	10 mg/m^3 (repeated) 12 mg/m^3 (continuous)	Moderate to severe eye irritation in rabbits and rats, nonspecific inflammatory changes in the lungs of all the species
Corley et al. (2005)	Various	Various	Various	--	--	PBPK model development using various studies
Corley et al. (2011)	Various	Various	Various	--	--	PBPK model development using various studies
Marshall and Cheng (1983)	Rats	32 mg/m^3 (vapor), 184 (aerosol) mg/m^3	30 min (vapor), 17 min (aerosol)	32 mg/m^3 (vapor), 184 mg/m^3 (aerosol)	--	Health effects not measured or reported
Tyl et al. (1995a)	Rats and mice	0, 150, 1000, and 2500 mg/m^3 (aerosol, whole body)	6 h/d on GD 6-15	1000 mg/m^3 (maternal) 150 mg/m^3 (fetal)	2500 mg/m^3 (maternal) 1000 mg/m^3 (fetal)	Increased resorptions, decreased fetal body weight, possible oral exposure
Tyl et al. (1995b)	Mice	0, 500, 1000, and 2500 mg/m^3 (aerosol, nose-only)	6 h/d on GD 6-15	500 mg/m^3 (maternal) 1000 mg/m^3 (fetal)	1000 mg/m^3 (maternal) 2500 mg/m^3 (fetal)	Increased maternal kidney weights, fetal skeletal variations

Table 15. Data extraction from mechanistic studies

Reference	Model	Exposure Concentration	Exposure Duration	NOAEL	LOAEL	Notes
Capo et al. (1993)	Rat embryonic nerve cells	0.01, 0.1, 1, 10, 100 µM	24 h	--	0.01 µM (IC50 0.26 µM)	Neuronal degeneration, decrease in cell number
Carney et al. (1996)	Rat whole embryo culture	0.5, 2.5, 12.5, 25, 50 mM EG or GA	48 h	50 mM EG, 2.5 mM GA	12.5 mM GA	Inhibition of embryo growth and development
Carney et al. (2008)	Rabbit whole embryo culture	2.5, 6, 12.5, 25, 50 mM GA	48 h	50 mM GA	--	No significant adverse effects on developing embryos
Guo et al. (2007)	Human proximal tubule cells	0-25 mM EG or metabolites	6 h	25 mM EG	2 mM oxalate	Cytotoxicity and decreased cell viability
Klug et al. (2001)	Rat whole embryo culture	0-200 mM EG or metabolites	48 h	200 mM EG	0.1 mM GAl, 3 mM GA	Embryotoxicity, morphological changes

GA – glycolate, GAl - glycoaldehyde

A.4 Study Quality and Risk of Bias (ROB)

Each of the selected studies was evaluated for study quality and ROB based on a number of attributes determined prior to this review. The attributes were scored on a scale of 1 to -1, with 1 meaning the study possessed the specific attribute, 0 meaning the study did not examine the attribute, and -1 meaning the study lacked the attribute. Each of these study quality attributes along with the criteria used in scoring them can be found in Table 16 (general studies), Table 17 (human studies), Table 18 (animal studies), Table 19 (in vitro studies), and Table 20 (reproductive and developmental studies).

Table 16. Study quality and ROB scoring criteria for general studies

Score Criteria	1	0	-1
Original data	Authors generated primary data	Authors used data from another source to draw their own conclusions	Review study, data from other sources mentioned but not further analyzed
Applicable route of exposure	Study looks at specific route of exposure relevant to ReV development	Unknown what the exact route of exposure was	Study states that a different route of exposure was studied
Single route of exposure	Study looks at a single route of exposure relevant to ReV development	Unknown if multiple routes were accounted for during exposure	Study states that multiple routes were examined
Single chemical exposure	Single chemical of interest or activate metabolite was used	Unknown whether additional chemicals may have been present	Study used multiple chemicals/mixture
Range of doses/ exposures	Study examines >2 exposure concentrations	Study examines one or two exposure concentrations	Exposure concentration unknown
Exposure concentration known/ measured	Study measures the exposure concentration (analytical)	Exposure concentration assumed but not measured/tested (nominal)	Exposure concentration unknown
Blinded study	Study specifically states that blind testing was used	Unclear whether blind testing was used	Study specifically states that blind testing was not used
Health effects relevant to ReV development	Measured health effects relevant to ReV development	Measured effects not relevant to ReV development (e.g. measured changes in protein expression, urinary excretion)	No health effects were measured (e.g. measured air or mixture concentrations)
Appropriate endpoints measured	Study examines target organ or adverse effects known or suspected in be involved in MOA	Study lacks information about certain relevant endpoints (e.g. measured urinary excretion but not irritation or other effects)	Appropriate endpoints not measured (study did not examine adverse effects or effects not part of MOA)
Measured outcomes reported	All measured outcomes were reported in a consistent manner	Some outcomes were reported, but not consistently	All measured outcomes were not reported
Study design sufficient/ clearly defined	Study designed clearly defined and detailed in methods	Study design not defined, detailed information not provided	Study design contains an obvious flaw or problem
Calculation of sample size	Study conducts calculation to determine appropriate sample size	Study does not calculate sample size but sample size appears to be appropriate	Study does not calculate sample size and size does not appear to be sufficient
Confounding factors	Study eliminates or controls for any possible confounding factors	Confounding factors not identified or addressed	Study has confounding factors (e.g. smoking, behavioral patterns)
Appropriate research practices	Study provides enough detail to assume quality, uniformity, consistency, and reproducibility	Study qualities not clearly or specifically stated	Study lacks a specific aspect of quality, uniformity, consistency, or reproducibility

Table 17. Study quality and ROB scoring criteria for human studies

Score Criteria	1	0	-1
Appropriate comparison groups	Comparison groups have similar baseline characteristics	Minor differences exist between groups, or it is unclear if differences exist	Significant differences exist between groups
Follow up of subjects	Subject follow up was complete and thorough	Unable or unnecessary to complete follow up (mortality study)	Subject follow up was needed but not completed
Temporal relation	Exposure of interest precedes the outcome	Unclear if the exposure of interest precedes the outcome	Outcome proceeds the expected exposure period
Study results consistent with other available evidence	Study outcome is consistent with other available evidence	Outcome is partially consistent or no other evidence is available for comparison	Overall study outcome is not consistent with other available evidence

Table 18. Study quality and ROB scoring criteria for animal studies

Score Criteria	1	0	-1
Multiple species	Studied examined effects in multiple species	Studied examined effects in a single species	Species not clearly stated
Both sexes	Studied examined effects in both sexes	Studied examined effects in a single sex	Sex not specified
Exposure regimes (repeated vs continuous)	Studied examined effects following different exposure regimes	Studied examined effects following a single exposure regime	Exposure regime not stated
Identical experimental conditions across study groups	Study used identical experimental methods across study groups	Minor differences exist, or it is unclear if identical experimental methods were used	Significant differences exist that could affect the outcome
Concentration relevant to human exposure	Study used a biologically and environmentally relevant exposure concentration	Unclear whether exposure concentration used was biologically and/or environmentally relevant	Exposure concentration was not biologically and/or environmentally relevant
Dose applicable to ReV development	Dose can be used directly to establish a POD for ReV development	Dose must be converted/calculated in order to establish a POD	Dose cannot be converted into an appropriate POD
Dose-response relationship	Critical effect showed a significant positive dose-response curve	Critical effect failed to show a significant dose-response curve	Critical effect showed a significant negative dose-response curve

Table 19. Study quality and ROB scoring criteria for mechanistic studies

Score Criteria	1	0	-1
Concentration is relevant to human exposure	Study used a biologically and environmentally relevant exposure concentration	Unclear whether exposure concentration used was biologically and/or environmentally relevant	Exposure concentration was not biologically and/or environmentally relevant
Dose is applicable to ReV development	Dose can be used directly to establish a POD for ReV development	Dose must be converted/calculated in order to establish a POD	Dose cannot be converted into an appropriate POD
Dose-response relationship	Critical effect showed a significant positive dose-response curve	Critical effect failed to show a significant dose-response curve	Critical effect showed a significant negative dose-response curve

Table 20. Study quality and ROB scoring criteria for reproductive/developmental studies

Score Criteria	1	0	-1
Critical window for effects	Exposure model based on appropriate critical window (e.g. GD 6-15 for rodents)	Study uses alternate exposure window than would be expected for the measured effect	Exposure window not described or detailed
Maternal and fetal toxicity	Study examines both maternal and fetal toxicity	Study examines either maternal or fetal toxicity	Study fails to appropriately measure maternal or fetal toxicity

Rankings for each of the identified studies can be found in Table 21 (human studies), Table 22 (animal studies), and Table 23 (in vitro studies). Note that total scores were added as a guide to compare within the study groups, but because each study group has a different number of scoring criteria, totals should not be compared across groups.

Table 21. Study quality and ROB scoring for the selected EG human studies

Study criteria	Bond 1985	Carstens 2003	Gerin 1997	Laitinen 1995	Troisi 1950	Upadhyay 2008	Wills 1974
General							
Original data	1	1	1	1	1	1	1
Applicable route of exposure	0	1	1	1	1	1	1
Single route of exposure	0	1	-1	-1	0	1	0
Single chemical exposure	-1	1	-1	-1	-1	1	1
Range of doses/exposures	-1	0	1	0	-1	0	1
Exposure concentration known/ measured	-1	1	1	1	-1	1	1
Blinded study	0	0	0	0	0	0	0
Health effects relevant to ReV development	1	0	0	0	0	0	1
Appropriate endpoints measured	1	0	0	0	0	0	1
Measured outcomes reported	1	1	1	1	0	1	1
Study design sufficient/ clearly defined	0	1	1	1	-1	1	0
Calculation of sample size	0	-1	0	-1	0	-1	0
Confounding factors	-1	0	0	0	-1	0	-1
Appropriate research practices	1	1	1	1	0	1	-1
Human							
Appropriate comparison groups	0	0	-1	1	-1	-1	1
Follow up of subjects	0	0	0	0	1	0	0
Temporal relation	1	1	1	1	1	1	1
Study results consistent with other available evidence	0	1	1	1	0	1	1
Total Points	**2**	**9**	**6**	**6**	**-2**	**8**	**9**
Study Selection – Key, supporting, or informative	**I**	**S**	**I**	**I**	**I**	**S**	**K**
Acute or chronic	**C**	**A**	**C**	**C**	**C**	**A**	**A/C**

Table 22. Study quality and ROB scoring for the selected EG animal studies

Study criteria	Coon 1970	Corley 2005	Corley 2011	Marshall 1983	Tyl 1995a	Tyl 1995b
General						
Original data	1	0	0	1	1	1
Applicable route of exposure	1	1	1	1	1	1
Single route	1	-1	0	1	-1	0
Single chemical exposure	1	1	1	1	1	1
Range of doses/ exposures	1	0	0	0	1	1
Exposure concentration known/ measured	1	0	0	1	1	1
Blinded study	0	0	0	0	0	0
Health effects relevant to ReV development	1	0	0	0	1	1
Appropriate endpoints measured	1	0	0	0	1	1
Measured outcomes reported	1	0	0	1	1	1
Study design sufficient/ clearly defined	0	1	1	1	1	1
Calculation of sample size	0	0	0	0	0	0
Confounding factors	0	0	0	0	0	-1
Appropriate research practices	0	0	0	1	1	1
Animal						
Multiple species	1	1	1	0	1	0
Both sexes	1	1	1	1	1	1
Exposure regimes (repeated vs continuous)	1	0	0	0	0	0
Concentration relevant to human exposure	0	0	0	0	0	0
Dose applicable to ReV development	1	0	0	1	1	1
Dose-response relationship	0	0	0	0	1	1
Reproductive/developmental						
Critical window for effects	-	-	-	-	1	1
Maternal and fetal toxicity	-	-	-	-	1	1
Total Points	**13**	**4**	**5**	**10**	**15**	**14**
Study Selection – Key, supporting, or informative	**S/K**	**I**	**I**	**S**	**I**	**S**
Acute or chronic	**A/C**	**A**	**A**	**A**	**A**	**A**

Table 23. Study quality and ROB scoring for the selected EG mechanistic studies

Study criteria	Capo 1993	Carney 1996	Carney 2008	Guo 2007	Klug 2001
General					
Original data	1	1	1	1	1
Applicable route of exposure	-1	-1	-1	-1	-1
Single route	1	1	1	1	1
Single chemical exposure	1	1	1	1	1
Range of doses/ exposures	1	1	1	1	1
Exposure concentration known/ measured	1	1	1	1	1
Blinded study	0	1	0	0	0
Health effects relevant to ReV development	0	1	1	0	1
Appropriate endpoints measured	0	1	1	1	1
Measured outcomes reported	1	1	1	1	1
Study design sufficient/clearly defined	0	1	1	0	1
Calculation of sample size	0	0	0	0	0
Confounding factors	0	0	0	0	0
Appropriate research practices	1	1	1	1	1
Mechanistic					
Concentration is relevant to human exposure	0	1	1	0	0
Dose is applicable to ReV development	0	0	0	0	0
Dose-response relationship	1	1	0	1	1
Reproductive/developmental					
Critical window for effects	-	1	1	-	1
Maternal and fetal toxicity	-	0	0	-	0
Total Points	**7**	**13**	**11**	**8**	**11**
Study Selection – Key, supporting, or informative	**I**	**I**	**I**	**I**	**I**
Acute or chronic	**A**	**A**	**A**	**A**	**A**

A.5 Evidence Integration

After addressing the study quality and ROB for each of the selected studies, the information from each of the data streams (human, animal, mechanistic) was compiled together and assessed for use as key, supporting, and informative studies. This information was put into the evidence integration tables found in Tables 24-26.

Table 24. Evidence Integration Table for Human Studies

Study	Species	Type	Reasoning
Bond et al. (1985)	Human	Informative	- No exposure concentrations available - Health effects not associated with exposure
Carstens et al. (2003)	Human	Supporting	- Health effects not directly measured, but also not reported - Free-standing NOAEL
Gérin et al. (1997)	Human	Informative	- Measured air concentrations, but actual exposure unknown - No measured health effects
Laitinen et al. (1995)	Human	Informative	- Measured air concentrations, but actual exposure unknown - No measured health effects
Troisi et al. (1950)	Human	Informative	- No exposure concentrations available - Multiple chemical exposure
Upadhyay et al. (2008)	Human	Supporting	- Health effects not directly measured, but also not reported - Free-standing NOAEL
Wills et al. (1974)	Human	Key	- Acute respiratory irritation, free-standing LOAEL - Subacute free-standing NOAEL for kidney toxicity biomarkers - Exposure concentration suitable for toxicity factor derivation

Table 25. Evidence Integration Table for Selected Animal Studies

Study	Species	Type	Reasoning
Coon et al. (1970)	Rats, guinea pigs, rabbits, monkeys, dogs	Key	- Multiple species examined - Acute ocular irritation free-standing LOAEL - Chronic systemic free-standing LOAEL - Few dose groups, NOAEL not identified
Corley et al. (2005)	Various	Informative	- PBPK model based on previous studies - No exposure/dose response data available
Corley et al. (2011)	Various	Informative	- PBPK model based on previous studies - No exposure/dose response data available
Marshall and Cheng (1983)	Rats	Supporting	- Health effects not directly measured, but also not reported - Free-standing NOAEL
Tyl et al. (1995a)	Rats and mice	Informative	- NOAEL and LOAEL for maternal and fetal toxicity - Two species tested - Significant oral exposure from grooming behaviors
Tyl et al. (1995b)	Mice	Supporting	- NOAEL and LOAEL for maternal and fetal toxicity - Minimum oral exposure due to nose-only exposure - Skeletal malformations linked to restraining apparatus

Table 26. Evidence Integration Table for Selected Mechanistic Studies

Study	Species	Type	Reasoning
Capo et al. (1993)	Rat embryonic nerve cells	Informative	- Informative for EG MOA - Not clear if dose is relevant to human inhalation exposure
Carney et al. (1996)	Rat whole embryo culture	Informative	- Informative for MOA of EG and metabolites - Developmental study, fetal toxicity - Not clear if dose is relevant to human inhalation exposure
Carney et al. (2008)	Rabbit whole embryo culture	Informative	- Informative for MOA of EG and metabolites - Developmental study, fetal toxicity - Not clear if dose is relevant to human inhalation exposure
Guo et al. (2007)	Human proximal tubule cells	Informative	- Informative for MOA of EG and metabolites - Not clear if dose is relevant to human inhalation exposure
Klug et al. (2001)	Rat whole embryo culture	Informative	- Informative for MOA of EG and metabolites - Developmental study, fetal toxicity - Not clear if dose is relevant to human inhalation exposure

A.6 Confidence Rating

Table 27 provides scoring criteria to rate the confidence and uncertainty for each aspect or element of the toxicity assessment. The table provides the name of the element and the magnitude of the confidence in each element using a qualitative ranking system of low, medium, or high confidence. Table 28 displays the overall confidence in the ethylene glycol a toxicity assessment.

Table 27. Confidence Scoring Criteria

Element	Low	Medium	High
Database Completeness	A single acute and/or chronic study was available	Several studies were available, but some important studies were missing.	Two studies in different species, one 2-generation reproductive study, two developmental studies
Systematic Review	A systematic approach was not used.	A systematic approach was considered and some criteria were applied, but a full review was not conducted	A systematic approach was used in study evaluation and clear criteria are established for judgment
Key Study Quality	Selected study has deficiencies, but is still considered useful	Selected study was reasonably well done but some restrictions must be considered	Selected study was well done and can be used without restriction
Critical effect	Critical effect or dose-response curve was moderate to severe. MOA information not available.	Critical effect was moderate; other studies are deemed necessary to determine the critical effect.	Critical effect was of minimal, or the confidence in the critical effect was high. MOA information available.
Relevance of Critical Effect	Critical effect identified in animal studies is only assumed to be relevant to humans; MOA is not known for the critical effect	Critical effect appears to be relevant to humans. MOA is known for the critical effect and possibly relevant to humans.	Critical effect based on a human study or matches observed human experience; MOA is well understood so critical effect is assumed relevant.
Point of Departure (POD)	Many uncertainties exist in POD; only a free-standing NOAEL or LOAEL identified; few dose groups; BMD modeling not possible	Some uncertainty exists in POD, NOAEL or LOAEL; few dose groups; difference between BMD and BMDL is large	Basis for POD well understood: NOAEL and LOAEL; multiple dose groups, BMD modeling conducted; difference between BMD and BMDL less than 2-fold
Human Equivalent POD (POD_{HEC})	Many uncertainties exist in the POD_{HEC}; no dosimetric adjustment from animal POD to POD_{HEC}	Default adjustments used and considered conservative; some uncertainty exists in adjustment to a HEC.	Human data available; HED/HEC is known from PBPK or dosimetry model or CSAF
Sensitive Populations	Many uncertainties on sensitive populations exist and are not addressed.	Information on sensitive population is not known but default procedures are presumed to be conservative.	Human data on sensitive populations are available and uncertainties are addressed.
Peer Review	Limited or no peer review; disregarded comments would significantly change risk value; no independent check	Adequate peer review. Most substantive comments addressed; disregarded comments would not significantly change value	High quality panel peer review with appropriate experts; all substantive comments addressed as per independent check
Toxicity Value Comparison	Relevant risk values show a greater than 10 fold difference.	Some relevant risk values agree within 3-fold of each other, and others disagree within 10-fold of each other	All relevant risk values agree within 3-fold of each other

Table 28. Confidence in the Toxicity Assessment

Element	Score	Basis
Database Completeness	Medium	- Several acute and chronic studies in multiple species - Two developmental studies in two species - Lacking a 2-generation reproductive study and additional chronic information
Systematic Review	High	- Systematic review conducted
Key Study Quality	Medium	- Acute study had confounding factors (smoking, varying chamber concentrations) - Chronic study lacked a NOAEL and detailed histopathology information
Critical effect	Medium	- Acute and chronic critical effects were mild - Both lacked NOAEL information
Relevance of Critical Effect	Medium	- Acute critical effect based on human study - Chronic critical effect is possibly relevant to humans
Point of Departure (POD)	Low	- Only free-standing LOAELs available - Few dose groups, BMD modeling not possible
Human Equivalent POD (POD_{HEC})	Medium	- Default adjustments used, considered conservative
Sensitive Populations	Medium	- No information on sensitive subpopulations - Default UF_H of 10 used and considered protective
Peer Review	-	- DSD will be proposed for public comment
Toxicity Value Comparison	-	- No other agencies have derived relevant inhalation toxicity factors

Confidence Scoring Summary			
Not Evaluated	**Low Confidence**	**Medium Confidence**	**High Confidence**
Peer Review Toxicity Value Comparison	Point of Departure	Database Completeness Key Study Quality Critical Effect Relevance of Critical Effect Human Equivalent POD Sensitive Populations	Systematic Review

* Criteria for scoring the individual elements adapted from Beck et al. (2015).