Method Version: GreenScreen® Version 1.2

Verified or Non-Verified: VERIFIED

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	Date: November 15 2013
	Verification Review Plan Prepared By: Dr. Eric Rosenblum
Verified GreenScreen® Prepared by Licensed Profiler:	Organization: ToxServices LLC
	Date: October 15, 2013

Ethylene Glycol (CAS# 107-21-1) GreenScreen® Assessment

Prepared for:

Clean Production Action

Date:

October 15, 2013 (Verified)

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GreenScreen® Executive Summary for Ethylene Glycol (CAS #107-21-1)

Ethylene glycol is a chemical that functions as a monomer in the production of polyethylene terephthalate (PET) plastic, is used as an antifreeze and deicing/anti-icing solution, is used as an ingredient in resins, inks, paints, waxes, heat transfer fluids, hydraulic fluids, and surfactants, and is a component of electrical boards and electrical condensers.

Ethylene glycol was assigned a GreenScreen® Benchmark Score of 1 ("Avoid – Chemical of High Concern") as it has a High hazard score for developmental toxicity (D). This corresponds to GreenScreen® benchmark classification 1e (High T (Group I Human)) in CPA 2011.

Data gaps (DG) exist for respiratory sensitization (SnR). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), ethylene glycol meets requirements for a GreenScreen® Benchmark Score of 1based only on the high hazard score for developmental toxicity. In a worst-case scenario, if ethylene glycol were assigned a High score for respiratory sensitization, it would still be categorized as a Benchmark 1 Chemical.

GreenScreen® Benchmark Score for Relevant Route of Exposure:
All exposure routes (oral, dermal and inhalation) were evaluated together, as a standard approach for GreenScreen® evaluations, so the GreenScreen® Benchmark Score of 1 ("Avoid – Chemical of High Concern") is applicable for all routes of exposure.

GreenScreen® Hazard Ratings for Ethylene Glycol

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
L	L	M	H	*L*	M	vH	H	H	L	L	DG	M	M	L	L	vL	L	L	L

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M and L) instead of three (i.e., H, M and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms

GreenScreen® Assessment for Ethylene Glycol (CAS #107-21-1)

GreenScreen® Version 1.2 Assessment

Chemical Name: Ethylene Glycol

CAS Number: 107-21-1

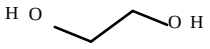
GreenScreen® Assessment Prepared By:
Name: Zach Guerrette, Ph.D.

Title: Toxicologist
Organization: ToxServices LLC
Date: March 25, 2013; October 7, 2013 (Revision #1)

Quality Control Performed By:
Name: Dr. Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.S.B., E.R.T., D.A.B.T.
Title: Managing Director and Chief Toxicologist
Organization: ToxServices LLC
Date: March 25, 2013; October 15, 2013 (Revision #1)

Confirm application of the *de minimus* rule[1]: Not applicable for ethylene glycol; not a mixture

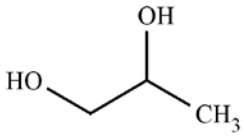
Chemical Structure(s):



Ethylene glycol (CAS #107-21-1)

Also called: 1,2-Ethanediol; Glycol; 1,2-Dihydroxyethane; 2-Hydroxyethanol; EINECS 203-473-3; Ethylene alcohol; Ethylene dehydrate; Glycol alcohol; Glycol, ethylene-; Monoethylene glycol (ChemIDplus 2013)

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:
No respiratory sensitization data were identified for ethylene glycol. Attempts were made to identify a suitable surrogate for this endpoint. Propylene glycol (CAS #57-55-6) was identified as an acceptable surrogate for ethylene glycol as both chemicals are alkanes with hydroxyl groups bonded to carbons 1 and 2.



Propylene glycol (CAS #57-55-6)

Notes related to production-specific attributes[2]: No information disclosed.

[1] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm

[2] Note any composition or hazard attributes of the chemical product relevant to how it is manufactured. For example, certain synthetic pathways or processes result in typical contaminants, by-products or transformation products. Explain any differences between the manufactured chemical product and the GreenScreen® assessment of the generic chemical by CAS #.

Identify Applications/Functional Uses:

1. Used as a monomer used with terephthalic acid in the manufacture of polyethylene terephthalate (PET) for use in bottles, film, and fibers (accounts for 78% of ethylene glycol consumption in 1999) (OECD 2004)
2. Used in antifreeze and deicing/anti-icing solutions (accounts for 13% of ethylene glycol consumption in 1999) (OECD 2004)
3. Used as an ingredient used in the following (accounts for 9% of ethylene glycol consumption in 1999) (OECD 2004):
    a. acrylic, urethane, and alkyd resins
    b. inks, paints, adhesives, waxes, and as a component of electrical boards and electrical condensers
    c. heat transfer fluids
    d. industrial hydraulic fluids and surfactants.

GreenScreen® Summary Rating for Ethylene Glycol:[3] Ethylene glycol was assigned a GreenScreen® Benchmark Score of 1 ("Avoid – Chemical of High Concern") as it has a High hazard score for developmental toxicity (D). This corresponds to GreenScreen® benchmark classification 1e (High T (Group I Human)) in CPA 2011. Data gaps (DG) exist for respiratory sensitization (SnR). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), ethylene glycol meets requirements for a GreenScreen® Benchmark Score of 1based only on the high hazard score for developmental toxicity. In a worst-case scenario, if ethylene glycol were assigned a High score for respiratory sensitization, it would still be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Ratings for Ethylene Glycol

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
L	L	M	H	*L*	M	vH	H	H	L	L	DG	M	M	L	L	vL	L	L	L

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M and L) instead of three (i.e., H, M and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

Transformation Products and Ratings:

Identify feasible and relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) and/or moieties of concern[4,5]

[3] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

[4] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

[5] The assessment of transformation products depends on the Benchmark Score of the parent chemical (see CPA Guidance 2013).

No environmental transformation products were identified from the literature for ethylene glycol. It is not expected to undergo hydrolysis or direct photolysis as it lacks functional groups susceptible to these reactions (HSDB 2012). Volatilized ethylene glycol can be degraded in the atmosphere via reaction with photochemically-produced hydroxyl radicals. The half-life for this reaction is estimated to be 2 days. Based on its molecular formula, possible combustion products of ethylene glycol are CO and CO_2, which are naturally occurring, ambient substances and not relevant with respect to the GreenScreen® Benchmark score for ethylene glycol.

Introduction

Ethylene glycol is produced through the hydrolysis of ethylene oxide obtained via direct oxidation of ethylene with air or oxygen gas (HSDB 2012). It is manufactured by a number of companies in the United States including Dow Chemical Company, Eastman Chemical Company, DuPont, and Steris Corporation. More than 1 billion pounds of ethylene glycol was produced in 2002. The major uses of ethylene glycol are in antifreeze solutions, including deicing and anti-icing solutions, and in the fiber and polymer industries (HSDB 2012). In 1999, the United States consumed 1.5 million metric tons of ethylene glycol to generate polyester and PET polymers, 0.7 million tons for antifreeze ingredients and 59 thousand metric tons for deicing fluids (OECD 2004).

ToxServices assessed Ethylene Glycol against GreenScreen® Version 1.2 (CPA 2013) following procedures outlined in ToxServices' SOP 1.37 - GreenScreen® Hazard Assessment (ToxServices 2013).

GreenScreen® List Translator Screening Results[6]

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen® benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2013) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. It checks all of the lists in the List Translator with the exception of the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b) and these should be checked separately in conjunction with running the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for ethylene glycol can be found in Appendix C and a summary of the results can be found below:

Ethylene glycol has a High hazard for the following endpoints:

- Developmental toxicity – U.S. National Toxicology Program (NTP), Office of Health Assessment and Translation (OHAaT) - Category A – clear evidence of adverse developmental toxicant effects
- Specific Target Organ Toxicity (Single Dose) –
    - GHS Japan – Category 1 STOT (single dose) toxicant
    - GHS New Zealand – Category 6.9A (oral), Toxic to human organs or systems (equivalent to GHS Category 1 STOT (single dose) toxicant)
- Specific Target Organ Toxicity (Repeated Dose) –
    - GHS Japan – Category 1 STOT (repeated dose) toxicant
    - GHS New Zealand – Category 6.9A (oral), Toxic to human organs or systems (equivalent to GHS Category 1 STOT (repeated dose) toxicant)

[6] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen® benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2013) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.

Ethylene glycol has a Medium hazard for the following endpoints

- Endocrine Activity – TEDX – Potential endocrine disrupter – less than three studies
- Acute mammalian toxicity
    - GHS Hazard Phrase H302 – harmful if swallowed
    - EU Risk Phrase R22 – harmful if swallowed
    - GHS Japan – Category 5 acute toxicity (oral)
    - GHS New Zealand – Category 6.1D (oral), Acutely toxic (equivalent to GHS Category 4 acute toxicant (oral))
    - Quebec Commission de la santé et de la sécurité du travail (CSST) – Workplace Hazardous Materials Information System (WHMIS) – D1B – toxic material causing immediate and serious toxic effects.
- Neurotoxicity –
    - Pattys Toxicology – Boyes Neurotoxicants – Neurotoxic
    - Lancet – Grandjean & Landrigan Neurotoxic Chemicals – Known to be neurotoxic in man
- Eye Irritation –
    - GHS Japan – Category 2B Eye irritant, Serious eye damage/eye irritation
    - GHS New Zealand – Category 6.4A – Irritating to eye (equivalent to GHS Category 2 Eye irritant
- Skin Irritation – GHS Japan – Category 3 skin irritant

Ethylene glycol is listed under U.S. DOT (2008a) as a hazardous substance with a reportable quantity of 5,000 lbs. It is not listed in U.S. DOT (2008b).

PhysioChemical Properties of Ethylene Glycol

The physiochemical properties of ethylene glycol are summarized in Table 1. Ethylene glycol is an organic chemical with chemical formula $C_2H_6O_2$ and a molecular weight of 62.1 g/mol. It is a colorless, nearly odorless liquid at 25 °C with low volatility. It is considered to be miscible with water and has a log K_{OW} value of -1.36. It is not expected to bioaccumulate in biota due to its low lipophilicity.

Table 1: Physical and Chemical Properties of Ethylene Glycol (CAS #107-21-1)

Property	Value	Reference
Molecular formula	$C_2H_6O_2$	OECD 2004
SMILES Notation	C(CO)O	ChemIDplus 2013
Molecular weight	62.1 g/mol	OECD 2004
Physical state	Liquid	OECD 2004
Appearance	Colorless, nearly odorless	ECHA 2013
Melting point	-13 C	EC 2000a, OECD 2004
Vapor pressure	0.1 hPa at 20ºC (DIN 51754)	EC 2000a
Water solubility	100% at 20ºC, Miscible	EC 2000a, OECD 2004
Dissociation constant	Not identified	
Density/specific gravity	1.11 g/cm^3 (DIN 51757),	EC 2000a, OECD 2004
Partition coefficient	Log K_{OW} = -1.36 (measured)	EC 2000a, OECD 2004

Hazard Classification Summary Section

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M or L): L

Ethylene glycol was assigned a score of Low for carcinogenicity based on negative results obtained from three 2-year rodent carcinogenicity bioassays. This chemical would not be classified for carcinogenicity under GHS (UN 2013). This GreenScreen® criteria classify chemicals as a low hazard for carcinogenicity when negative data and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- DePass et al. 1986 –
  - A 24-month carcinogenicity study was performed with CD-1 mice administered oral doses of ethylene glycol (purity 99.93%) of 40, 200, or 1,000 mg/kg/day via the diet. There were no treatment-related effects on mortality, body weight, or diet consumption over the course of the study. There were no biologically significant increases in the incidence of lymphosarcomas, total hepatocellular neoplasms, or hepatocellular adenomas in treated male mice. For females, a decrease in the latency period was observed for lymphosarcomas in the high dose group. However this result was deemed to be equivocal based on significant differences in the latency period for the two control groups. There was no evidence of an increase in any other tumor type in female animals.
  - A 24-month carcinogenicity study was performed with Fischer 344 rats administered oral doses of ethylene glycol (purity >99.93%) of 40, 200, or 1,000 mg/kg/day via the diet. No increased mortality was observed in treated females but all high dose males died by 16 months. These deaths were attributed to oxalate nephritis. Dietary consumption was not altered by ethylene glycol treatment. Water consumption for the high dose males was significantly higher than controls after 365 days but was unaltered for treated female rats. Body weights were significantly reduced in high dose males prior to death. No treatment-related increase in tumors was observed in the study.
- ECHA 2013 –
  - A 103-week, GLP-compliant carcinogenicity study performed according to an NTP-internal standard was performed with B6C3F1 mice administered oral ethylene glycol (purity >99%) at doses of 0, 6,250, 12,500, or 25,000 ppm for males (corresponding to 0, 1,500, 3,000, and 6,000 mg/kg/day respectively) and 0, 12,500, 25,000, or 50,000 ppm for females (corresponding to 0, 3,000, 6,000, and 12,000 mg/kg/day, respectively). Ethylene glycol treatment did not alter survival, mean body weights, or clinical findings, and the incidence of gross lesions in treated animals did not differ from the controls over the course of the study. Males in all treated groups and females at the intermediate and high dose groups had an increased incidence of hepatocellular hyaline degeneration at the 15-month evaluation and cetrilobular hepatocyte hyaline degeneration was increased at the end of the 2-year period in the mid and high dose males and the high-dose females. Transient nephropathy was noted in treated male mice (dose groups not identified) after 15 months. An increased incidence of urethral suppurative inflammation was observed in high-dose males and urinary bladder chronic inflammation was increased in all treated males compared to controls at the end of the study. An increased incidence of medial hyperplasia of the small pulmonary arteries and/or arterioles was observed in the high-dose females during the 15-month evaluation and in females of all treated groups at the 2-year evaluation. Although the severity of this lesion did not increase with dose during the 15-month evaluation, it was considered to be treatment-related based on the dose-related

increase in incidence observed at the 2-year evaluation. No treatment-related neoplasms were identified during the 15-month or 2-year evaluations.

- Based on the weight of evidence, ethylene glycol is not a suspected carcinogen. In three 1-2-year carcinogenicity studies, administration of ethylene glycol to rodents was not associated with an increased incidence of tumors.

Mutagenicity/Genotoxicity (M) Score (H, M or L): L

Ethylene glycol was assigned a score of Low for mutagenicity/genotoxicity based on negative results obtained from *in vitro* and *in vivo* mutagenicity and genotoxicity assays. This chemical would not be classified for mutagenicity/genotoxicity under GHS (UN 2013). GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- EC 2000a –
  - *In vitro*
    - Ethylene glycol (purity not specified) produced negative results in a DNA damage and repair assay conducted with *Escherichia coli* WP2, WP2uvrA, WP67, CM611, WP100, W311polA+, and p3478pola- strains when used at concentrations up to 60,000 µg/plate, with and without metabolic activation.
    - No dose-related increase in the incidence of mutations in a forward gene mutation test in Chinese hamster ovary (CHO) cells were observed after treatment with ethylene glycol at concentrations of 9.1-15.2% (v/v), with or without metabolic activation.
    - Ethylene glycol tested negative in a sister chromatid exchange assay conducted in CHO cells with and without metabolic activation (concentration not specified).
    - Ethylene glycol produced negative results in an unscheduled DNA synthesis assay conducted in rat hepatocytes with and without metabolic activation (concentration not specified).
- ECHA 2013 –
  - *In vitro*
    - Ethylene glycol (purity ≥99.5%) was negative in Ames assays using *Salmonella typhimurium* TA 1535, TA 1537, TA 98 and TA 100 strains when tested at 0, 20, 100, 500, 2500, and 5000 µg/plate, with and without metabolic activation.
    - Ethylene glycol (purity not specified) was not mutagenic towards mouse lymphoma L5178Y cells, at concentrations up to 5,000 µg/ml, with and without metabolic activation.
    - Ethylene glycol (purity 99.979%) produced negative results in a GLP-compliant chromosomal aberration assay performed in Chinese hamster ovary cells when tested at 10-100 mg/ml, with and without metabolic activation.
  - *In vivo*
    - Ethylene glycol (purity 99.93%) did not produce chromosomal aberrations in a dominant lethal assay with Fischer 344 rats administered oral doses of 40, 200, or 1,000 mg/kg/day via the diet.
- Based on the weight of evidence, ethylene glycol is not expected to be a mutagen or genotoxicant. Negative results were obtained in *in vitro* mutagenicity and clastogenicity assays and no induction of chromosome aberrations was observed in an *in vivo* assay.

Reproductive Toxicity (R) Score (H, M, or L): M

Ethylene glycol was assigned a score of Moderate for reproductive toxicity based on the finding of reproductive toxicity in animal studies. This chemical meets the criteria as a Category 2 reproductive toxicant (H361f: Suspected of damaging fertility) under GHS (UN 2013) and therefore meets GreenScreen® criteria as a Moderate hazard for reproductive toxicity(CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Listed by U.S. NIH, NTP-Office of Health Assessment and Translation (OHAaT) as a category F (Some evidence of no adverse reproductive toxicant effects) reproductive toxicant.
  - *Screening:* not listed in any screening lists
- Neeper-Bradley et al. 1995 –
  - A GLP-compliant reproductive study was performed in pregnant CD-1 mice administered oral doses of ethylene glycol ("essentially" 100% purity) of 0, 50, 150, 500, or 1,500 mg/kg/day during GD 6-15. Animals were sacrificed on GD 18. No maternal toxicity resulting from treatment was observed. No differences in the number of implantations per litter, number of corpora lutea, or in the sex ratio based on treatment were observed. Fetal body weights were significantly reduced in the 1,500 mg/kg/day group compared to controls. No treatment-related renal lesions were observed upon histologic examination of the fetuses. No oxalate crystals were observed in kidney sections. A reproductive NOAEL of 1,500 mg/kg/day was established for this study based on no treatment-effects on the number of implantations per litter, number of corpora lutea, or in the sex ratio at the highest dose tested.
- Tyl et al. 1995a –
  - A GLP-compliant reproductive study was performed in pregnant CD-1 mice administered whole-body inhalation doses of ethylene glycol (purity nearly 100%) of 0, 150, 1,000 or 2,500 mg/m^3 (equivalent to 0.0, 0.15, 1.00, and 2.50 mg/L, respectively) for 6 hours/day during GD 6-15. Animals were sacrificed on GD 18. No animals died prior to the scheduled sacrifice. No differences in pregnancy rate were observed across dose. One female in the high dose group had a totally resorbed litter. Reduced maternal body weights and body weight gains were observed in the 1.00 and 2.50 mg/L groups over the course of the study and at sacrifice. Gravid uterine weight was also reduced in the 1.00 and 2.50 mg/L groups compared to controls such that body weights corrected for gravid uterine weight were unaffected by treatment. No changes in maternal absolute or relative liver or kidney weights were observed with treatment. The number of total implantations, numbers of corpora lutea, and percent of pre-implantation loss per pregnant dam were not affected by treatment. At 2.50 mg/L a decrease in the number of viable implantations per litter was observed. A significant increase in late resorptions was observed at 1.00 mg/L and a significant increase in late resorptions and in dead fetuses was observed at 2.5 mg/L. A reproductive LOAEL of 1.00 mg/L was established for this study based on the increase in late resorptions observed at 1.00 mg/L and the decrease in viable implantations observed per litter at 2.50 mg/L.
- EC 2000a –
  - In a reproductive study conducted in mice (strain not specified), were administered oral doses of ethylene glycol (purity not specified) of 250, 750, or 2,500 mg/kg/day via gavage to males and females for 5 days (males) or 7 days (females) prior to cohabitation, for 5 days during cohabitation, and for 7days of pregnancy. After a total exposure of 17 days for males and 19 days for females, the animals were sacrificed and evaluated for the

number of live and dead fetuses and implantation sites (females) and organ weights, testicular histology, and total epididymal sperm counts and motility (males). Reduced embryonic/fetal survival was observed at 2,500 mg/kg/day but there were no effects observed on male or female fertility or on the testes. The reproductive LOAEL was identified as 2,500 mg/kg/day based on reduced embryonic/fetal survival in the high dose group.

- ECHA 2013 –
  - A GLP-compliant reproductive study was performed in pregnant Sprague-Dawley rats administered oral doses of ethylene glycol (99.6% purity) of 0, 250, 1,250, or 2,250 mg/kg/day via gavage on gestational days (GD) 6-20. The treated dams were sacrificed on postnatal day (PND) 1 and the treated pups were reared by untreated females. All remaining animals were sacrificed on PND 22. Maternal body weight and body weight gain were decreased in the 2,250 mg/kg/day group and the gestational period was significantly longer in dams in the 1,250 and 2,250 mg/kg/day groups. On PND 1, the absolute and relative maternal kidney weights and postpartum uterine weights were decreased in the 2,250 mg/kg/day group. An increased incidence of renal pathologies was observed in the mid (4 of 15 animals or 27%) and high-dose (5 of 15 animals or 33%) groups compared to controls (0 of 15 animals or 0%). The live litter size and neonatal body weights of pups were decreased and cumulative mortality of offspring was increased in the high dose group. Treatment had no impact on the development of external genitalia or on the age of incisor eruption. A reproductive LOAEL of 1,250 mg/kg/day was established for this study based on increased gestational periods observed at this and higher doses.
  - A three-generation study was performed with Fischer 344 rats administered oral doses of ethylene glycol (purity 99.93%) of 40, 200, or 1,000 mg/kg/day via the diet. Three generations of matings were produced in this study: the initial parental (F_0), first generation (F_1), and second generation (F_2). Parental body weights and food consumption were not affected by treatment and no mortality was observed for parental rats for any of the three generations mated. The fertility indices and pup weights were not altered by treatment. No treatment-related histopathological findings were noted in the F_2 parents or F_3 weanlings. A reproductive NOAEL of 1,000 mg/kg/day was established for this study.
  - A GLP-compliant, continuous breeding fertility assessment was performed with CD-1 mice administered oral doses ethylene glycol (purity 99.6%) of approximately 0.25, 0.5, or 1% via drinking water (equivalent to 500, 1,000, and 2,000 mg/kg/day, respectively) for 18 weeks. This time period was broken up into treatments for 1 week prior to cohabitation, 14 weeks of cohabitation, and 3 weeks post habitation. Treatment with 1% ethylene glycol caused a significant reduction in the average number of litters, average total litter size, the number of male pups per litter, and the weights of male and female pups. No differences in the proportion of live pups or sex ratio were observed between control animals and those in the 2,000 mg/kg/day group. A significant number of pups from the 2,000 mg/kg/day group had facial deformities including possible cleft lip/palate. Other deformities observed in the high dose group included shortened and sometimes curved frontal and nasal passages, fused pairs of ribs, branched ribs, abnormal centra, and parietals with smaller than the normal width. There were no treatment-related effects on gestation period, pup survival, or water consumption by pups. First generation pups (F1) of the 2,000 mg/kg/day group were reared to adulthood while being continuously exposed to ethylene glycol in the drinking water. When twenty pairs of the F1 pups from

the control and 2,000 mg/kg/day groups were randomly selected and mated, there was a significantly lower mating index (number of copulatory plugs/number of cohabited pairs) for the treated pups compared to the controls (74% compared to 90%) and a significantly lower fertility index (number of fertile pairs/number of cohabited pairs) for the treated pups compared to controls (61% and 80%, respectively). The study authors concluded that ethylene glycol is a "weak reproductive toxicant, but a potential teratogen." A reproductive LOAEL of 2,000 mg/kg/day was established for this study based on reduced mating and fertility indices of the F1 pups in the high dose group.

- A GLP-compliant, 4-week dermal exposure study performed according to OECD 410 was completed with male beagle dogs. Ethylene glycol (purity >92.5%) was applied at 0.5, 2.0, or 8.0 ml/kg/day (equivalent to 550, 2,200, or 8,800 mg/kg/day, respectively) to approximately 60% of the total body surface area after shaving. No treatment-related effects were observed in animals administered 550 mg/kg/day. Histopathological evaluation identified testicular atrophy accompanied by moderate diffuse impairment of spermatogenesis in one animal in the mid dose group. Four of five (80%) of high dose animals died prematurely and these animals were diagnosed with uremic gastroenteritis. Diffuse impairment of spermatogenesis was observed in all high dose animals. Some cases of testicular atrophy were also identified. A NOAEL of 550 mg/kg/day and a LOAEL of 2,200 mg/kg/day were identified based on effects to testicles observed at 2,200 and 8,800 mg/kg/day.
- A GLP-compliant, 4-week dermal exposure study performed according to OECD 410 was completed with male beagle dogs. Ethylene glycol (purity >92.5%) was applied at 0.5, 2.0, or 8.0 ml/kg/day (equivalent to 550, 2,200, or 8,800 mg/kg/day, respectively) to approximately 60% of the total body surface area after shaving. No treatment-related effects were observed in low dose animals. Pathological evaluation identified testicular atrophy accompanied by moderate diffuse impairment of spermatogenesis in one animal in the mid dose group. Four of five (80%) of high dose animals died prematurely and these animals were diagnosed with uremic gastroenteritis. Oxalate nephrosis, consisting of intratubular oxalate crystals and liquefaction foci, and diffuse impairment of spermatogenesis were observed in all the animals in the high dose group. Some cases of testicular atrophy were also identified. A NOAEL of 550 mg/kg/day and a LOAEL of 2,200 mg/kg/day were identified based on effects to the testicles observed at 2,200 and 8,800 mg/kg/day.

- Based on the weight of evidence, ethylene glycol is associated with reproductive toxicity in animal studies. Reproductive toxicity effects included increased number of late resorptions and decreased number of viable implantations per litter, reduced embryonic and fetal survival, increased gestational length, reduced mating and fertility indices, and adverse effects to testicles. Ethylene glycol is considered a moderate hazard for reproductive toxicity.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M or L): H
Ethylene glycol was assigned a score of High for developmental toxicity based on it being designated as a Category A developmental toxicant by NTP. GreenScreen® criteria classify chemicals as a High hazard for developmental toxicity when a U.S. NIH, NTP-OHAaT Category A (Clear evidence of adverse developmental toxicant effects) designation is available for a chemical (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Listed by U.S. NIH, NTP-OHAaT as a Category A (Clear evidence of adverse developmental toxicant effects) developmental toxicant (Pharos 2013).
  - *Screening:* GHS Japan – Category 1B Reproductive toxicant – may damage fertility or

the unborn child.
    - Based on results observed in mouse continuous breeding and rat teratogenicity tests, including malformations, retarded ossification and unossification in offspring at dosing levels not toxic to dams.

- ECHA 2013 –
    - The GLP-compliant reproductive study performed in pregnant Sprague-Dawley rats administered oral doses of ethylene glycol (99.6% purity) of 0, 250, 1,250, or 2,250 mg/kg/day via gavage on gestational days (GD) 6-20 is summarized in the reproductive toxicity section. The live litter size and neonatal body weights of pups were decreased and cumulative mortality of offspring was increased in the high dose group. Treatment had no impact on the development of external genitalia or on the age of incisor eruption. No adverse effects on wire grasping skills, exploratory behavior, or visual discrimination performance were observed based on prenatal ethylene glycol exposure. A significant increase in the incidence of skeletal malformations was observed in the 2,250 mg/kg/day group. Relative kidney weights were reduced in the 1,250 and 2,250 mg/kg/day pups. No treatment-related pathologies were noted after microscopic examination of the kidneys or liver of the treated pups. Maternal and fetal NOAELs of 250 mg/kg/day were identified for this study.
    - A GLP-compliant developmental toxicity study conducted according to an EPA TSCA Testing Guideline was performed with pregnant Sprague-Dawley rats administered oral doses of ethylene glycol (purity >99.9%) of 0, 150, 500, 1,000, or 2,500 mg/kg/day via gavage on gestational days (GD) 6-15. All pregnant females were sacrificed on GD 21 and evaluated for maternal toxicity. Fetuses were evaluated for external and visceral abnormalities. No effect on maternal weight or weight gain was observed over the course of the experiment in animals administered up to 1,000 mg/kg/day. In the 2,500 mg/kg/day, maternal weight gain was significantly reduced over the first three days of treatment (GD 6-9), the entire treatment period (GD 6-15), the period subsequent to treatment (GD 15-18 and 15-21), and over the entire gestational period (GD 0-21) compared to controls. Increased water consumption over the course of treatment was also observed in the high dose group. At sacrifice, terminal body weight and gravid uterine weight were significantly reduced in the 2,500 mg/kg/day group compared to controls. No treatment-related effects were observed on corrected body weight change (gestational weight gain minus gravid uterine weight). Significantly increased maternal kidney and relative kidney weights were observed in the 2,500 mg/kg/day group and increased liver weights were observed in the 1,000 and 2,500 mg/kg/day groups. No renal lesions were observed after microscopic evaluation of the kidneys in 2,500 mg/kg/day group. Fetal body weights per litter were significantly reduced in the 1,000 and 2,500 mg/kg/day groups relative to controls. An increased incidence of gastroschisis (improper closure of the anterior abdominal wall which allows extrusion of the abdominal contents) was observed at the highest dose. In the 2,500 mg/kg/day group, an increased incidence of visceral defects, including umbilical hernia, hydrocephaly, and lateral ventricle dilation with tissue depression were observed. An increased incidence of skeletal malformations involving the thoracic region, including fused thoracic arches, missing thoracic arches and centra, and rudimentary ribs, was also observed in the 2,500 mg/kg/day group. In the 1,000 mg/kg/day group, an increased incidence of missing ribs and missing thoracic arches was observed. When the incidences of malformations were pooled, an increased incidence of skeletal malformations was observed in the 1,000 mg/kg/day group and increased incidences of skeletal, visceral, external and total

malformations were observed in the 2,500 mg/kg/day group. The incidence of fetal atelectasis (collapse of part of or all of a lung) was also increased in the highest dose group, while the incidence of dilated renal pelvis (unilateral or bilateral) was reduced in the 500 and 2,500 mg/kg/day groups. This latter observation was not dose-related so maternal and fetal NOAELs of 500 mg/kg/day were identified for this study.

- The GLP-compliant, continuous breeding fertility assessment performed with CD-1 mice administered oral doses ethylene glycol (purity 99.6%) of 500, 1,000, or 2,000 mg/kg/day for 18 weeks is summarized in the reproductive toxicity section. No maternal toxicity resulting from treatment was observed. Treatment with 2,000 mg/kg/day ethylene glycol caused a significant reduction in the average number of litters, average total litter size, the number of male pups per litter, and the weights of male and female pups. No differences in the proportion of live pups or sex ratio were observed between control animals and those in the 2,000 mg/kg/day dose group. A significant number of pups born from breeding pairs administered the 2,000 mg/kg/day had facial deformities including possible cleft lip/palate. Other deformities observed in the high dose group included shortened and sometimes curved frontal and nasal passages, fused pairs of ribs, branched ribs, abnormal centra, and parietals with smaller than the normal width. There were no treatment-related effects on gestation period, pup survival, or water consumption by pups. The study authors concluded that ethylene glycol is a "weak reproductive toxicant, but a potential teratogen." The developmental NOAEL for this study was 1,000 mg/kg/day based on the increased incidence of deformities observed in the 2,000 mg/kg/day pups.
- A GLP-compliant reproductive study in pregnant CD-1 mice administered oral doses of ethylene glycol (“essentially” 100% purity) of 0, 50, 150, 500, or 1,500 mg/kg/day during GD 6-15is summarized in the reproductive toxicity section. No maternal toxicity resulting from treatment was observed. Fetal body weights were significantly reduced in the 1,500 mg/kg/day group compared to controls. There were no treatment-related differences in the incidence of individual or pooled visceral or external malformations. There was a treatment-associated increase in the incidence of skeletal variations in one or more treatment groups, with 23 variations having a statistically increased incidence in the 1,500 mg/kg/day group. This included poorly ossified or unossified cervical centra, lumbar centra, proximal phalanges, and sternebrae as well as extra ribs. Extra ribs were also observed in the 500 mg/kg/day group. No treatment-related renal lesions were observed upon histologic examination of the fetuses. No oxalate crystals were observed in kidney sections. A maternal NOAEL of 1,500 mg/kg/day was established based on the lack of maternal toxicity observed at the highest dose tested, and a fetal NOAEL of 150 mg/kg/day was established based on the observation of extra ribs in fetuses of dams administered 500 mg/kg/day.
- The Tyl et al. (1995a) reproductive/developmental GLP-compliant reproductive study in pregnant CD-1 mice administered whole-body inhalation doses of ethylene glycol (purity nearly 100%) of 0, 150, 1,000 or 2,500 mg/m^3 (equivalent to 0.0, 0.15, 1.00, and 2.50 mg/L, respectively) for 6 hours/day during GD 6-15is summarized in the reproductive toxicity section. One female in the high dose group had a totally resorbed litter. The number of total implantations, numbers of corpora lutea, and percent of pre-implantation loss per pregnant dam were not affected by treatment. A significant increase in late resorptions was observed at 1.00 mg/L and a significant increase in late resorptions and in dead fetuses was observed at 2.5 mg/L. At both 1.00 and 2.50 mg/L fetal body weights per litter, as male, female, and total, were reduced. A developmental NOAEL of 0.150 mg/L and a LOAEL of 1.00 mg/L were established based on decreased fetal body weights and increased resorptions observed at 1.00 and 2.50 mg/L.

  - A GLP-compliant reproductive study was performed in pregnant CD-1 mice administered dermal doses of ethylene glycol (purity 99.6-100%) of 0, 12.5, 50, or 100% (equivalent to approximately 0, 404, 1,677, or 3,549 mg/kg/day, respectively) on GD 6-15. Animals were sacrificed on GD 18. No treatment-related effects were observed for maternal body weights or weight gain over the course of the study. Maternal terminal body weight, absolute weight gain, liver weights (absolute and relative), and kidney weight (absolute and relative) were also not affected by treatment, but maternal gestational body weight change, the weight change from GD 0-18 minus the gravid uterine weight, was significantly increased in the 3,549 mg/kg/day group. There were no treatment-related differences in the total number of viable or nonviable implantations per litter, in the number of corpora lutea per dam, or on the sex ratio of the offspring. Ethylene glycol treatment did not increase the incidence of any individual or total external malformations. In the 3,549 mg/kg/day group, a statistically significant increase in the incidence of poorly ossified parietal skull bone and unossified intermediate phalanges of the hind limb were observed. Maternal and fetal NOAELs of 1,677 mg/kg/day were established for this study based on increased maternal gestational body weight change and increased skeletal malformations observed at 3,549 mg/kg/day.
  - A GLP-compliant (according to the authors) developmental study was performed in pregnant New Zealand White rabbits administered oral doses of ethylene glycol (purity 98%) of 0, 100, 500, 1,000, or 2,000 mg/kg/day via gavage on GD 6-19. Animals were sacrificed on GD 30. Maternal toxicity was evident at the highest dose as 8 of 17 (42.1%) animals died over the course of the study. Early deliveries and an aborted pregnancy were also observed at this dose. Histologic evaluations demonstrated renal lesions in the 2,000 mg/kg/day group. These lesions were limited to the cortical renal tubules and included intraluminal crystals, epithelial necrosis, and tubular dilatation and degeneration. The most severe findings were observed in those animals that died prior to the end of the study and the cause of death was determined to be renal failure. No other maternal parameters or gestational parameters were altered by ethylene glycol treatment. No embryotoxicity, fetotoxicity, or teratogenicity resulting from ethylene glycol treatment was observed. The maternal NOAEL was 1,000 mg/kg/day based on morbidity and renal lesions at the high dose and the fetal NOAEL was 2,000 mg/kg/day for this study based on the lack of developmental toxicity observed at the highest dose tested.
- Based on the weight of evidence, ethylene glycol is considered to be a developmental toxicant. Developmental toxicity was manifested in animal studies as decreased ossification, extra ribs, and increased incidences of malformations. Ethylene glycol is designated in authoritative (NTP-OHAaT) and screening lists (GHS Japan) as a developmental toxicant. And therefore it is considered to be a high hazard for developmental toxicity.

Endocrine Activity (E) Score (H, M or L): *L*

Ethylene glycol was assigned a score of Low for endocrine disruption based on it being listed as a 3C chemical by the European Commission. Chemicals that have 3C classifications have data available that indicate there is no scientific basis for the chemical's inclusion in the EU's list of endocrine disruptors, which indicates classification of low based on GreenScreen® criteria (CPA 2012a). .

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists.
  - *Screening:* Listed in TEDX as a potential endocrine disrupter – less than three studies.
- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.

- Not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- Ren et al. 1996 –
    - Ethylene glycol was used as a solvent to dissolve and deliver hydrophobic β–estradiol or nonylphenol to rainbow trout. The gene expression of vitellogenin was measured following treatment. Control fish exhibited increases in vitellogenin mRNA levels when exposed to ethylene glycol alone, suggesting that ethylene glycol is a weak estrogen.
        - This study was the basis for the TEDX listing.
        - Vitellogenin is an inducible biomarker of exposure for estrogens and antiestrogens, including endocrine disrupting chemicals, in juvenile and adult fish (Hutchinson et al. 2006).
- EC 2000b –
    - Ethylene glycol is listed as a 3C chemical (data available indicating no scientific basis for inclusion in list of endocrine disrupters) for endocrine disruption.
- Based on the weight of evidence, ToxServices considers ethylene glycol to have a low hazard for endocrine activity. The conclusion of the European Commission is that there is no scientific basis for its inclusion on the list of EU-recognized endocrine disrupters. Although the data generated by Ren et al. (1996) suggests some estrogenic activity by ethylene glycol in fish, the review by the European Commission is more current and was produced by an authoritative body reviewing the state of the literature available for ethylene glycol. Therefore, ToxServices placed more weight on the European Commission's conclusion.

Group II and II* Human Health Effects (Group II and II* Human)

Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

Acute Mammalian Toxicity (AT) Group II Score (vH, H, M or L): M

Ethylene glycol was assigned a score of Moderate for acute toxicity based on the oral LD50 value of 1,650 mg/kg in cats, reports of lethal human doses of 1,000-2,000 mg/kg, the GHS classification in the ESIS database of Acute Tox. 4 (H302 – Harmful if swallowed), and the association with the EU Risk Phrase R22 (Harmful if swallowed). GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when oral LD_{50} values are >300-2,000 mg/kg, when a chemical is associated with EU Risk Phrase R22, or has a GHS classification of Acute Tox. 4 (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Associated with GHS classification Acute Tox. 4 (H302) – Harmful if swallowed (ESIS 2012).
    - *Authoritative:* Associated with EU Risk Phrase R22 – Harmful if swallowed (ESIS 2012)
    - *Screening:* GHS Japan – Category 5 acute toxicity (oral)
        - Based on oral LD_{50} values of 4,000-10,200 mg/kg in rats
    - *Screening*: GHS New Zealand – Category 6.1D (oral), Acutely toxic (equivalent to GHS Category 4 acute toxicant (oral))
    - *Screening*: Quebec Commission de la santé et de la sécurité du travail (CSST) – Workplace Hazardous Materials Information System (WHMIS) – D1B – toxic material causing immediate and serious toxic effects.

- EC 2000a –
  - *Oral* - LD_{50} (rat) = 5,000 mg/kg
  - *Dermal* - LD_{50} (rabbit) = 10,600 mg/kg
- WHO 2002 –
  - *Oral* – LD_{50} (rat) = 4,000-10,020 mg/kg
  - *Oral* – LD_{50} (mice) = 5,500-8,350 mg/kg
  - *Oral* – LD_{50} (guinea pig) = 6,610 mg/kg
  - *Oral* – minimum lethal dose (rat) = 3,800 mg/kg
- HSDB 2012 –
  - *Oral* - LD_{50} (rat) = 4,700 mg/kg
  - *Oral* - LD_{50} (mouse) = 7,500 mg/kg
  - *Oral* - LD_{50} (guinea pig) = 8,200 mg/kg
  - *Oral* - LD_{50} (dog) = 5,500->8,810 mg/kg
  - *Oral* - LD_{50} (cat) = 1,650 mg/kg
  - *Dermal* - LD_{50} (rabbit) = 9,530 mg/kg
  - Lethal doses of 1,000-2,000 mg/kg in humans have been reported for ethylene glycol.
- ECHA 2013 –
  - *Oral* - LD_{50} (Sprague-Dawley rats) = 7,712 mg/kg (as a 30% solution), performed according to BASF internal standards. Animals exhibited clinical signs of depression and narcosis with death resulting from kidney damage.
  - *Inhalation* - LC_{50} (COBS CD (SD)BR rats) >2.5 mg/L for 6 hours ("nearly 100%" purity); determined during a GLP compliant developmental toxicity test using aerosolized ethylene glycol.
  - *Dermal* - LD_{50} (CD-1 mice) >3,500 mg/kg; determined during a GLP compliant developmental toxicity test.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)
Group II Score (single dose)(vH, H, M or L): **vH**
Ethylene glycol was assigned a score of Very High for systemic toxicity (single dose) based on GHS Category 1 classifications for systemic toxicity following single doses. In addition, lethal doses in humans of 1,000-2,000 suggest systemic toxicity at or below this dose range. GreenScreen® criteria classify chemicals as a Very High hazard for systemic toxicity (single dose) when a GHS Category 1 classification for systemic toxicity (single dose) is available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* GHS Japan – Category 1 STOT (single dose) toxicant
    - Based on the human evidence including: "consciousness disorder, convulsions and stupor (after 34 days of accidental ingestion); an increase in urea nitrogen, creatinine and uric acid concentrations (blood examination); albuminuria, hematuria and nephropathy (urine examination); degeneration of convoluted tubules (renal biopsy); mild pulmonary congestion," "acute effects are observed in four stages: effects on the central nervous system (after 0.5-12 hours of exposure); effects on the heart-lung system (after 12-36 hours of exposure); nephropathy in specimens surviving from Stage 1 and 2 (exposure to ethylene glycol); degeneration of the central nervous system"
  - *Screening:* GHS New Zealand – Category 6.9A (oral), Toxic to human organs or systems (equivalent to GHS Category 1 STOT (single dose) toxicant)
- HSDB 2012 –

  - Lethal doses of 1,000-2,000 mg/kg in humans have been reported for ethylene glycol.
  - Pregnant female rats (strain and number not identified) administered oral doses of ethylene glycol at 2,500 mg/kg via gavage developed a clear but mild metabolic acidosis (decreased pH of bodily tissues).
  - In an acute toxicity study, dogs (number not identified) were administered 9.5 mL/kg of ethylene glycol (equivalent to 10,545 mg/kg assuming a density of 1.11 g/cm^3) by oral intubation and were evaluated for up to 72 hours following exposure. After 1-3 hours, the dogs exhibited polydipsia (excessive thirst) and increased urine output, and there was evidence of serum hyperosmolality and metabolic acidosis. After 6 hours, calcium oxalate crystalluria was observed, and decreased renal excretory function was noted after 48 hours.
  - In laboratory animals, ethylene glycol is known to be a protoplasmic and vascular poison and is capable of causing vascular edema and necrosis. Following acute exposures, ethylene glycol causes erythrocyte hemolysis and disrupts the oxidation-reduction processes of homeostasis.
  - Following inhalation exposure to ethylene glycol in humans, tachypnea (rapid breathing), respiratory irritation, and adult respiratory distress syndrome have been reported.
  - In humans, ethylene glycol poisoning manifests itself in three stages: initially as central nervous system effects similar to those caused by ethanol (summarized in the Neurotoxicity section below) and metabolic disturbances characterized by hyperkalemia, hypocalcemia, and acidosis, followed by effects on the heart and lungs, and finally leading to renal toxicity and renal failure.
- ECHA 2013 –
  - In the oral acute study performed in Sprague-Dawley rats (20/dose) that generated an LD_{50} value of 7,712 mg/kg, 0/20, 5/20, 16/20, and 19/20 animals died in the 3,200, 6,400, 8,000, and 10,000 mg/kg groups, respectively. The deaths resulted from kidney damage (no further details provided).
- Based on the weight of evidence, ethylene glycol is considered to be a high hazard for systemic toxicity following single exposure. Lethal human exposures have been reported to be 1,000-2,000 mg/kg, suggesting that systemic toxicity occurs at or below these doses. Ethylene glycol is listed as a GHS Category 1 single dose toxicant by Japan and New Zealand indicating that it is a high hazard following a single dose.

Group II* Score (repeated dose)**(H, M, L): H**

Ethylene glycol was assigned a score of High for systemic toxicity (repeated dose) based on it being classified as a GHS Specific Target Organ Toxicant (STOT) (repeat dose) Category 1 toxicant. GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (repeated dose) when a GHS STOT (repeat dose) Category 1 classification is available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* GHS Japan – Category 1 STOT (repeated dose) toxicant
    - Based on human evidence including "loss of consciousness and nystagmus," "mild headache and backache, upper respiratory tract irritation" (MOE Risk Assessment vol. 3 (2004)), and the evidence from animal studies including "inflammatory degeneration of the lung and heart" (MOE Risk Assessment vol. 3 (2004) The effects on experimental animals were observed at dosing levels within the guidance value ranges for Category 1.

  - *Screening:* GHS New Zealand – Category 6.9A (oral), Toxic to human organs or systems (equivalent to GHS Category 1 STOT (repeated dose) toxicant)
- DePass et al. 1986 –
  - A 24-month carcinogenicity study was performed with CD-1 mice administered oral doses of ethylene glycol (purity 99.93%) of 40, 200, or 1,000 mg/kg/day via the diet. There were no treatment-related effects on mortality, body weight, or diet consumption over the course of the study. An increased frequency of renal tubular degeneration was observed in high dose female mice after 18 months of treatment. This was not considered to be a treatment-related effect since high dose female mice did not exhibit an increased incidence of renal tubular degeneration after 24 months of treatment. Harderian gland lymphoid infiltration was observed in high dose female mice at 24 months but this effect was also observed in control animals. A non-cancer systemic toxicity NOAEL of 1,000 mg/kg/day was identified by ToxServices based on the lack of systemic toxicity observed at the highest dose tested.
  - A 24-month carcinogenicity study was performed with Fischer 344 rats administered oral doses of ethylene glycol (purity >99.93%) of 40, 200, or 1,000 mg/kg/day via the diet. No increased mortality was observed in treated females but all high dose males died within 16 months of treatment. These deaths were attributed to oxalate nephritis. Dietary consumption was not altered by ethylene glycol treatment. Water consumption for the high dose males was significantly higher than controls after 365 days but was unaltered for treated female rats. Body weights were significantly reduced in high dose males prior to death. Transient organ weight changes in the kidneys were observed during the course of the study in male and female rats and transient changes in the liver, heart, brain, and lung weights were observed for males. At 12 months, high dose males had significantly reduced serum glutamic pyruvic transaminase (SGPT) and significantly increased serum creatinine and urea nitrogen. High dose animals also exhibited deleterious hematopoietic effects including significantly decreased hematocrit, red blood cells, hemoglobin, and mean cell volume and a significant increase in neutrophils in males at 12 months, and a significant decrease in mean corpuscular hemoglobin concentrations and a significant increase in mean cell volume at 24 months in females. High dose males had a significant increase in urine volume and calcium oxalate crystals in the urine at 12 months. These animals had calculi of calcium oxalate in the kidney, ureters, and urinary bladders at necropsy. Intermediate dose males displayed a decrease in urine-specific gravity at 24 months of exposure. At 6 months, renal lesions, including tubular cell hyperplasia, peritubular nephritis, and tubular dilation, were observed in high dose male rats. At 12 months, high dose male rats displayed calcium oxalate calculi in urinary bladders and ureters and renal calcium oxalate crystalluria with associated chronic nephritis. At 18 months, no treatment-related pathologies were identified in the low- and mid-dose groups. After 24 months of treatment, mineralization of the seminiferous tubules, pulmonary vessels, and the optic sclerae in males in the low and mid dose groups were deemed to be treatment-related. High dose females had a marked increase in the frequency of fatty metamorphosis of the liver along with an increase in mononuclear cell infiltrates. ToxServices identified a non-cancer systemic toxicity LOAEL of 40 mg/kg/day for ethylene glycol based on the mineralization of the seminiferous tubules, pulmonary vessels, and optic sclerae observed in the low and mid-dose group males.
- Schladt et al. 1998 –
  - A 28-day study performed according to OECD 407 was completed with Wistar rats administered oral doses of 0, 220, 660, or 2,000 mg/kg/day of ethylene glycol (purity

100%) via gavage. Water intake was higher in animals administered ethylene glycol: 16% higher in males and 21% higher in females. Hematological and serum chemistry parameters were either not altered with ethylene glycol treatment or were within historical norms for control animals. In females administered 220 mg/kg/day, urinary pH was significantly increased and osmolarity significantly decreased while the excretion of inorganic calcium, potassium, and phosphate were significantly decreased in males in the 220 mg/kg/day dose group. On day 2, excretion of oxalate was increased in treated males and females (dose groups not identified). The relative kidney weights of treated animals (dose groups not identified) were slightly increased over controls, with males having 14% and females 10% higher values. Histopathology of the kidneys of treated animals (dose groups not specified) identified crystals in the renal pelvis, kidney tubuli, and urinary bladder, and epithelial hyperplasia and tubulopathy in the renal pelvis. A LOAEL was not clearly identified for this study due to the lack of dose groups specified for the histopathological effects.

- Corley et al. 2008
    - A 12-month dietary study performed according to OECD 452 was completed with male Wistar rats administered oral doses of 0, 50, 150, 300, or 400 mg/kg/day of ethylene glycol (purity not defined). Mortality was observed in 5 of 20 (25%) of the animals administered 300 mg/kg/day during days 111-221 and in 4 of 20 (20%) of animals administered 400 mg/kg/day during days 43-193. The animals that died exhibited transitional cell hyperplasia accompanied by inflammation and hemorrhage of the bladder wall. The remaining animals in the 400 mg/kg/day group were euthanized on day 203 due to excessive weight loss. Calculi (calcium oxalate crystals) in the renal pelvis and bladder and crystal nephropathy consisting of birefringent crystals in the pelvic fornix, transitional cell hyperplasia, or basophilic foci, tubule, or pelvic dilation were observed in the 300 and 400 mg/kg/day groups. The oxalate levels increased proportionate to the level of nephrotoxicity at these doses. A NOAEL of 150 mg/kg/day and a LOAEL of 300 mg/kg/day were established based on morbidity and nephrotoxicity observed at 300 mg/kg/day and higher doses.
- HSDB 2012 –
    - A 90-day repeat dose study was performed with Sprague-Dawley rats (10/sex/dose) administered oral doses of ethylene glycol in drinking water. Male rats were provided water containing 0, 0.25, 0.5, 1.0, or 2.0% (equivalent to 0, 346, 693, 1,386, and 2,772 mg/kg/day, respectively[7]) ethylene glycol and female rats were provided water containing 0, 0.5, 1.0, 2.0, or 4.0% (equivalent to 0, 7650, 1,520, 3,039, and 6,078 mg/kg/day, respectively[4]) ethylene glycol. In the high dose groups, mortality was observed for 8/10 females and 2/10 males over the course of the study. Reductions in body weights were observed in both males and females in a dose-dependent manner. In female rats, leukocyte counts were significantly reduced in a dose-dependent manner. Dose-dependent increases in the incidence and severity of renal tubular dilation, degeneration,

[7] The equivalent doses in units of mg/kg/day were not provided by the study authors. They are ToxServices' estimations based on the information provided by the authors and the recommended values for body weight and water consumption for male and female Sprague-Dawley rats in a subchronic study from U.S. EPA (1988)
male body weight = 0.267 kg; female body weight = 0.204 kg; male water consumption = 0.037 L/day; female water consumption = 0.031 L/day
Equivalent dose = dose (ppm or mg ethylene glycol/kg feed) ÷ body weight (kg bw) * water consumption (L/day)
Example for males: 10,000 ppm (1% dose) ÷ 0.267 kg * 0.037 L/day = 1,386 mg/kg/day
Example for females: 10,000 ppm ÷ 0.204 kg * 0.031 L/day = 1,520 mg/kg/day

acute inflammation, and the presence of oxalate crystals. Dilution of the urinary pelvis, hyperplasia of the kidney pelvis epithelium, and granulomatous inflammation in the interstitium were also observed in the kidney. A LOAEL could not be identified due to the lack of data regarding which dose groups exhibited the adverse effects to the kidney.

- ECHA 2013 –
  - A GLP compliant, 90-day study performed according to OECD 408 was completed with male Wistar and Fischer 344 rats (10/strain/dose group) administered oral doses of 50, 150, 500, or 1,000 mg/kg/day of ethylene glycol (purity 99.9%) in the diet. No treatment-related effects were observed in the 50 or 150 mg/kg/day groups. Two of ten Wistar rats (20%) died in the 1,000 mg/kg/day group and displayed emaciation and dermal atonia prior to death. Lower mean body weights and mean cumulative body weight changes were observed in Wistar rats administered the two highest doses. Higher mean water consumption in the Wistar strain was observed after treatment with 500 mg/kg/day while higher mean water consumption in both strains and lower mean food consumption in the Wistar strain were observed in the 1,000 mg/kg/day groups. Calcium oxalate crystals were observed in the urine of both strains at 500 and 1,000 mg/kg/day, and higher mean total urine volume, the presence of white blood cells in urine, and lower mean urine specific gravity were noted in the Wistar strain at 500 mg/kg/day and in both strains at 1,000 mg/kg/day. At 500 and 1,000 mg/kg/day, higher mean absolute and relative (to body weight) kidney weights and crystal nephropathy were observed in both rat strains, with Wistar rats exhibiting more severe nephropathy than the Fischer 344 rats. The differences between the strains were related to the levels of oxalic acid in the blood and kidneys, with the Wistar rats having significantly higher levels than the Fischer 344 rats. A NOAEL of 150 mg/kg/day and LOAEL of 500 mg/kg/day were identified based on effects to the kidney observed at 500 and 1,000 mg/kg/day in both strains.
  - A GLP compliant, 13-week study performed according to an NTP guideline was completed with B6C3F1 mice. The animals were administered oral doses of ethylene glycol (purity >99%) via diets containing concentrations of 0, 3,200, 6,300, 12,500, 25,000, or 50,000 ppm (equivalent to 0, 577, 1,136, 2,255, 4,509, and 9,019 mg/kg/day for males and 624, 1,229, 2,439, 4,878 and 9,756 mg/kg/day for females[8]) ethylene glycol. No mortality was observed over the course of the study. Male mice administered 2,255 or 9,019 mg/kg/day had significantly lower mean body weight gains compared to controls but this observation was not dose-related. No biologically significant alterations in hematology parameters, clinical chemistry parameters, final mean body weights, or absolute or relative organ weights were observed in either sex with treatment. Treatment-related histopathological lesions were observed in the livers and kidneys of male mice in the two highest dose groups. This included hyaline degeneration in centrilobular hepatocytes of the liver. The affected cells contained cytoplasmic accumulations of eosinophilic (hyaline), nonbirefringent, crystalline, or globular material which resembled erythrocytes in shape, size, and tinctorial properties. Nephropathy was also observed and was characterized by several renal tissue alterations including cytoplasmic vacuolation,

[8] The equivalent doses in units of mg/kg/day were not provided by the study authors or ECHA. They are ToxServices' estimations based on the information provided in the REACH dossier (ECHA 2013) and the recommended values for body weight and food consumption for male and female B6C3F1 mice in a subchronic study from U.S. EPA (1988).
male body weight = 0.0316 kg; female body weight = 0.0246 kg; male food intake = 0.0057 kg feed/day; female food intake = 0.0048 kg feed/day
Equivalent dose = dose (ppm or mg ethylene glycol/kg feed) ÷ body weight (kg bw) * food intake (kg feed /day)
Example for males: 50,000 ppm ÷ 0.0316 kg * 0.0057 kg feed/day = 9,019 mg/kg/day
Example for females: 50,000 ppm ÷ 0.0246 kg * 0.0048 kg feed/day = 9,756 mg/kg/day

tubule dilatation, or regenerative hyperplasia of tubule epithelial cell that were randomly distributed, focal, and of minimal to mild severity. No treatment-related lesions were observed in any organs in female animals. The NOAEL values were identified as 2,255 mg/kg/day for males based on histopathological lesions observed in the liver and kidney at the two highest doses and 9,756 mg/kg/day for females based on the lack of toxicity observed in female mice.

- A GLP-compliant, 4-week dermal exposure study performed according to OECD 410 was completed with male beagle dogs. Ethylene glycol (purity >93.4%) was applied at 2.0 or 4.0 ml/kg/day (equivalent to 2,200 mg/kg/day and 4,400 mg/kg/day, respectively[9]) to approximately 60% of the total body surface area after shaving. No treatment-related effects were identified in the 2,200 mg/kg/day group. In the 4,400 mg/kg/day group, calcium oxalate crystals were identified in the urine of 3 of the 4 dogs (75%), with some of the animals showing a positive calcium oxalate reaction upon histopathological evaluation. One animal had several birefringent precipitates in the kidney. No adverse effects on the testicles were observed. The NOAEL for this study was identified as 2,200 mg/kg/day based on effects observed at 4,400 mg/kg/day.
- A second GLP-compliant, 4-week dermal exposure study performed according to OECD 410 was completed with male beagle dogs. Ethylene glycol (purity >92.5%) was applied at 0.5, 2.0, or 8.0 ml/kg/day (equivalent to 550, 2,200, or 8,800 mg/kg/day, respectively) to approximately 60% of the total body surface area after shaving. No treatment-related effects were observed in animals administered 550 mg/kg/day. At 2,200 mg/kg/day, there were single cases of polyuria, increased incidence of round and squamous epithelial cells, and sporadic calcium oxalate crystals. Upon pathological evaluation, testicular atrophy accompanied by moderate diffuse impairment of spermatogenesis was observed in one animal. At 8,800 mg/kg/day, all dogs experienced apathy and/or somnolence, with further signs of toxicity observed in individual animals including weakness of extremities, vomiting, staggering gait, diarrhea, lateral position, reduced feed consumption, and loss of body weight. Four of five (80%) of high dose animals died prematurely and these animals were diagnosed with uremic gastroenteritis. Clinical and chemical observations included increased creatinine and urea levels in plasma and increased calcium oxalate crystals and renal and round epithelial cells in urine. Polyuria and reduced urine specific gravity were also identified upon urinalyses. Oxalate nephrosis, consisting of intratubular oxalate crystals and liquefaction foci, and diffuse impairment of spermatogenesis were observed in all the animals. Some cases of testicular atrophy were also identified. A NOAEL of 550 mg/kg/day and a LOAEL of 2,200 mg/kg/day were identified based on effects to the kidneys and testicles observed at 2,200 and 8,800 mg/kg/day.

- Based on the weight of evidence, ethylene glycol is considered to be a high hazard for systemic toxicity, repated dose. It is classified as a GHS Specific Target Organ Toxicant (STOT) (repeat dose) Category 1 toxicant and animal studies consistently identified adverse effects on the kidneys and testicles of treated animals and a LOAEL of 40 mg/kg/day was identified in a 24-month study in rats.

[9] For the two dermal repeat-dose studies performed in beagle dogs according to OECD 410, the equivalent doses in mg/kg/day were not provided by the study authors or by ECHA. They are ToxServices' estimations based on the 1.11 g/cm^3 density value for ethylene glycol provided by the key study in the REACH dossier (ECHA 2013). A simple multiplication operation provided the equivalent dermal dose.
Example calculation: 4.0 ml/kg/day * 1.11 g/cm^3 * 1,000 mg/g = 4,440 mg/kg/day.

Neurotoxicity (N)

Group II Score (single dose)**(vH, H, M or L): H**

Ethylene glycol was assigned a score of High for neurotoxicity (single dose) based on the adverse neurological effects following acute exposures to ethylene glycol in animal studies and resulting from poisoning events in humans. Based on GHS Guidance (UN 2013), ethylene glycol is a Category 2 Specific Target Organ Toxicity (single dose) chemical due to the severity of adverse effects noted in humans and animals. The GHS classification of ethylene glycol as a Specific Target Organ/Systemic Toxicity (single exposure) Category 1 chemical by Japan supports the high hazard score following single exposures. GreenScreen® criteria classify chemicals as a High hazard for neurotoxicity (single dose) when a chemical is classified as a GHS Category 2 Specific Target Organ Toxicity (single exposure) for neurotoxicity (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* Grandjean & Landrigan 2006 - listed as a developmental neurotoxicant
  - *Screening:* Pattys Toxicology – Boyes Neurotoxicants – Neurotoxic
  - Screening: GHS Japan – Specific Target Organ/Systemic Toxicity (Single exposure) Category 1 chemical
    - Based on the human evidence including: "consciousness disorder, convulsions and stupor (after 34 days of accidental ingestion); "acute effects are observed in four stages: effects on the central nervous system (after 0.5-12 hours of exposure); effects on the heart-lung system (after 12-36 hours of exposure); nephropathy in specimens surviving from Stage 1 and 2 (exposure to ethylene glycol); degeneration of the central nervous system"
- ATSDR 2010 –
  - Adverse neurologic effects are among the first effects to appear in humans after acute oral ingestion of ethylene glycol and are attributed to non-metabolized ethylene glycol.
  - Neurologic symptoms following acute exposure in humans include slurred speech, ataxia, confusion, somnolence, irritation, disorientation, restlessness, unresponsiveness, and semi-consciousness. If untreated, generalized seizures and coma may develop.
  - In a case of ethylene glycol poisoning, deafness, dysphagia (difficulty of swallowing), and dysarthria (difficulty speaking) developed 7 days after exposure and full paralysis occurred 12 days afterwards.
  - Rats administered a single gavage dose of 4,000 mg/kg/ exhibited ataxia and coma prior to death.
  - Abnormal gait, convulsions, loss of reflexes, and central nervous system depression were observed in cats after a single oral gavage dose of 4,440 mg/kg.
  - In dogs, neurotoxic effects following acute exposures to 4,880-10,743 mg/kg in food include convulsions, ataxia, and/or central nervous system depression.
- HSDB 2012 –
  - Ingestion of ethylene glycol can result in central nervous system intoxication resembling that caused by ethanol. This includes drowsiness, ataxia, slurred speech, and possible stupor. Signs of toxicity that arise 48-72 hours following an acute exposure include cerebral edema can be manifested as prolonged seizures, progressive CNS depression, or herniation syndrome. If left untreated, poisoning events can lead to coma, convulsions, and death. Poisoning events have also been associated with Parkinsonism, optic nerve injury, cranial nerve deficits, quadriparesis (muscle weakness in all four limbs), and peripheral neuropathy.
- ECHA 2013 –

  - In the oral acute study performed in Sprague-Dawley rats (20/dose) that generated an LD_{50} value of 7,712 mg/kg, depression and narcosis were observed prior to death.
- Based on the weight of evidence, ethylene glycol is considered to be a high hazard for neurotoxicity following single doses. It is classified as a GHS Category 1 STOT (single exposure) by Japan, due in part to adverse neurological effects observed in cases of acute human exposures. Although adverse effects resulted from very high levels of exposures in humans and animals, GHS guidance notes that a chemical may be classified as a Category 2 Specific Target Organ Toxicant (single dose) based on the nature and severity of the effects following a single exposure. Case studies of human poisoning events indicate that ethylene glycol may cause severe adverse effects to the nervous system, and a Category 2 classification for this endpoint is appropriate to be protective of human health.

Group II* Score (repeated dose)**(H, M, L): L**

Ethylene glycol was assigned a score of Low for neurotoxicity (repeated dose) based on the lack of neurotoxicity or histopathological changes in the nervous system in animal studies evaluating the repeat dose toxicity of ethylene glycol. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when negative studies, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* Grandjean & Landrigan 2006 - listed as a developmental neurotoxicant
  - *Screening:* Pattys Toxicology – Boyes Neurotoxicants – Neurotoxic
- ATSDR 2010 –
  - A 13-week study involving F344 rats administered oral doses of ethylene glycol via the diet demonstrated the formation of calcium oxalate crystals in the brains of males administered 5,000 mg/kg/day, but no significant tissue responses to the crystals or clinical signs of neurotoxicity were observed. No crystals were observed in the brains of males administered 2,500 mg/kg/day or in any treated females.
  - No clinical signs of neurotoxicity or histopathological changes in nervous system tissues resulting from exposures to ethylene glycol were observed in sub-chronic to chronic studies of rats or mice with the following study designs:
    - A 4-week study with Wistar rats administered oral exposures of up to 2,000 mg/kg/day via gavage.
    - A 90-day study with Sprague-Dawley rats administered oral exposures of up to 5,744 mg/kg/day via drinking water.
    - A 16-week with Wistar rats administered oral exposures of up to 1,128 mg/kg/day via the diet.
    - A 1-year study with F344 rats administered oral exposures of up to 1,000 mg/kg/day via the diet
    - A 2-year study with Sprague-Dawley rats administered oral doses of up to 3,000 mg/kg/day via the diet.
    - A 13-week study with B6C3F1 mice administered oral doses of up to 16,000 mg/kg/day via the diet.
    - A 2-year study with B6C3F1 mice administered oral doses of up to 12,000 mg/kg/day via the diet.
    - A 2-year study with CD-1 mice administered oral doses of up to 1,000 mg/kg/day via the diet.

    - In a 10-day study, Sprague-Dawley rats were administered oral doses of ethylene glycol at up to 7,327 mg/kg/day via drinking water. No adverse effects on the histopathology of brain and sciatic nerve were observed with treatment.
- Based on the weight of evidence, ethylene glycol is not considered a neurotoxicant following repeat doses. Numerous studies with exposures lasting between 4 weeks and 2 years did not produce adverse neurological effects in rodents following oral doses to ethylene glycol. The basis for it being on the screening lists as a neurotoxicant is not known.

Skin Sensitization (SnS) Group II* Score (H, M or L): L
Ethylene glycol was assigned a score of Low for skin sensitization based on a low incidence of allergic skin reactions in a human volunteer patch test and negative results obtained in a guinea pig repeated insult test. Based on the results from these studies, ethylene glycol would not be classified for skin sensitization under GHS (UN 2013). GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when negative studies, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* not listed in any authoritative lists
    - *Screening:* not listed in any screening lists
- Hannuksela et al. 1975 –
    - Ethylene glycol produced allergic skin reactions in 15 out of 1556 (1%) dermatitis patients in a closed patch test and was deemed to be non-sensitizing (no further details provided).
- Hindson and Ratcliffe 1975, Dawson 1976 –
    - Allergic dermatitis developed in two workers using aqueous solutions of 25 or 33% ethylene glycol for 3-4 months. Sensitization was confirmed via positive reactions in 48-hour closed patch test following application of 3% ethylene glycol in ethanol or 5% ethylene glycol in water. The individual that developed a positive reaction towards the 3% solution in ethanol did not react to the 5% aqueous solution, suggesting that ethylene glycol may not be the allergen triggering the dermatitis in this individual.
- Kurihara et al. 1996 –
    - A Magnusson and Kligman guinea pig maximization test was performed with two guinea pigs administered induction and challenge doses via 0.2% by weight ethylene glycol solution dissolved in olive oil and acetone (7:3 v/v). No positive sensitization responses were observed in this study.
- Based on the weight of evidence, ethylene glycol is not considered a dermal sensitizer. Negative data are available from a guinea pig maximization test and only 1% of dermatitis patients produced a positive reaction towards ethylene glycol in a closed patch test. The results of two cases of allergic dermatitis in workers are inconsistent. Therefore, ethylene glycol has a low potential for dermal sensitization.

Respiratory Sensitization (SnR) Group II* Score (H, M or L): DG
Ethylene glycol was assigned a data gap for respiratory sensitization based on no data identified for respiratory sensitization by ethylene glycol or its surrogate propylene glycol.

- Authoritative and Screening Lists
    - *Authoritative:* not listed in any authoritative lists
    - *Screening:* not listed in any screening lists
- No respiratory sensitization data were identified for ethylene glycol or its surrogate propylene glycol.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M or L): M

Ethylene glycol was assigned a score of Moderate for skin irritation/corrosivity based on evidence of slight to moderate irritation in animal studies. Insufficient data is available to categorize this chemical for skin irritation/corrosivity under GHS (UN 2013GreenScreen® criteria classify chemicals as a Moderate hazard for skin irritation/corrosivity based on mild to moderate irritation in animal studies and a GHS Category 3 classification by Japan (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* GHS Japan – Category 3 skin irritant
- Clark et al. 1979 –
  - New Zealand white rabbits (sex and number not identified) were administered 0.5 mL (550 mg total) ethylene glycol to shaved skin. Minimal skin irritation was observed 24-72 hours after treatment.
- Tyl 1988, Tyl et al. 1995b –
  - During a developmental toxicity study, pregnant female mice were administered occluded dermal doses of ethylene glycol at 3,549 mg/kg/day for 6 hours/day on gestational days 6-15. No dermal effects were observed following dermal treatment with ethylene glycol.
- TKL Research 1989 –
  - In a human exposure test (no details on study design available), a human skin primary irritation index of 53.9/300 was determined for ethylene glycol. Primary irritation indices are scored as follows: 0 = no irritation; >0-10 = no clinically significant irritation; >10-50 = minimal irritation, >50 = evidence of irritation. A primary irritation index of 53.9, therefore, indicates evidence of dermal irritation to human skin by ethylene glycol.
- EC 2000a –
  - In three separate Draize tests, ethylene glycol was moderately irritating (purity not specified), slightly irritating (>99% purity), and slightly irritating (>99% purity) when applied to the skin of rabbits.
  - Ethylene glycol was slightly irritating to the skin when applied to rabbits during two patch tests, one of which used undiluted ethylene glycol (no purity information was provided for the other patch test). A 10% aqueous solution of ethylene glycol was not irritating.
  - Ethylene glycol was applied to the skin of human volunteers in a patch test as a 3% solution in ethanol or as a 5% solution in water. The 3% solution induced weak irritation reactions and the 5% solution produced no reactions.
  - Ethylene glycol did not produce significant irritant effects on the skin when applied to human volunteers. Slight maceration (softening) of the skin similar to that observed following application of glycerin to the skin was observed following prolonged exposures to ethylene glycol.
- ECHA 2013 –
  - When ethylene glycol (purity not specified) was applied to the skin of rabbits in a test performed according to BASF internal standards, no irritation effects were observed.
- Based on the weight of evidence, ethylene glycol appears to be a mild skin irritant. In humans, ethylene glycol produced no to slight irritation. The weight of evidence indicates that ethylene glycol is a mild irritant corresponding to a moderate hazard under GreenScreen® criteria and this is supported by the GHS Category 3 classification by Japan.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M or L): M

Ethylene glycol was assigned a score of Moderate for eye irritation/corrosivity based on findings of ocular irritation that resolved within 7 days of treatment. This classification is supported by GHS Japan's designation of ethylene glycol as a Category 2B eye irritant. GreenScreen® criteria classify chemicals as a Moderate hazard for eye irritation/corrosivity when a Category 2B eye irritation GHS classification is available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* GHS Japan – Category 2B Eye irritant, Serious eye damage/eye irritation
  - *Screening:* GHS New Zealand – Category 6.4A – Irritating to eye (equivalent to GHS Category 2 Eye irritant)
- Coon et al. 1970 –
  - Moderate to severe ocular irritation was observed in rats and rabbits administered continuous inhalation doses of ethylene glycol at 12 mg/m^3 (equivalent to 0.012 mg/L) for 90 days. The effects in rabbits included erythema, edema, and discharge, and the effects in rabbits included corneal opacity and apparent blindness in 2 of 15 (13%) of the animals.
  - However, no ocular irritation was observed in a separate study where rats and rabbits (strain, sex, and number not provided) were administered inhalation doses of ethylene glycol at 57 mg/m^3 (equivalent to 0.057 mg/L) for 8 hours/day, 5 days/week, for 6 weeks.
- McDonald et al. 1972 –
  - New Zealand White rabbits (6 animals total) had ethylene glycol solutions of 0, 0.03, 0.4, 4, or 40% applied to the eyes. The treatments lasted for 10-minute intervals for a total of 36 applications over a 6-hour period. 0.4% ethylene glycol was the highest concentration that was non-irritating. In the 4 and 40% treatment groups, chemosis, swelling, and conjunctival redness was observed following treatment. All signs of ocular irritation resolved within 7 days.
- Guillot et al. 1982 –
  - In a rabbit exposure test (no details on study design available), a rabbit acute ocular irritation score of 11.3/110 was determined for ethylene glycol, indicating minor eye irritation resulting from treatment with ethylene glycol. No further details provided.
- EC 2000a –
  - Ethylene glycol was non-irritating to moderately irritating to the eyes when applied to rabbits during a Draize test (purity not reported).
  - Ethylene glycol caused slight edema and erythema when applied to the eyes of rabbits at 10%, 20%, or 50% solutions but produced moderate to severe edema and erythema which were observed 48 hours post-treatment when applied undiluted.
  - A single application of 0.5 ml 80% ethylene glycol was not irritating to the eyes of rabbits. The maximum non-irritating concentration of ethylene glycol when applied for five times per day for 21 consecutive days was 20%.
  - No ocular irritation was observed when guinea pigs were continuously exposed to ethylene glycol at a concentration of 12.6 mg/m^3 for 47 days.
- ECHA 2013 –
  - When 0.05 mL of undiluted ethylene glycol was applied to the eyes of Vienna White rabbits in a test performed according to BASF internal standards, no irritation effects were observed 1 hour or 24 hours after installation of the compound.
- Based on the weight of evidence, ethylene glycol appears to be mildly irritating to eyes. One study in rats and rabbits indicated moderate to severe irritation, however these results could not

be duplicated. All of the other studies resulted in no or mild irritation and the GHS classification to Category 2B supports a hazard score of moderate.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M or L): L

Ethylene glycol was assigned a score of Low for acute aquatic toxicity based on the L/EC_{50} values being >100 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when acute aquatic toxicity values are >100 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- EC 2000a -
  - 24-hr LC_{50} (*Artemia salin*a, brine shrimp) > 20,000 mg/L.
  - 48-hr LC_{50} (*Ceriodaphnia* sp.) = 13,900 mg/L, a GLP-compliant, ASTM static test.
  - 48-hr LC_{50} (*Daphnia magna*) = 46,300 mg/L, performed according to ASTM Standard E 729-80.
  - 96-hr LC_{50} (*Lepomis macrochirus*, bluegill) >10,000 mg/L
  - 96-hr LC_{50} (*Oncorhynchus myskiss*, rainbow trout) = 40,761 mg/L, performed according to a U.S. EPA test method
  - 96-hr LC_{50} (*Pimephales promelas*, fathead minnow) = 53,000 mg/L for fries, 49,000 mg/L for juveniles, and 57,000 mg/L for sub-adult fish, performed according to an ASTM.
- WHO 2000 –
  - 96-hr LC_{50} (*Oncorhynchus myskiss*, rainbow trout) > 18,500 mg/L
  - 96-hr LC_{50} (*Oncorhynchus myskiss*, rainbow trout) = 17,800-45,600 mg/L
  - 96-hr LC_{50} (*Lepomis macrochirus*, bluegill) >111,300 mg/L
  - 96-hr LC_{50} (*Lepomis macrochirus*, bluegill) = 27,540 mg/L
  - 96-hr LC_{50} (*Pimephales promelas*, fathead minnow) >10,000 mg/L
  - 96-hr LC_{50} (*Pimephales promelas*, fathead minnow) = 49,000-57,000 mg/L
  - 96-hr LC_{50} (*Pimephales promelas*, fathead minnow) = 72,860 mg/L
  - 48-hr immobilization EC_{50} (*Daphnia magna*) >10,000 mg/L
  - 48-hr immobilization EC_{50} (*Daphnia magna*) = 50,000 mg/L
  - 48-hr immobilization EC_{50} (*Daphnia magna*) = 41,000-51,000 mg/L
  - 48-hr immobilization EC_{50} (*Daphnia magna*) = 74,400 mg/L
  - 48-hr immobilization EC_{50} (*Daphnia magna*) = 14,828 mg/L (based on ethylene glycol content of a deicer solution)
  - 96-hr growth EC_{50} (*Selenastrum capricornutum*, green algae) = 6,500-7,500 mg/L
  - 96-hr growth EC_{50} (*Selenastrum capricornutum*, green algae) = 9,500 -13,000 mg/L
- OECD 2004 –
  - 48-hr LC_{50} (*Daphnia magna*) = 46,300 mg/L
  - 48-hr LC_{50} (*C. dubia*) = 10,000 mg/L
  - 96-hr LC_{50} (*Oncorhynchus mykiss*, rainbow trout) = 22,810 mg/L
  - 96-hr LC_{50} (*Pimephales promelas*, fathead minnow) = 49,000-57,000 mg/L
- ECHA 2013 –
  - 96-hr growth rate EC_{50} (*Pseudokirchnerella subcapitata*, microalgae) = 6,500-13,000 mg/L, performed according to EPA 60/9-78-018.

- 48-hr immobilization EC_{50} (*Daphnia magna*) >100 mg/L, GLP-compliant and performed according to OECD 202

Chronic Aquatic Toxicity (CA) Score (vH, H, M or L): L
Ethylene glycol was assigned a score of Low for chronic aquatic toxicity based on chronic toxicity values greater than 8,000 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity values are >10 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- WHO 2000 –
  - 7-day mortality NOEC (*Pimephales promelas*, fathead minnow) = 32,000 mg/L
  - 7-day growth NOEC (*Pimephales promelas*, fathead minnow) = 15,380 mg/L
- OECD 2004 –
  - 7-day LC_{50} (guppy) = 49,000 mg/L
  - 7-day reproduction IC_{25} (*Ceriodaphnia dubia*) = 9,226 mg/L
  - 7-day reproduction IC_{50} (*Ceriodaphnia dubia*) = 16,315 mg/L
- ECHA 2013 –
  - 7-day reproduction NOEC (Ceriodaphnia sp.) = 8,590 mg/L, performed according to EPA 600/4-90/027.
  - 7-day NOEC (endpoint not specified) (*Pimephales promelas*, fathead minnow) = 15,380 mg/L

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): vL
Ethylene glycol was assigned a score of Very Low for persistence based on it being able to meet the 10-day window for biodegradation in tests using standardized protocols. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when a chemical meets the 10-day window for biodegradation (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- EC 2000a–
  - A GLP-compliant biodegradation test performed 100 mg/L according to OECD 301 C "Ready Biodegradability: Modified MITI Test" produced 56% biodegradation for ethylene glycol after 28 hours.
  - A biodegradation test performed with activated sludge according to a protocol in EPA guidelines (1980) Standard Methods for the Examination of Water and Wastewater, 15th edition, produced 60% biodegradation after 5 days, 82% biodegradation after 10 days, and 89% biodegradation after 20 days.
  - A second biodegradation test performed with activated sludge according to a protocol in EPA guidelines (1980) Standard Methods for the Examination of Water and Wastewater, 15th edition, produced 78% biodegradation after 10 days and 97% biodegradation after 20 days.
- WHO 2000 –

  - A biodegradation test performed with an acclimated sewage sludge inoculum and equivalent ethylene glycol concentration of 20 mg carbon/liter produced no significant biodegradation until day 14 of the test but 71% degradation was achieved by day 21.
  - Adapted activated sewage sludge achieved 96.8% biodegradation of ethylene glycol after 120 hours based on chemical oxygen demand (COD) measurements and an initial COD of 200 mg/L.
  - Greater than 90% degradation for ethylene glycol was achieved after 4 days in a batch biodegradability study.
  - After 5 days 63% degradation as biological oxygen demand (BOD) was achieved when ethylene glycol was incubated with previously adapted sludge.
  - Using a domestic sewage sludge inoculum, 39%, 73%, and 96% of the theoretical BOD for ethylene glycol was achieved after 5, 10, and 20 days, respectively.
  - In one study using a municipal sewage sludge inoculum, only 5.7% degradation of ethylene glycol at 0.05mg/L was reported after 5 days.
  - A biodegradation half-life between 11.5-21.5 hours was determined using primary sewage treatment effluent as the inoculum. An initial lag period of 3 days was observed for the biodegradation.
- OECD 2004 –
  - A biodegradation test performed according to OECD 301 D "Ready Biodegradability: Closed Bottle Test" produced 96% biodegradation after 28 days.
- ECHA 2013 –
  - A GLP-compliant biodegradation test performed according to OECD 301 A "Ready Biodegradability: DOC Die Away Test" produced 7% biodegradation after 1 day, 14% biodegradation after 3 days, 93% biodegradation after 5 days, and 100% biodegradation after 7 days for ethylene glycol (93% purity used).

Bioaccumulation (B) Score (vH, H, M, L, or vL): L

Ethylene glycol was assigned a score of Low for bioaccumulation based on measured bioconcentration factors of up to 200. GreenScreen® criteria classify chemicals as a Low hazard for bioaccumulation when bioaccumulation values are >100 but <500 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- EC 2000a –
  - A bioconcentration factor (BCF) of 200 was observed after activated sludge was exposed to 50 µg/L ethylene glycol for 5 days.
  - A BCF of 190 was observed after *Chorella fusca* (green algae) were exposed to 50 µg/L ethylene glycol for 1 day.
  - BCF values of 0.21-0.60 were obtained in the gills, muscle, hepatopancreas, and gastrointestinal tract of crayfish (*Procambarus* sp.) exposed to 1,000 mg/L ethylene glycol for 61 days.
  - A BCF of 10 was observed after *Leuciscus idus melanotus* (golden ide, fish) were exposed to 50 µg/L ethylene glycol for 3 days.
  - A measured logK_{OW} of -1.36 suggests a low potential for bioaccumulation by ethylene glycol.
- WHO 2000 –
  - A BCF of 10 was obtained after ethylene glycol exposure to the golden orfe (*Leuciscus idus melanotus*).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M or L): L
Ethylene glycol was assigned a score of Low for reactivity based on not having any chemicals or functional groups expected to contain high energy bonds or oxidizing species which may cause reactivity. This chemical would not be classified for reactivity under GHS (UN 2013). GreenScreen® criteria classify chemicals as a Low hazard for reactivity when it does not have a GHS classification (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- EC 2000a –
  - Ethylene glycol was considered to not be explosive based on an experiment conducted according to EC Directive 92/69/EEC, A.14. However, in the presence of an exposed flame it poses a moderate explosion hazard.
  - Ethylene glycol does not exhibit oxidizing properties

Flammability (F) Score (vH, H, M or L): L
Ethylene glycol was assigned a score of Low for flammability based on it having a flash point exceeding 93°C. This temperature exceeds the upper limit for a liquid to be considered flammable under GHS (UN 2013). GreenScreen® criteria classify chemicals as a Low hazard for flammability when a chemical is not classified as flammable under GHS (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* not listed in any authoritative lists
  - *Screening:* not listed in any screening lists
- EC 2000a –
  - Ethylene glycol has a flash point of 111°C from an experiment conducted according to DIN 51758. This value exceeds the 93°C cut-off criteria to be classified as a flammable liquid by GHS (UN 2013).
- ECHA 2013 –
  - Ethylene glycol has an autoflammability/self-ignition temperature of 398 ºC.

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APPENDIX A: Hazard Benchmark Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(Cr) Corrosion/ Irritation (Skin/ Eye)

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Ethylene Glycol (CAS #107-21-1)

GreenScreen™ Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
									S	R *	S	R *	*	*								
Table 2: Chemical Details																						
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	Ethylene Glycol	107-21-1	L	L	M	H	*L*	M	vH	H	H	L	L	DG	M	M	L	L	vL	L	L	L

Table 3a: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	Yes		
2	STOP						
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen™ Benchmark Score
Ethylene Glycol	1

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

Chemical Name	Final GreenScreen™ Benchmark Score
Ethylene Glycol	1

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												1
2												
3												
4												

APPENDIX C: Pharos Output for Ethylene Glycol (CAS #107-21-1)

ETHYLENE GLYCOL

CAS RN: 107-21-1

Direct Chemical and Compound Hazard Quickscreen — Detailed Hazard Listings

High Hazard of...

DEVELOPMENTAL	US NIH - Reproductive & Developmental Monographs (NTP-OHAaT): A-Clear evidence of adverse developmental toxicant effects - GreenScreen Benchmark 1
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan): Specific target organs/systemic toxicity following repeated exposure - Category 1 - GreenScreen Benchmark Unspecified {and 7 others}
ORGAN TOXICANT	New Zealand HSNO/GHS (GHS-New Zealand): 6.9A (oral) - Toxic to human target organs or systems - GreenScreen Benchmark Unspecified

Medium Hazard of...

ENDOCRINE	TEDX - Potential Endocrine Disruptors (TEDX): Potential Endocrine Disruptor - less than three studies - GreenScreen Possible Benchmark 1
NEUROTOXICITY	Pattys Toxicology - Boyes Neurotoxicants (Boyes-N): Neurotoxic - GreenScreen Benchmark Unspecified {and 1 other}
EYE IRRITATION	New Zealand HSNO/GHS (GHS-New Zealand): 6.4A - Irritating to the eye - GreenScreen Benchmark Unspecified {and 1 other}
SKIN IRRITATION	Japan METI/MOE - GHS Classifications (GHS-Japan): Skin corrosion / irritation - Category 3 - GreenScreen Benchmark Unspecified
TERRESTRIAL	New Zealand HSNO/GHS (GHS-New Zealand): 9.3C - Harmful to terrestrial vertebrates - Not evaluated by GreenScreen

Low Hazard of...

REPRODUCTIVE	US NIH - Reproductive & Developmental Monographs (NTP-OHAaT): F-Some evidence of no adverse reproductive toxicant effects - GreenScreen Benchmark Unspecified
RESTRICTED LIST	German FEA - Substances Hazardous to Waters (VwVwS): Class 1 Low Hazard to Waters - GreenScreen Benchmark Unspecified - occupational hazard only {and 1 other}

This chemical is NOT present on the hazard lists scanned for the following health and ecotoxicity endpoints...

PBT	CANCER	GENE MUTATION	RESPIRATORY	SKIN SENSITIZE
ACUTE AQUATIC	CHRON AQUATIC	FLAMMABLE	REACTIVE	GLOBAL WARMING
OZONE DEPLETION				

Lifecycle Hazard Quickscreen

Full Lifecycle Map

Research Status: Preliminary literature review drafted
The Pharos team has undertaken a preliminary literature review of some of the processes involved in the manufacture of this substance and identified the following chemicals. This list of chemicals is not exhaustive of all chemicals that may be involved in the production or life cycle of this substance.

May contain residual manufacturing chemicals that have a hazard of...

Comes from additional manufacturing chemicals that have a hazard of...

CANCER	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
DEVELOPMENTAL	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
REPRODUCTIVE	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
ENDOCRINE	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
GENE MUTATION	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
RESPIRATORY	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
NEUROTOXICITY	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
MAMMALIAN	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
EYE IRRITATION	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
SKIN IRRITATION	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
SKIN SENSITIZE	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
ORGAN TOXICANT	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
ACUTE AQUATIC	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
TERRESTRIAL	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
FLAMMABLE	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
REACTIVE	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock
RESTRICTED LIST	ETHYLENE OXIDE [75-21-8] - Frequent Feedstock

Description: "Approximately 35% of all ethylene glycol produced is used to make PET solid-state resins, 26% is used in antifreeze, 24% is used to make polyester fibers, 4% is used to make polyester film, 3% is used in PET chip resin exports, and 8% is used in surface coatings, polyester and alkyd resins, chemical intermediates, and other miscellaneous industrial applications (CMR 2004)." (From ATSDR Toxicological Profile)

VOC designation: VOC (Boiling point: 197 degrees Celsius)

More Information: http://www.atsdr.cdc.gov/toxprofiles/tp96.pdf

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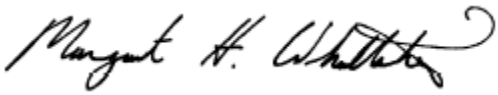

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