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DIETHYLENE GLYCOL

(CAS #111-46-6)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: September 27, 2019[a]

Expiration Date: September 27, 2024

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[a] ToxServices incorporated January 2020 comments submitted by the Washington State Department of Ecology into this document.

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GreenScreen® Executive Summary for Diethylene Glycol (CAS #111-46-6)

Diethylene glycol is a non-flammable, viscous liquid at room temperature that is not expected to be significantly volatile. Diethylene glycol is a chemical with industrial and household applications as well as cosmetic applications. However, almost all diethylene glycol produced is used by the industry sector. Diethylene glycol is mainly used as a chemical intermediate to produce polyurethanes (27% of total consumption in the U.S.), unsaturated polyester resins (27%), triethylene glycol and tetraethylene glycol (13%) and morpholine, lubricants and explosives (9%). It is also used as an antifreeze agent (13%), solvent for cleaning polyester filters (11%), in separating aromatic and paraffinic hydrocarbons, and in printing inks, paint pigments and dyes, a plasticizer intermediate for nitrocellulose lacquers, enamels and adhesives, and a plasticizer for paper, composition cork, glues and adhesives. Typical use levels or use ranges as a solvent could not be identified. Diethylene glycol has been reported as an impurity in glycerol and polyethylene glycols. It is prohibited in personal care products in the EU and limited to 0.1% as an impurity at the product level. Diethylene glycol is produced commercially as a by-product of ethylene glycol production, and it can be produced by reaction between ethylene glycol and ethylene oxide.

Diethylene glycol was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2e
  - Moderate Group I Human Toxicity (reproductive-R and developmental-D)
- Benchmark 2f
  - Very High Group II Human Toxicity (systemic toxicity (single dose)-STs and neurotoxicity (single dose)-Ns)
  - High Group II* Human Toxicity (systemic toxicity (repeated dose)-STr* and neurotoxicity (repeated dose)-Nr*)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), diethylene glycol meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if diethylene glycol were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

GreenScreen® Hazard Summary Table for Diethylene 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	repeat*	single	repeat*										
L	**L**	*M*	*M*	DG	**M**	**vH**	**H**	*vH*	*H*	**L**	*L*	*M*	**L**	**L**	**L**	**L**	**vL**	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. 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. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

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GreenScreen® Chemical Assessment for Diethylene Glycol (CAS #111-46-6)

Method Version: GreenScreen® Version 1.4
Assessment Type[1]: Certified
Assessor Type: Licensed GreenScreen® Profiler

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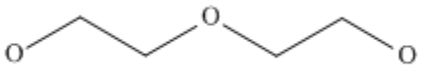
Date: September 27, 2019

Expiration Date: September 27, 2024[2]

Chemical Name: Diethylene glycol

CAS Number: 111-46-6

Chemical Structure(s):



Also called:
1,5-Dihydroxy-3-oxapentane; 2,2'-Dihydroxydiethyl ether; 2,2'-Dihydroxyethyl ether; 2,2'-Oxybisethanol; 2,2'-Oxydiethanol; 2,2'-Oxyethanol; 2-(2-Hydroxyethoxy)ethanol; 3-Oxapentamethylene-1,5-diol; 3-Oxapentane-1,5-diol; beta,beta'-Dihydroxydiethyl ether; Bis(2-hydroxyethyl) ether; Bis(beta-hydroxyethyl) ether; Brecolane ndg; Deactivator E; DEG; Dicol; Digenos; Diglycol; Digol; Dihydroxydiethyl ether; Dissolvant APV; EINECS 203-872-2; Ethanol, 2,2'-oxybis-; Ethanol, 2,2'-oxydi; Ethylene diglycol; Glycol ether; Glycol ethyl ether (ChemIDplus 2019).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
A complete dataset was available for diethylene glycol. However, a data gap exists for chronic aquatic toxicity. Therefore, data for members of the "ethylene glycol and higher glycols" category, including ethylene glycol (CAS #107-21-1) and triethylene glycol (CAS #112-27-6), were used as read-across to fill the data gap for this endpoint. These chemicals are included in the ECHA REACH dossier as key

[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment expires three years from the date of completion if completed before January 1, 2019 (CPA 2018a).

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read-across chemicals (ECHA 2019a). They differ from the target chemical by having one fewer or more unit of ethylene oxide.

Ethylene Glycol (CAS #107-21-1)

Triethylene Glycol (CAS #112-27-6)

Identify Applications/Functional Uses: (HSDB 2009)
1. Production of polyurethane and unsaturated polyester resins as well as triethylene glycol
2. Fabric softener
3. Petroleum solvent extraction
4. Dehydrate natural gas, plasticizers, and surfactants
5. Solvent for nitrocellulose, dyes, and oils
6. Humectant for tobacco, casein, synthetic sponges, and paper products
7. Cork composition and book binding adhesives
8. Dyeing assistant
9. Cosmetic and antifreeze solutions

Known Impurities[3]:
Common impurities include ethylene glycol (CAS #107-21-1) and triethylene glycol (CAS #112-27-6) (UNEP 2007). The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for Diethylene Glycol[4,5,6,7]: Diethylene glycol was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 2e
  - Moderate Group I Human Toxicity (reproductive-R and developmental-D).
- Benchmark 2f
  - Very High Group II Human Toxicity (systemic toxicity (single dose)-STs and neurotoxicity (single dose)-Ns).

[3] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[4] 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.
[5] See Appendix A for a glossary of hazard endpoint acronyms.
[6] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[7] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen® Guidance v1.4 Annex 2.

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- High Group II* Human Toxicity (systemic toxicity (repeated dose)-STr* and neurotoxicity (repeated dose)-Nr*).

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), diethylene glycol meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if diethylene glycol were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for Diethylene 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	repeat*	single	repeat*										
L	**L**	*M*	*M*	DG	**M**	**vH**	**H**	*vH*	*H*	**L**	*L*	*M*	**L**	**L**	**L**	**L**	**vL**	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. 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. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

Environmental Transformation Products

No transformation products were identified for diethylene glycol. As diethylene glycol is rapidly biodegradable (see persistence section below), no relevant environmental transformation products are expected to be formed as any products are not expected to persist in the environment.

Introduction

Diethylene glycol is a chemical with industrial and household applications as well as cosmetic applications (NICNAS 2013). However, almost all diethylene glycol produced is used by the industry sector. Diethylene glycol is mainly used as a chemical intermediate to produce polyurethanes (27% of total consumption in the U.S.), unsaturated polyester resins (27%), triethylene glycol and tetraethylene glycol (13%) and morpholine, lubricants and explosives (9%). It is also used as an antifreeze agent (13%), solvent for cleaning polyester filters (11%), in separating aromatic and paraffinic hydrocarbons, and in printing inks, paint pigments and dyes, a plasticizer intermediate for nitrocellulose lacquers, enamels and adhesives, and a plasticizer for paper, composition cork, glues and adhesives (UNEP 2004, MEGlobal 2005). Diethylene glycol has been reported as an impurity in glycerol and polyethylene glycols (SCCP 2008). It is prohibited in personal care products in the EU and limited to 0.1% as an impurity at the product level (EC 2019). Diethylene glycol is produced commercially as a by-product of ethylene glycol production, and it can be produced by reaction between ethylene glycol and ethylene oxide (HSDB 2009).

ToxServices assessed diethylene glycol against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2016).

U.S. EPA Safer Choice Program's Safer Chemical Ingredients List

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2018). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for

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compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

Diethylene glycol is not listed on the U.S. EPA SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2019) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for diethylene glycol can be found in Appendix C.

- Diethylene glycol is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Diethylene glycol is on the following lists for multiple endpoints:
  - Environment Canada (EC) – CEPA Domestic Substances List (DSL) – Inherently Toxic to Humans (iTH).
  - German FEA – Substances Hazardous to Waters – Class 1 – Low Hazard to Waters.
- Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
- Diethylene glycol is not listed on the U.S. DOT lists.

Hazard Statement and Occupational Control

The harmonized H statement for diethylene glycol is listed in Table 1. Personal protective equipment and occupational exposure limits for diethylene glycol, if any, are shown in Table 2.

Table 1: H Statements for Diethylene Glycol (CAS #111-46-6) (ECHA 2019b)

H Statement	H Statement Details
H302	Harmful if swallowed

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Diethylene Glycol (CAS #111-46-6)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Eye/face protection: face shield and safety glasses	Sigma Aldrich 2018	German MAK: 10 ppm; 44 mg/m^3	DFG 2012
Skin protection: handle with gloves			
Body protection: complete suit protecting against chemicals – selected according to the concentration and amount of the substance at the specific workplace		WEEL: 8-hr TWA 10 mg/m^3	HSDB 2009

[8] DOT lists are not required lists for GreenScreen® List Translator v1.4. They are reference lists only.

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Respiratory protection: Full face respirator with respirator cartridge where risk assessment shows air-purifying respirators are appropriate			
German MAK: Maximum Workplace Concentration WEEL: Workplace Environmental Exposure Level TWA: Time Weighted Average			

Physicochemical Properties of Diethylene Glycol

Diethylene glycol is a viscous liquid at room temperature that is not expected to be significantly volatile. It is very soluble in water and hydrophilic. Its log K_{ow} of -1.98 to -1.47 suggests it is unlikely to bioaccumulate.

Table 3: Physical and Chemical Properties of Diethylene Glycol (CAS #111-46-6)

Property	Value	Reference
Molecular formula	$C_3H_{10}O_3$	ChemIDplus 2019
SMILES Notation	O(CCO)CCO	ChemIDplus 2019
Molecular weight	106.12 g/mol	ChemIDplus 2019
Physical state	Liquid	ECHA 2019a
Appearance	Colorless; syrupy	ECHA 2019a
Melting point	-8 to -6°C; -18°C	ECHA 2019a; UNEP 2007
Boiling point	244.9°C	ECHA 2019a, UNEP 2007
Vapor pressure	0.008-0.013 hPa at 25°C (0.006 mm Hg at 25°C); 0.00783 mm Hg at 25°C	ECHA 2019a; UNEP 2007
Water solubility	1,000 g/L	ECHA 2019a
Dissociation constant	n/a	
Density/specific gravity	1.118 at 20°C	ECHA 2019a, UNEP 2007
Partition coefficient	log K_{ow} = -1.98 to -1.47	ECHA 2019a, UNEP 2007

Toxicokinetics

Absorption

- UNEP 2007, NICNAS 2009
  - Diethylene glycol is rapidly and almost completely absorbed via the oral route. In a study with rats, up to 96% diethylene glycol was absorbed within 2 hours following single gavage doses of 1 and 5 mL/kg (reported to be equivalent to 1.12 and 5.6 g/kg). When administered a high dose of 10 mL/kg (11.2 mg/kg), diethylene glycol was almost completely absorbed over 150-240 minutes.
  - Diethylene glycol is slowly absorbed through the skin. When a dermal dose of 50 mg/12 m^2 was applied to rats, a cumulative total of 9% and 0.9% of the dose was recovered in excreta and tissues, respectively. Calculation with the dermal absorption model SkinPerm indicates a maximal skin permeation of 0.1 mg/cm^2/h under steady-state conditions when skin absorption equals systemic delivery.
  - No studies on the absorption of diethylene glycol after inhalation exposure are available. However, because of its polar and hygroscopic characteristics, diethylene glycol in vapor or aerosol form is likely to be absorbed soon after it enters the upper respiratory passages.

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Distribution

- UNEP 2007, NICNAS 2009
    - Diethylene glycol is well distributed throughout the aqueous tissues of the body, with lower concentrations in adipose tissue. Following gavage dosing of ^{14}C-diethylene glycol in rats, radioactivity was rapidly distributed from the blood into the organs and tissues in the order of kidneys → brain → spleen → liver → muscle → fat, with the volume of distribution determined as 1 L/kg.

Metabolism

- UNEP 2007, NICNAS 2009
    - The postulated pathway for metabolism of diethylene glycol in animals is oxidation via alcohol dehydrogenases and aldehyde dehydrogenases.
    - Identified metabolites include CO_2, 2-(hydroxyethoxy)acetic acid (2-HEAA), and oxalic acid; however, oxalic acid was not a significant metabolite in rats.
- ECHA 2019a
    - After a single high dose of diethylene glycol, no metabolism to either monoethylene glycol or oxalate was observed in rats; however, in long-term experiments, an increase in the level of oxalate excreted in the urine of male rats was reported. This indicates that the ether bridge can be split; however, the oxalic acid concentrations in the blood and kidneys after administration of diethylene glycol remain lower than after administration of the same amounts of ethylene glycol.
    - In another study in rats, following a single oral administration of diethylene glycol at 2 mg/kg and 10 mg/kg, 2-HEAA was the primary metabolite in the urine, with only minor amounts of urinary diglycolic acid (DGA). Small amounts of ethylene glycol, but not oxalate or glycolate, were observed in the urine.

Excretion

- UNEP 2007, NICNAS 2009
    - Following gavage and drinking water dosing, a dose related increase in the percent elimination of diethylene glycol and its metabolite 2-HEAA were noted in the urine of rats. Approximately 45 - 70% of the total diethylene glycol dose is excreted unchanged in the urine within 48 hours, with approximately 11 - 37% as 2-HEAA after oxidative metabolism. However, when the dose was increased, the fraction oxidized to CO_2 decreased from 1.3% to 0.3%.
    - One study reported biological half-lives of 8 h and 12 h after oral doses in rats of 6 and 12 mL/kg (6.7 and 13.4 g/kg, respectively). These data indicate the plasma half-life was dose-dependent and that the metabolism and/or elimination of diethylene glycol may become saturated.
    - Excretion in the feces accounts for minor amounts, between 0.7 - 2.2% of the total dose.
    - In a study in dogs, a larger portion (up to 92%) of the administered diethylene glycol was excreted in the urine unchanged. Repeated administration to dogs for a week did not lead to a consistent increase in urinary oxalate; however, the urinary oxalate was increased in rats maintained on water containing diethylene glycol.
- ECHA 2019a
    - After a single oral or intravenous dose of 1.1 g/kg ^{14}C-labeled diethylene glycol, no ether cleavage products were found in the urine of male rats, only the administered substance. After 6 and 12 hours about 20% and 32% of the dose was recovered as 2-HEAA, respectively. After administration of single oral doses of 1, 5 and 10 mL/kg ^{14}C-diethylene

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glycol to male rats, the radioactivity in the blood was found to decrease with a half-life of about 3.5 hours; 73% - 96% of the total radioactivity was excreted with the urine. As a result of the diuretic effect, the two higher doses of diethylene glycol were excreted at a faster rate than was the low dose.

In summary, diethylene glycol is rapidly and almost completely absorbed via the oral route, is slowly absorbed via the dermal route, and is likely to be absorbed following inhalation. Following absorption, it distributes to the aqueous tissues throughout the body, with lower concentrations detected in adipose tissues. The expected metabolic pathways for diethylene glycol is oxidation via the activity of alcohol and aldehyde dehydrogenases, although the detection of oxalate in rat urine suggests cleavage of the ether bond may also occur. Diethylene glycol is primarily eliminated via the urine, with small amounts excreted in the feces and via exhaled carbon dioxide.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): L
Diethylene glycol was assigned a score of Low for carcinogenicity based on the lack of carcinogenicity reported in two 2-year oral studies in rats. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2019a, UNEP 2007
  - A 108-week carcinogenicity study was performed to evaluate the potential carcinogenicity of diethylene glycol. Diethylene glycol was administered to male and female Fischer 344 rats (n=50/sex/dose) via drinking water at concentrations of 0, 1.25, or 2.5% (97% purity; stated by the authors to be equivalent to 0, 1,210, or 2,630 mg/kg/day for males and 0, 1,160, or 2,550 mg/kg/day for females). Mortality was evaluated, and water consumption was measured for all animals. Hematological and serum-biochemistry were evaluated, and complete necropsy was performed on all animals. Water consumption was increased in both male and females. No significant hematological differences were reported between dosed and control groups. Additionally, no differences were reported in organ weights between controls and treated groups. No increase in tumor incidence was reported. Overall, there was no evidence of carcinogenicity. Both European Chemicals Agency (ECHA) and United Nations Environmental Programme (UNEP) assigned a Klimisch score of 2 (reliable with restrictions) for this study, due to it being from published literature and meeting generally accepted scientific principles.
- UNEP 2007
  - In a second 2-year carcinogenicity study, diethylene glycol was administered to male and female Carworth Farms Nelson rats (n=15 - 20/sex/dose) at 0, 2 and 4% in the feed (>99.9% purity). Males fed 4% diethylene glycol in the diet (reported by authors as 2,300 mg/kg/day) developed few bladder stones and only one papilloma. However, the authors contributed the occasional tumors that formed in rats to the development of calcium oxalate stones and the mechanical damage they produce in the rat bladder. No stone or tumors developed in in

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male rats fed 2%, nor in treated female rats. Overall, there was no evidence of carcinogenicity. UNEP assigned a Klimisch score of 2 (reliable with restrictions) for this study, due to the group size, which may weaken the strength of conclusions.

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

Diethylene glycol was assigned a score of Low for mutagenicity/genotoxicity based on consistently negative results in *in vitro* and *in vivo* genotoxicity assays. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2019a
  - *In vitro:* Diethylene glycol was negative for mutagenicity in a GLP-compliant bacterial reverse mutation assay according to OECD Guideline 471, EU Method B.13/14 and EPA OPPTS 870.5100. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP_2 were exposed to diethylene glycol (99.8% purity; water vehicle) at concentrations of 0, 33, 100, 333, 1,000, 2,500 and 5,000 µg/plate with and without metabolic activation (phenobarbital and β-naphthoflavone treated Wistar rat S9 liver mix). No cytotoxicity was observed and positive, negative, and vehicle controls were valid. There were no increases in the frequency of revertants in any strain at any concentration in the presence or absence of metabolic activation. ECHA dossier authors assigned a Klimisch score of 1 (reliable without restriction) for this study.
  - *In vitro:* Diethylene glycol was negative in a GLP-compliant sister chromatid exchange (SCE) assay similar to OECD Guideline 479. Chinese hamster ovary (CHO) cells were exposed to diethylene glycol (99.3% purity; cell culture medium solvent) at concentrations of 30 - 50 mg/mL with and without metabolic activation (rat liver S9 mix). Cytotoxicity was observed at >50 mg/mL; positive, negative, and vehicle controls were valid. There were no statistically significant increases in the number of SCEs at any concentration in the presence or absence of metabolic activation. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study, as it meets generally accepted scientific principles and is acceptable for assessment.
  - *In vivo:* Diethylene glycol was negative in a GLP-compliant micronucleus assay according to OECD Guideline 474. Male NMRI mice (5/dose) were administered a single intraperitoneal dose of diethylene glycol (99.932% purity) in water at doses of 500, 1,000, and 2,000 mg/kg, and bone marrow was harvested 24 and 48 hours post-exposure. Positive, negative, and vehicle controls were valid. There were no increases in the number of polychromatic erythrocytes containing either small or large micronuclei observed at any dose level. ECHA dossier authors assigned a Klimisch score of 1 (reliable without restriction) for this study.
- ECHA 2019a, UNEP 2007
  - *In vitro:* Diethylene glycol was negative for mutagenicity in a GLP-compliant Ames reverse mutation assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. Cells were exposed to diethylene glycol (99.3% purity; water vehicle) at concentrations of 1, 3, 10, 30 and 111.8 mg/plate with and without metabolic activation (rat liver S9 mix). Cytotoxicity was observed at >111.8 mg/plate; positive, negative and vehicle controls were valid. There were no increases in the frequency of revertants in any strain at any

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concentration in the presence or absence of metabolic activation. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study, as it meets generally accepted scientific principles and is acceptable for assessment; however, UNEP assigned a Klimisch score of 1 (reliable without restrictions) for this study.
    - *In vitro:* Diethylene glycol was negative for clastogenicity in a GLP-compliant chromosome aberration assay similar to OECD Guideline 473. CHO cells were exposed to diethylene glycol (99.3% purity; cell culture medium solvent) at concentrations of 0, 30, 35, 40, 45, and 50 mg/mL with and without metabolic activation (rat liver S9 mix). Cytotoxicity was observed at >50 mg/mL; positive, negative and vehicle controls were valid. There were no statistically significant increases in the number of chromosome aberrations at any concentration in the presence or absence of metabolic activation. Both ECHA and UNEP assigned a Klimisch score of 2 (reliable with restrictions) for this study, as it meets generally accepted scientific principles and is acceptable for assessment.
- UNEP 2007
    - *In vitro:* Diethylene glycol was negative for mutagenicity in a non-GLP Ames reverse mutation assay in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537. Cells were exposed to diethylene glycol (98% purity) at concentrations of 5-300 µmol/plate (use of metabolic activation not specified). There were no increases in the frequency of revertants observed in any strain at any dose. No further details were reported. UNEP assigned a Klimisch score of 2 (reliable with restrictions) for this study, due to unspecified reasons.
    - *In vitro:* Diethylene glycol was negative for mutagenicity in a non-GLP *E. coli* SOS-chromotest in strain PQ37. Cells were exposed to diethylene glycol (purity not reported) at a concentration of 10 µL with and without metabolic activation (Aroclor-1254 induced Sprague-Dawley rat liver homogenate S9). There was no mutagenic response in the *E. coli* strain. UNEP assigned a Klimisch score of 2 (reliable with restrictions) for this study, due to unspecified reasons.

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

Diethylene glycol was assigned a score of Moderate for reproductive toxicity based on effects to fertility and reproductive performance in a continuous breeding study in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when there is limited or marginal evidence of reproductive toxicity in animal studies and a GHS Category 2 classification is warranted (CPA 2018b). The confidence in the score is reduced as effects occurred at extremely high doses in animals.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists.
    - *Screening:* Japan GHS – Toxic to Reproduction – Category 2.
- ECHA 2019a, UNEP 2007
    - *Oral:* In a GLP-compliant reproductive toxicity study according to the continuous breeding protocol, male and female CD-1 mice (20-40/sex/dose) received diethylene glycol (>99% purity) in drinking water at levels of 0, 0.35, 1.75, or 3.5% (0, 610, 3,060, or 6,130 mg/kg/day) for 7 days prior to mating, 98 days during cohabitation, and 21 days after separation (F0 animals). Final F1 litters of control and high dose groups were reared, continuously treated, and paired with non-siblings from the same dose group. These animals were co-habituated for 1 week or until a copulatory plug was detected, and litters produced. For the F0 and F1 parental animals, maternal toxicity was reported at 3.5% due to a 7% decrease in body weight and decreases in liver and pituitary weights. Exposure of the breeding pairs to 3.5% diethylene glycol for 14 weeks statistically significantly reduced the number of litters/pair, live pups/litter, proportion of pups born alive, live pup weight, and the

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number of pairs producing third, fourth, and fifth litters. In addition, a significant increase in cumulative days to litter was also found at this dose. For the F1 and F2 offspring, decreased body weight was observed at birth with poor postnatal survival and craniofacial malformations (exencephaly and cleft palate) for the F1 generation at the highest dose. No adverse effects on reproduction were noted in the F1 mice at 1.75%. The authors concluded that diethylene glycol was a reproductive toxicant affecting fertility and reproductive performance at high doses. UNEP established the NOAEL and LOAEL at 1.75 and 3.5% (3,060 and 6,130 mg/kg/day, respectively) both for the F0 and F1 generations. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study, as it is comparable to a guideline study; however, UNEP assigned a Klimisch score of 1 (reliable without restrictions) for this study.

- ECHA 2019a
    - *Oral:* Diethylene glycol was administered to male and female albino rats (n=10/sex/dose) via gavage in water at a dose of approximately 2,200 mg/kg. A control group was also used. Duration of treatment was daily for 8 weeks prior to mating for both males and females. Administration was through birth for 5 of the females, and administration continued through weaning for the other 5 females. No effects were observed on time to conception, litter size or development of offspring. Onset of estrus and growth were not affected. No differences were observed between dosed and control groups with regard to endocrine gland size and structure. The F1 generation was untreated and allowed to mate, and weight gain, onset of sexual maturity, and body weight of the F2 generation was comparable to controls. Additionally, histology of the organs was comparable to controls in the F2 generation. No reproductive toxicity was observed in any generation. Based on the results of this study, the authors assigned a reproductive NOAEL of 2,200 mg/kg/day for both the parental and F1 generations. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study, as it is was a test procedure in accordance with national standard methods.
- NITE 2008
    - Diethylene glycol is classified as a Category 2 reproductive toxicant in Japan based on the results of a two-generation study in mice that reported reduced litter size and craniofacial malformations, and clear cases of reproductive toxicity at doses that induce general toxicity in parental animals.
- Based on the weight of evidence, a conservative score of Moderate was assigned. Effects on fertility and reproductive performance occurred at an extremely high dose (6,130 mg/kg/day) in a continuous breeding study in rats. The GHS criteria (UN 2017) specify that adverse effects on reproduction only seen at very high doses would not normally lead to classification, unless human exposure could occur at similar doses. However, GHS defined "very high doses" as those that "cause prostration, severe inappetence, excessive mortality", which were not observed in the studies described above on diethylene glycol. In addition, while GHS criteria agree with the concept of a limit dose above which adverse effects would not lead to classification, the actual limit dose could not be established due to species differences in toxicokinetics and lack of information on human exposure levels. Therefore, in light of evidence that humans are as much as 10-times more sensitive than animals to the effects of diethylene glycol (discussed below), ToxServices conservatively considered the observed reproductive effects reflective of specific reproductive effects rather than secondary to systemic toxicity.

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Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
Diethylene glycol was assigned a score of Moderate for developmental toxicity based on MAK Pregnancy Risk Group C classification and equivocal evidence of developmental toxicities only observed at very high doses in the presence of maternal toxicity in animals. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicity in animal studies (CPA 2018b). The confidence in the score is reduced as effects occurred at extremely high doses in animals in the presence of maternal toxicity.

- Authoritative and Screening Lists
  - *Authoritative:* MAK – Pregnancy Risk Group C.
  - *Screening:* Not present on any screening lists.
- ECHA 2019a, UNEP 2007
  - The developmental toxicity of diethylene glycol was evaluated in an OECD Guideline 414 study. Diethylene glycol (99.7% purity) was administered to female Himalayan rabbits (n=15/dose) via gavage (water vehicle) at doses of 0, 100, 400, or 1,000 mg/kg from gestation day 7 to 19. Food consumption, body weight, and body weight gains were evaluated throughout the study as well as clinical signs and mortality. On day 29, the dams were sacrificed and fetuses removed from the uterus. Gross pathology was performed on the dams. Uterine weight and the number of corpora lutea were measured. The number and distribution of implantation sites were classified as live fetuses, dead implantation, early resorptions, late resorptions, or dead fetuses. Fetuses were weighed and examined macroscopically for any malformations. Viability of fetuses and the condition of the placenta, umbilical cord, fetal membranes and fluids were evaluated. Additionally, soft tissues were evaluated for any malformations/changes. Organs were evaluated macroscopically. The fetuses were sexed, and, if any malformations were observed in the heads of the fetuses, they were decapitated and preserved for further evaluation. Skeletal evaluations were also performed. No effects were observed on food consumption. A statistically significant increase in food consumption was observed in the high dose group; however, the authors stated this was not biologically significant. Body weights and weight gain were comparable to controls. Marked edema in the anogenital region of one low dose female and one mid dose female that had an accidental lesion on the left hindlimb were reported; however, these were considered to be spontaneous, and no other clinical signs were observed. No mortality was observed. Uterine weights of dosed groups were comparable to controls. No effects were observed on conception rate, mean number of corpora lutea, mean number of implantations sites, in values calculated for the pre- and post-implantation loss, the number of resorptions, or the number of viable fetuses. The sex distribution of the fetuses from the dosed groups was comparable to controls. Placental weights of the dosed groups were also comparable to controls. No effects were observed on the mean fetal weights, and no skeletal malformations were observed. Two types of organ malformations were observed in fetuses. In one fetus from the high dose maternal group, a septal defect was observed; however, this is common in the strain of rabbit used in this study. As a result, it was not considered to be toxicologically relevant. Additionally, one high dose fetus had agenesis of the gallbladder; however, again this is a common finding in this strain of rabbit and, therefore, was not considered to be toxicologically relevant. This conclusion was supported by a lack of dose-response. A statistically significantly increased number of fetuses occurred in all dosed groups; however, it was considered to be incidental. Other variations, including hypoplasia of the gallbladder, dilated renal pelvis, and ovary bipartite, also occurred without dose response and were comparable to historical incidences of these effects. Several fetuses in all dose groups had focal liver necrosis or blood coagula around

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the bladder; however, no additional information about these effects was presented. In one control fetus, one mid dose fetus and 3 high dose fetuses, malformations of the ribs and/or vertebral column were observed. Skeletal variations included skull, rib, vertebral column, and sternum variations; however, none were statistically significantly different from the controls. Skeletal retardations were also observed, but, again, these effects lacked dose-response and were not statistically significant. Based on the results of this study, the authors concluded that the NOAEL for maternal toxicity, embryotoxicity, and fetotoxicity was greater than 1,000 mg/kg/day. ECHA dossier authors assigned a Klimisch score of 1 (reliable without restriction) for this study; however, UNEP assigned a Klimisch score of 2 (reliable with restrictions) for this study, due to unspecified reasons.

- An OECD Guideline 414 study was performed to evaluate the potential developmental toxicity of diethylene glycol. Diethylene glycol (99.9% purity) was administered to pregnant female Sprague-Dawley rats (n=25/dose) via gavage (no vehicle) at doses of 0, 1.0, 4.0, or 8.0 mL/kg/day (equivalent[9] to 0, 1,118, 4,472, or 8,944 mg/kg/day) on gestation day 6 to gestation day 15. The maternal generation was evaluated for body weight, food consumption, water consumption, and clinical signs. The maternal group was sacrificed on gestation day 21. Gravid uterus, ovaries, cervix, vagina and abdominal cavities were examined. Corpora lutea were counted. Maternal liver, uterine, and kidney weights were measured. Fetal examinations were also performed and included evaluation of litters for live and dead fetuses. Resorption sites were also noted and recorded. Live fetuses were weighed and sexed. Both live and dead fetuses were evaluated for external variations and malformations. Live fetuses were sacrificed and examined for thoracic and abdominal visceral abnormalities. Half of the sacrificed fetuses were decapitated and evaluated for craniofacial structural abnormalities. Skeletal malformations were also evaluated in all fetuses. In the high dose group, 3 of the 25 females died on gestation day 11. In two of these animals, cold extremities, slow or audible respiration, and/or hypoactivity were observed. Moderate to severe microscopic kidney lesions were observed in all three of these animals. No treatment related deaths were observed in the low and mid dose groups. No treatment related abortions, early deliveries, or pregnancy rate reductions were observed. Non-viable implants were not treatment-related. In the high dose group, maternal gestational body weights and weight gain were reduced. In the mid and high dose group, food consumption decreased and water consumption increased. Corrected gestational weight gain was slightly decreased in the mid and high dose groups. In the high dose group, increased incidence of basophilic and interstitial nephritis was observed, indicating repair of damaged renal tubules. In offspring from the high dose group, fetal body weights per litter were significantly reduced. Incidence of malformations were comparable with controls. Additionally, no treatment related difference was observed for individual external or visceral variations or for pooled external, visceral, skeletal or total variations. In the mid and high dose groups, individual skeletal variations were observed which suggested delayed ossification had occurred. Based on the results of the study, the authors established a NOEL for maternal toxicity and developmental toxicity of 1.0 mL/kg/day (equivalent to 1,118 mg/kg/day) based on maternal toxicity observed in both the mid and high dose groups and an increased incidence of skeletal malformations observed in the mid and high dose group offspring. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study, as it is a guideline study; however, UNEP assigned a Klimisch score of 1 (reliable without restrictions) for this study.

[9] (X mL/kg bw/day)*(1.118 g/mL)*(1,000 mg/g) = Y mg/kg bw/day.

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- UNEP 2007
    - In a non-GLP Chernoff-Kavlock teratogenicity screening test, female CD-1 mice received diethylene glycol at 0 or 11,180 mg/kg/day by daily gavage on days 6-13 of gestation. A very minimal difference in 3-day pup growth was found but was not considered evidence of a developmental effect by UNEP. No other developmental effects were observed. UNEP established the NOAEL at 11,180 mg/kg/day for maternal toxicity and teratogenicity. No further details were provided. UNEP did not assign a Klimisch score for this study.
- ECHA 2019a
    - A GLP-compliant prenatal developmental toxicity study similar to OECD Guideline 414 was performed to evaluate the potential developmental toxicity of diethylene glycol. Diethylene glycol (purity not reported) was administered to pregnant Swiss mice (n=29-31/dose) via gavage (water vehicle) at doses of 0, 1,250, 5,000, and 10,000 mg/kg/day) on gestation days 6-15. The maternal generation was evaluated for body weight, food consumption, water consumption, and clinical signs. The maternal group was sacrificed on gestation day 17. Gravid uterus, ovaries, cervix, vagina and abdominal cavities were examined. Corpora lutea were counted. Maternal liver, uterine, and kidney weights were measured. Fetal examinations were also performed and included evaluation of litters for live and dead fetuses. Resorption sites were also noted and recorded. Live fetuses were weighed and sexed. Both live and dead fetuses were evaluated for external variations and malformations. Live fetuses were sacrificed and examined for visceral abnormalities. Half of the sacrificed fetuses were decapitated and evaluated for craniofacial structural abnormalities. Skeletal malformations were also evaluated in all fetuses. Relative water intake was increased at 5,000 mg/kg/day and above, and food consumption was decreased at 10,000 mg/kg/day. In the high dose group, one female was sacrificed in extremis on gestation day 10; necropsy revealed evidence of renal degeneration. Necropsy of remaining animals showed increased absolute and relative kidney weight at 5,000 mg/kg/day and above. Renal lesions (tubular degeneration or regeneration) were noted in 2 of 27 females in the 10,000 mg/kg/day group. Mean fetal body weight was associated with a significant decreasing linear trend, and a significant decrease was reached in the high dose group. No further details on fetal examinations were reported. Based on the reported observations, a maternal toxicity NOAEL of 1,250 mg/kg/day and a developmental toxicity NOAEL of 5,000 mg/kg/day were established in this study. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study, as it is comparable to a guideline study.
- Based on a weight of evidence, a score of Moderate was assigned. Diethylene glycol is listed by MAK as a Pregnancy Risk Group C, which corresponds to a score of Low to Moderate. Developmental toxicity studies in rats, rabbits and mice have reported equivocal evidence of developmental toxicities observed at very high doses in the presence of maternal toxicity animals. In light of evidence that humans are as much as 10-times more sensitive than animals to the effects of diethylene glycol, ToxServices conservatively assigned a score of Moderate.

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

Diethylene glycol was assigned a score of Data Gap for endocrine activity based on insufficient data identified for this endpoint.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists.
    - *Screening:* TEDX – Potential Endocrine Disruptor.

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- TEDX 2019
    - Diethylene glycol was placed on the TEDX list of potential endocrine disruptors in 2017. This listing appears to be based on reproductive toxicity. The study abstract was reviewed and is summarized below:
        - Williams et al. (1990) reported on the reproductive toxicity of diethylene glycol in a continuous breeding study in CD-1 mice. Diethylene glycol was shown to affect fertility and reproductive performance in CD-1 mice, based on decreased litters, live pups per litter, pup weight, at high doses.
- U.S. EPA 2019
    - Diethylene glycol was inactive in 15/15 high-throughput tests for estrogen receptor agonist/antagonist activities, 8/8 tests for androgen receptor activities, and 3/3 thyroid receptor activities (Appendix D).
- Based on the weight of evidence a Data Gap was assigned. Diethylene glycol is present on the TEDX - Potential Endocrine Disruptors screening list, which corresponds to a preliminary score of Moderate to High. The reason provided for classification appears to be based on affects to fertility and reproductive performance observed in a continuous breeding study in mice. However, it was not clear from the Williams et al. (1990) study that diethylene glycol-related reproductive toxicity was causally related to endocrine disruption. Additionally, diethylene glycol tested negative for estrogen, androgen and thyroid receptor binding activities in high throughput screening assays. According to GreenScreen® guidance, a chemical should be assigned a preliminary Moderate hazard classification if there is an indication of endocrine activity in the scientific literature, and it may remain a Moderate or be modified to a High score when there is a plausible related adverse effect corresponding to a Moderate or High, respectively. As the TEDX classification is based only on limited evidence of reproductive and developmental effects, with no evidence of endocrine activity, ToxServices did not consider this classification to be sufficient to warrant conservatively assigning a score of Moderate in order to be precautionary.

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

Note: Group II and Group II* endpoints are distinguished in the v 1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen® Guidance v1.4, Annex 2 for more details.

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

Diethylene glycol was assigned a score of Moderate for acute toxicity based on the oral LD_{50} of 1,490 mg/kg in humans and its presence on authoritative and screening lists. GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when oral LD_{50} values are >300-2,000 mg/kg and they are classified as H302 (CPA 2018b). The confidence in the score is high as it is based on human data and an authoritative list.

- Authoritative and Screening Lists
    - *Authoritative:* EU GHS H Statements – H302: Harmful if swallowed.
    - *Screening:* Quebec CSST – WHMIS 1988 – Class D1B: Toxic material causing immediate and serious toxic effects.
    - *Screening:* New Zealand GHS – 6.1E (oral): Acutely Toxic.
    - *Screening:* Australia GHS – H302: Harmful if swallowed.
- ECHA 2019a
    - *Oral:* LD_{50} (male Sprague-Dawley rat) = 19,600 mg/kg (Klimisch score of 2, reliable with restrictions).

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  - *Oral:* LD_{50} (male and female rat, strain not reported) = 16,500 mg/kg (Klimisch score of 2, reliable with restrictions).
  - *Dermal:* LD_{50} (rabbit, sex and strain not reported) = 13,300 mg/kg (Klimisch score of 4, reliability not assignable).
  - *Inhalation (aerosol):* 4h LC_{50} (rats, sex and strain not reported) > 4.6 mg/L (max attainable aerosol concentration) (Klimisch score of 4, reliability not assignable).
- NICNAS 2013 (no Klimisch scores assigned)
  - *Oral:* LD_{50} (rat, sex and strain not reported) = 15,600 mg/kg.
  - *Oral:* LD_{50} (human) = approximately 1,490 mg/kg.
  - *Dermal:* LD_{50} (rabbit, sex and strain not reported) = 12,500 mg/kg.
  - *Inhalation:* 2h LC_{50} (mouse, sex and strain not reported) > 130 mg/m^3 (0.13 mg/L).
  - *Inhalation:* 4h LC_{50} (rat, sex and strain not reported) > 4,600 mg/m^3 (4.6 mg/L).
- UNEP 2007
  - *Oral:* LD_{50} (male Wistar rat) = 25,300 mg/kg (Klimisch score of 2, reliable with restrictions).
  - *Dermal:* LD_{50} (male New Zealand white rabbit) = 12,500 mg/kg (Klimisch score of 2, reliable with restrictions).
  - *Inhalation:* 4h LC_{50} (male and female Aplk:AP_fSD rat) > 5.08 mg/L (Klimisch score of 1, reliable without restriction).
- CCID 2019
  - Diethylene glycol is classified as 6.1E (oral): Acutely Toxic in New Zealand, which corresponds to a GHS Category 5, based on an LD_{50} value of 3,300 mg/kg in cats.
- Based on the weight of evidence, a score of Moderate was assigned. Diethylene glycol is a class D1B material, which corresponds to a score of Moderate to Very High. Diethylene glycol is also associated with the EU Harmonized H-statement of H302: Harmful if swallowed, which corresponds to an oral LD_{50} of 300 – 2,000 mg/kg in animal studies, and a score of Moderate. The basis of this H statement is not clear, and none of the oral LD_{50} values identified in animals fall below 2,000 mg/kg. However, a median lethal dose of 1,490 mg/kg was reported in humans, suggesting that humans are 10 times more sensitive to the acute toxicity of diethylene glycol compared to animals (NICNAS 2013). Therefore, ToxServices assigned a score of Moderate for this endpoint.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) Score (vH, H, M, or L): vH
Diethylene glycol was assigned a score of Very High for systemic toxicity (single dose) based on significant toxicity in humans observed in case reports and epidemiological studies, and ToxServices classifying it to GHS Category 1. GreenScreen® criteria classify chemicals as a Very High hazard for systemic toxicity (single dose) when a GHS Category 1 classification is warranted (CPA 2018b). The confidence in the score is high as it is based on human evidence.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* Not present on any screening lists.
- ECHA 2019a
  - *Oral:* Diethylene glycol (>99% purity) was administered to male Sprague-Dawley rats (10/dose) at single doses of 1.12, 5, 10, 12.5, 15, and 17.5 mL/kg via oral gavage and animals were observed for 7 days. The following effects developed consecutively: narcotic phase, diuretic phase and thirst, drop of the pH of the urine and blood, either recovery or hydrotropic degeneration of the renal tubules and anuria, accumulation of urea and uric acid in the blood, and finally death after 2-7 days from non-compensated metabolic acidosis and

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uremia. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study, as it meets generally accepted scientific principles and is acceptable for assessment.

- *Oral:* Diethylene glycol (purity not reported) was administered to male and female rats (10/dose, strain not specified) at single doses of 11,160, 12,555, 13,950, 16,740, 19, 530, 20,925, and 22,320 mg/kg via oral gavage and animals were observed for 5 days. Clinical signs included thirst, diuresis, ruffled coat, and refusal of food. After the first 2 to 3 days there was cessation of urine excretion with heavy proteinuria. Prostration, dyspnea, bloated appearance, coma, and pronounced lowering of body temperature were reported for about 24 hours before death. Histopathology revealed extensive degeneration of the renal cortex with vacuolar (hydropic) degeneration of the convoluted tubules; widespread diffuse hydropic degeneration of the central of lobules in the liver; congestion, edema and focal interstitial pneumonia and hemorrhage in the lungs of some animals; and excessive phagocytosis of blood pigment in the spleen. An LD_{50} of 16,500 mg/kg was established. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study, as it meets generally accepted scientific principles and is acceptable for assessment.
- *Inhalation (aerosol):* In an acute inhalation study in rats (number, sex and strain not reported), animals were exposed to diethylene glycol at the maximum attainable concentrations of 4.4 – 4.6 mg/L for 4 hours and observed for 14 days. The mass median aerodynamic diameter (MMAD) of particles were 2.6 – 3.1 μm with 96% < 10 μm. No mortalities were observed. Clinical observation found decreased activity during exposure (rapidly reversible after exposure), nasal discharge and lacrimation that lasted for several days indicative of minor irritation. Animals experienced a transient loss of body weight which was recovered in 3 – 5 days. No gross pathological abnormalities were found upon sacrifice. ECHA dossier authors assigned a Klimisch score of 4 (not assignable) for this study, as it is from secondary literature.

- UNEP 2007
  - *Oral:* Diethylene glycol (purity not reported) was administered to male Wistar-derived rats (5/dose) at single doses of 16 or 32 mL/kg (reported by authors as 36,000 and 18,000 mg/kg) via oral gavage and animals were observed for 14 days. At 16 mL/kg 0/5 animals died; however, 5/5 animals died at 32 mL/kg. In those animals that died, necropsy revealed lungs with reddening or petechiae, mottled livers, transparent stomachs, yellow, transparent, gas-filled intestines, slightly reddened kidney, and full bladders. The surviving animals had reddened lungs. An LD_{50} of 25,300 mg/kg was established. UNEP assigned a Klimisch score of 2 (reliable with restrictions) for this study, as it is from a report with documented test parameters.
  - *Dermal:* In an acute dermal toxicity study, male New Zealand White rabbits (4/dose) were administered diethylene glycol (purity not reported) to clipped, intact skin at doses of 5, 10 and 20 mL/kg (reported by authors as 5,600, 11,200, and 22,400 mg/kg, respectively) under occlusive conditions for 24 hours, and were observed for 14 days. At 5, 10, and 20 mL/kg, 0/4, 2/4 (by day 7), and 4/4 (by day 5) animals died, respectively. Necropsy revealed dark lungs and livers and pale kidneys of those animals that died. Surviving animals had pale, mottled kidneys. An LD_{50} of 11.2 mL/kg (12,500 mg/kg) was established for this study. UNEP assigned a Klimisch score of 2 (reliable with restrictions) for this study, as it is from a report with documented test parameters.
  - *Inhalation (vapor):* In an acute inhalation toxicity study, male and female Sprague-Dawley rats (5/sex/dose) were exposed to saturated vapor of diethylene glycol (purity not reported) for 6 hours, and were observed for 14 days. There were no deaths, no clinical signs of

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toxicity, and no abnormalities reported at necropsy. An LC_{50} value could not be calculated for this study. UNEP assigned a Klimisch score of 2 (reliable with restrictions) for this study, as it is from a report with documented test parameters.
    - *Inhalation:* In a GLP-compliant acute inhalation toxicity study according to OECD Guideline 403 and US EPA 870.1300, male and female Aplk:SD rats (5/sex/dose) were exposed nose-only to diethylene glycol (99.9% purity) for 4 hours at a concentration of 5.08 mg/L, and were observed for 14 days. There were no deaths reported. Clinical signs included some salivation, wet fur, stains around the snout, and chromodacryorrhea during exposure and immediately post-exposure on day 1, which was attributed to restraint. All animals completely recovered by day 2. An LC_{50} value of >5.08 mg/L is reported for this study. UNEP assigned a Klimisch score of 1 (reliable without restriction) for this study.
    - *Inhalation:* In an ASTM E-961-84 sensory irritation assay, male Swiss Webster mice (4/dose) were exposed to 1.9, 2.8, 4.3, 4.4, 5.1, 5.1, 9.8 and 11.3 mg/L diethylene glycol for 30 minutes and observed for respiratory depression. The concentration determined to produce a 50% depression in respiration rate was 11.6 mg/L. The authors concluded diethylene glycol causes respiratory depression but did not display characteristics of a "pure" upper airway sensory irritant. UNEP assigned a Klimisch score of 1 (reliable without restriction) for this study.
- NICNAS 2013
    - Toxicity in humans following acute diethylene glycol exposure have been recorded. Typical features of acute toxicity include neurological impairment, metabolic acidosis and acute renal failure. Early mortality and morbidity are high, with most deaths occurring within the first two weeks following diethylene glycol exposure. Humans appear to be 10 times more susceptible to acute oral toxic effects of diethylene glycol compared with experimental animals.
    - The critical health effects for risk characterization include systemic acute effects.
- HSDB 2009
    - There are numerous case reports and epidemiological studies reporting ingested medicines contaminated with diethylene glycol causing severe neurological, kidney and liver toxicities as well as death in children.
- Based on the weight of evidence, a score of Very High was assigned. Although effects in animals occurred at extremely high doses greater than the guidance values, human case reports and epidemiological studies have demonstrated that diethylene glycol produces significant toxicity in humans. Therefore, ToxServices considers a GHS Category 1 classification to be warranted for diethylene glycol and assigned a score of Very High.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*) Score (H, M, or L): H

Diethylene glycol was assigned a score of High for systemic toxicity (repeated dose) based on human evidence of kidney and liver toxicity, and even death, and its classification to GHS Category 1 in Japan. GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (repeated dose) when a GHS Category 1 classification is warranted (CPA 2018b). The confidence in the score is high as it is based on human evidence with support from a screening list.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists.
    - *Screening:* Japan GHS – Specific target organs/systemic toxicity following repeated exposure – Category 1.
    - *Screening:* New Zealand GHS – 6.9B (oral): Harmful to human target organs or systems

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(Category 2).

- ECHA 2019a
    - *Oral:* An OECD Guideline 407 study was performed to evaluate the potential systemic toxicity of diethylene glycol. Diethylene glycol (99.7% purity) was administered via feed to male and female Wistar rats (n=10/sex/dose for control and high dose groups; n=5/sex/dose for all other test groups) at doses of 0, 500, 2,500, 10,000, and 40,000 mg/kg/day for 28 days. Body weight was measured throughout the study, and food consumption was also measured. Animals were also observed for clinical signs. Hematological analysis, clinical chemistry, urinalysis, organ weight analysis, and pathological analysis were performed on all animals. No clinical signs were observed, and no early mortality occurred. No effects were measured on body weight, body weight gain, food consumption, or water consumption. Additionally, no effects were observed upon ophthalmoscopic examination, hematological analysis, clinical chemistry, gross pathology, or histopathology. A significant increase in oxalic acid was observed in males in the high dose group. In the 2,500 and 10,000 mg/kg/day groups, a high concentration of oxalic acid was measured in the urine on day 23 of the study; however, the authors stated that this was not test substance related because no increases in the oxalic acid levels were observed between day 13 and 23. A recovery period of 3 weeks was imposed, and, during that time, the oxalic acid levels resolved in the highest dose group. In females, a significant increase in oxalic acid was also observed in the high dose group; however, this was only at day 23. No effects were observed in any other female dose group. The effects observed in the high dose females were also reversible during the recovery period. High dose females had decreased absolute brain weights; however, the authors stated this effect did not appear to be test substance related, but no explanation was provided as to why. Based on the results of the study, the authors assigned a NOAEL and LOAEL of 10,000 and 40,000 mg/kg/day, respectively, based on increased oxalic acid levels in both sexes. ECHA dossier authors assigned a Klimisch score of 1 (reliable without restriction) for this study.
        - The guidance values are for 90-day studies. As this study was only 28-days, the guidance value of 100 mg/kg/day should be tripled to account for the difference in exposure time. Nevertheless, the NOAEL and LOAEL of 10,000 and 40,000 mg/kg/day, respectively, both exceed the guidance value of 300 mg/kg/day.
- ECHA 2019a, UNEP 2007, NICNAS 2013
    - *Oral:* Diethylene was administered to male and female Wistar rats (n=10/sex/dose) via feed at doses of 0, 0.085, 0.17, 0.4, and 2.0% (stated by the ECHA REACH dossier to be equivalent to 0, 64, 128, 300, or 1,500 mg/kg/day) for 225 days. Body weights and food and water intake were observed throughout the study. Urine samples were collected in week 8, 13, and 19 from males and in week 9, 14, and 19 from females over 24-hour periods. During urine collection, animals were not provided with food or water. The samples were analyzed for oxalic acid. Urine analyses, renal concentration, dilution tests, and urinary cell counts were performed during the last week of study. Postmortem examinations, organ weight analyses, and hematological examination were performed. Oxalate crystalluria and mild defects in renal function were reported in the 0.4% and 2.0% dose groups. In the 0.17% dose group, a 13.2% increase in urinary oxalate excretion was measured in males. No effects were observed in the 0.085% group. The authors questioned the increase in oxalate excretion in the 0.17% group, but no explanation was provided as to why it was not considered to be toxicologically significant. Based on the results of this study, the authors established a NOAEL of 128 mg/kg/day and a LOAEL of 300 mg/kg/day based on effects on the kidneys in the 0.4% and 2.0% dose groups. Both ECHA and UNEP assigned a

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Klimisch score of 2 (reliable with restrictions) for this study as it is a test procedure in accordance with national standard methods with documented test parameters.

- HSDB 2009
    - There are numerous case reports and epidemiological studies reporting ingested medicines contaminated with diethylene glycol causing severe neurological, kidney and liver toxicities as well as death in children.
- CCID 2019
    - Diethylene glycol is classified as a 6.9B (oral) toxicant in New Zealand, which corresponds to a GHS Category 2, based on kidney toxicity observed in an epidemiological study in pediatric population of Haiti. Accidental poisoning through diethylene glycol-contaminated acetaminophen syrup caused acute renal failure with clinical symptoms of renal failure, hepatitis, pancreatitis, central nervous system (CNS) impairment, coma and death.
- NITE 2008
    - Diethylene glycol is classified to GHS Category 1 in Japan based on liver and kidney toxicities observed in epidemiological studies in humans reporting death, progressive kidney damage, kidney failure and liver damage.
- Based on the weight of evidence, a score of High was assigned. While animal studies indicate that diethylene glycol is not classifiable for systemic toxicity, clear human evidence indicates that humans are more sensitive to diethylene glycol toxicity than animals, and sufficient evidence supports classification to GHS Category 1 for systemic toxicity.

Neurotoxicity (single dose, N-single) Score (vH, H, M, or L): *vH*
Diethylene glycol was assigned a score of Very High for neurotoxicity (single dose) based on evidence of neurological effects in humans and ToxServices classifying it to GHS Category 1. GreenScreen® criteria classify chemicals as a Very High hazard for neurotoxicity (single dose) when a GHS Category 1 classification is warranted (CPA 2018b). The confidence in the score is reduced as limited details are available for the human data.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists.
    - *Screening:* G&L – Neurotoxic Chemicals - Neurotoxic.
- NICNAS 2013 (no Klimisch scores assigned)
    - A typical feature of acute toxicity includes neurological impairment (encephalopathy, demyelinating neuropathy, optic neuritis, unilateral facial paralysis, cerebral edema and hemorrhages). Humans appear to be 10 times more susceptible to acute oral toxic effects of diethylene glycol compared with experimental animals.
    - Neurological effects were noted during severe intoxications after uptake of diethylene glycol in patients with burns. The patients developed acute anuric renal failure with metabolic acidosis and concomitant severe neurological abnormalities progressing to coma and finally death. It is not clear from the reports whether the episodes of human ingestion of diethylene glycol were single or repeated occurrences.
- Based on the weight of evidence, a score of Very High was assigned. Clear human evidence from case reports and epidemiological studies demonstrate diethylene glycol results in neurological effects. Therefore, there is sufficient evidence to support classification to GHS Category 1 for neurotoxicity (single dose).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): *H*
Diethylene glycol was assigned a score of High for neurotoxicity (repeated dose) based on evidence of neurological effects in humans and ToxServices classifying it to GHS Category 1. GreenScreen®

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criteria classify chemicals as a High hazard for neurotoxicity (repeated dose) when a GHS Category 1 classification is warranted (CPA 2018b). The confidence in the score is reduced as limited details are available from animal and human studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* G&L – Neurotoxic Chemicals - Neurotoxic.
- HSDB 2009
  - Diethylene glycol poisoning produces CNS depression, and in severe cases cerebral edema may be observed.
  - Administration of diethylene glycol to rats at 1, 2, 5, 10 and 20% in drinking water resulted in CNS depressant effects and caused paralysis of the respiratory and cardiac centers.
  - Application of 2.8 g/kg/day diethylene glycol for 2 months to the skin of rats resulted in edema of the brain, plethora, and minute brain hemorrhages.
  - Numerous case reports and epidemiological studies reported severe neurological toxicity following ingestion of medicines contaminated with diethylene glycol.
- NICNAS 2013
  - Neurological effects were noted during severe intoxications after uptake of diethylene glycol in patients with burns. The patients developed acute anuric renal failure with metabolic acidosis and concomitant severe neurological abnormalities progressing to coma and finally death. Typically, paracetamol elixirs have been involved, explaining the preponderance of pediatric deaths. Large overlaps in ranges of lethal and non-lethal doses have been noted for adults and children. It is not clear from the reports whether the episodes of human ingestion of diethylene glycol were single or repeated occurrences.
- Based on the weight of evidence, a score of High was assigned. Clear human evidence from case studies and epidemiological studies demonstrate diethylene glycol results in neurological effects. Therefore, there is sufficient evidence to support classification to GHS Category 1 for neurotoxicity (repeated dose).

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L

Diethylene glycol was assigned a score of Low for skin sensitization based on lack of evidence of skin sensitization in animal and human studies. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on consistently negative results in both animal and human studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* Not present on any screening lists.
- ECHA 2019a
  - A GLP-compliant guinea pig maximization study according to EU Method B.6 was performed to evaluate the potential dermal sensitization of diethylene glycol. For the induction phase, diethylene glycol (99.7% purity) was administered to female Pirbright White Dunkin guinea pigs (n=10 for test group; n=5 for control group) intracutaneously at a concentration of 5%. The second induction application was administered one week after the first induction under epicutaneous occlusive conditions at a concentration of 75%. At 21 days after the first induction administration, the challenge dose was administered under epicutaneous occlusive conditions at a concentration of 50%. Observations for sensitization were performed at 24 hours after challenge administration, and no animals in the test group had a positive dermal sensitization reaction. Based on the results of the study, the authors

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determined the test substance was not dermally sensitizing. ECHA dossier authors assigned a Klimisch score of 1 (reliable without restriction) for this study.
    - A dermal sensitization assay was performed in human volunteers to evaluate the potential dermal sensitization of diethylene glycol. For the induction phase, diethylene glycol (>96% purity) was administered to 40 male volunteers epicutaneously under occlusive conditions at a concentration of 20%. At 24 and 48 hours after patch removal, observations were recorded. At 14 days after the induction phase, the challenge phase was administered epicutaneously under occlusive conditions at a concentration of 20%. None of the participants in the study had a positive dermal sensitization reaction. Based on the results of this study, the authors determined the test substance was not dermally sensitizing. ECHA dossier authors assigned a Klimisch score of 4 (not assignable) for this study as it is from secondary literature.
- UNEP 2007
    - Diethylene glycol (purity not stated) was not a dermal sensitizer in a repeated insult patch test with 397 human volunteers. The induction phase consisted of 9 consecutive 24 hour applications, with new patches applied at 48 hours, of 0.2 mL diethylene glycol under occlusive and semi-occlusive conditions. After a two-week rest period, subjects were challenged with 0.2 mL diethylene glycol for 24 hours, and sites were graded at 48 and 72 hours. There was no evidence of sensitization. UNEP assigned a Klimisch score of 2 (reliable with restrictions) for this study as it is a quality study with documented test parameters.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*

Diethylene glycol was assigned a score of Low for respiratory sensitization based on lack of dermal sensitization potential according to ECHA's (2017) guideline. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists.
    - *Screening:* Not present on any screening lists.
- OECD 2019
    - Diethylene glycol does not contain any structural alerts for respiratory sensitization (Appendix E).
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As diethylene glycol was not sensitizing to the skin (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by diethylene glycol, and as diethylene glycol does not contain any structural alerts for respiratory sensitization (OECD 2019), diethylene glycol is not expected to be a respiratory sensitizer.

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

Diethylene glycol was assigned a score of Moderate for skin irritation/corrosivity based on slight dermal irritation observed in humans. GreenScreen® criteria classify chemicals as a Moderate hazard for skin irritation/corrosivity when a GHS Category 3 classification is warranted (CPA 2018b). The confidence in the score is reduced as no irritation was observed in animal studies, and there is no clear guidance on how to quantitatively classify chemicals based on human evidence under GHS.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* Not present on any screening lists.
- ECHA 2019a
  - An *in vivo* Draize test was performed to evaluate the potential dermal irritation of diethylene glycol. Diethylene glycol (0.5 mL; no information on purity) was administered to the shaved skin of male rabbits (n=6; strain not specified) for 23 hours. The average primary cutaneous irritation index score was 0.04. After 6 weeks, the mean maximum cutaneous irritation score was 0.47. No additional details were provided. Based on the results, the authors determined this test substance to be non-irritating. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study, as it is a test procedure in accordance with national standard methods, and the basic information was provided.
  - Diethylene glycol (purity not specified) was applied to the skin of male and female human volunteers (n=5/sex). Three occlusive patches were applied: one for 2 hours, one for 4 hours, and one for 6 hours. Observations were recorded at time of patch removal and again at 1, 4, and 24 hours after patch removal. Slight erythema was observed at 4 hours and marked erythema was observed at 6 hours in one male subject. Slight erythema was observed at 6 hours in one female subject, and a second female subject had marked erythema at 6 hours. These reactions resolved within 24 hours. Based on the results of this study, the test substance was determined to be slightly irritating.
  - An OECD Guideline 439 dermal irritation study was performed to evaluate the potential dermal irritation of diethylene glycol. Diethylene glycol (purity: 99.85%) was administered to human tissues in a well plate at a volume of 30 µL per well. After 24 hours, the tissues were transferred into a different well plate with 0.9 mL of medium and allowed to incubate for 18 hours. After incubation, the medium was replaced with 0.3 mL MTT solution and the tissues were incubated for 3 hours. After incubation, the tissues were rinsed with PBS to stop incubation. The tissues were incubated in 2 mL isopropanol for 2 hours at room temperature so that the formazan that was metabolically produced by the tissues could be extracted. The relative tissue viability was 94.5%; therefore, diethylene glycol was determined by the study authors to be non-irritating to the skin. ECHA dossier authors assigned a Klimisch score of 1 (reliable without restriction) for this study.
- UNEP 2007
  - Diethylene glycol produced minimal irritation in a primary irritation patch test in human volunteers. Subjects (n=103) were exposed to 0.1 mL diethylene glycol (purity not reported) under occlusive conditions for 48 hours. The primary irritation index was 46.5/300, indicating minimal irritation. UNEP assigned a Klimisch score of 2 (reliable with restrictions) for this study as it is a quality study with documented test parameters and human studies are preferred for assessment of human health risk.
- HSDB 2009
  - Application of diethylene glycol for 3 days following the standard Draize protocol resulted in mild irritation on human skin.
- Based on the weight of evidence a score of Moderate was assigned. Human studies consistently

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demonstrate that diethylene glycol is at most slightly irritating, which corresponds to at most GHS Category 3.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M, or L): L
Diethylene glycol was assigned a score of Low for eye irritation/corrosivity based on lack of ocular irritation in acute irritation studies in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on well conducted studies for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* Not present on any screening lists.
- ECHA 2019a
  - Diethylene glycol (purity not provided) was administered to the eyes of rabbits (n=5; strain, sex not provided) for 24 hours. The average ocular irritation score was 0-1 for all animals. Based on the results of the study, the authors concluded that diethylene glycol was not irritating to the eye. No additional details were provided. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study as it is a well-documented study that meets generally accepted scientific principles and is acceptable for assessment.
  - Diethylene glycol (purity not provided) was administered to the eye of male albino rabbits (n=6). The exposure time was not provided; it was only stated that the eyes were not washed. Observations were performed at 1 and 24 hours, and 2, 3, 4, and 7 days after application of the test substance. The mean irritation score for all animals was 11.67. As this is below the threshold of 15, the test substance was determined to be non-irritating to the eye. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study as it is a test procedure in accordance with national standard methods and basic information was provided.
- UNEP 2007
  - In an ocular irritation assay, 0.005, 0.01 and 0.1 mL diethylene glycol (purity not provided) was administered to the eye of male and female New Zealand white rabbits (3/sex/dose), and animals were observed for ocular irritation at 1, 4, 24, 48, and 72 hours and 7 days. The cornea and iris scores were both 0 at all times and doses. The conjunctivae score was 1.2 (max 4) at 1 hour for the 0.1 mL dose. After 24 hours, no ocular irritation was evident in any rabbit. Based on the results of this study, diethylene glycol is not considered to be an ocular irritant. UNEP assigned a Klimisch score of 2 (reliable with restrictions) for this study as it is a report with well-documented test parameters.

<u>Ecotoxicity (Ecotox)</u>

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): L
Diethylene glycol was assigned a score of Low for acute aquatic toxicity based on L/EC_{50} values of >1,000 mg/L in all three trophic levels. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when acute aquatic toxicity values are greater than 1,000 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target chemical on all three trophic levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* Not present on any screening lists.

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- ECHA 2019a
    - 96h LC_{50} (*Pimephales promelas*, fathead minnow) = 75,200 mg/L (Klimisch score of 2, reliable with restrictions).
    - 96h LC_{50} (*Oncorhynchus mykiss*, rainbow trout) = 66,000 mg/L (Klimisch score of 2, reliable with restrictions).
    - 48h LC_{50} (*Daphnia magna*, water flea) = 62,630 mg/L (Klimisch score of 2, reliable with restrictions).
    - 24h EC_{50} (*D. magna*, water flea) >10,000 mg/L (Klimisch score of 2, reliable with restrictions).
    - 96h LC_{50} (*Hyalella azteca*, aquatic crustacean) = 65,980 mg/L (Klimisch score of 2, reliable with restrictions).
    - 8day EC_{50} (*Scenedesmus quadricauda*, green algae) = 2,700 mg/L (Klimisch score of 2, reliable with restrictions).
- UNEP 2007
    - 96h LC_{50} (*P. promelas*, fathead minnow) = 77,900 mg/L (Klimisch score of 2, reliable with restrictions).
    - 48h EC_{50} (*D. magna*, water flea) = 48,900 mg/L (Klimisch score of 2, reliable with restrictions).
    - 24h LC_{50} (*Artemia salina*, brine shrimp) > 10,000 mg/L (Klimisch score of 2, reliable with restrictions).
    - 24h EC_{10} (*Chloroacoccales*, green plankton algae) > 1,000 mg/L (Klimisch score of 2, reliable with restrictions).

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): L

Diethylene glycol was assigned a score of Low for chronic aquatic toxicity based on chronic toxicity values of greater than 10 mg/L for the surrogate. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity values are greater than 10 mg/L for all three trophic levels (CPA 2018b). The confidence in the score is high as it is based on reliable data for strong surrogates for all three trophic levels, supported by modeled data on diethylene glycol.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists.
    - *Screening:* Not present on any screening lists.
- ECHA 2019a
    - *Surrogate: Triethylene Glycol (CAS #112-27-6):* 28-day LC_{50} (*Menidia peninsulae*, tidewater silverside) >1,500 mg/L (Klimisch score of 2, reliable with restrictions).
    - *Surrogate: Triethylene Glycol (CAS #112-27-6):* 21-day NOEC (*D. magna*, water flea) = 7,500-15,000 mg/L (growth), >15,000 mg/L (reproduction and survival) (Klimisch score of 2, reliable with restrictions).
    - *Surrogate: Triethylene Glycol (CAS #112-27-6):* 28-day NOEC (*D. magna*, water flea) >= 5,500 mg/L (reproduction) (Klimisch score of 2, reliable with restrictions).
    - *Surrogate: Triethylene Glycol (CAS #112-27-6):* 23-day NOEC (*Americamysis bahia*, shrimp) >= 1,000 mg/L (reproduction) (Klimisch score of 2, reliable with restrictions).
    - *Surrogate: Triethylene Glycol (CAS #112-27-6):* 8-day NOEC (*S. quadricauda*, green algae) = > 10,000 mg/L (growth rate) (Klimisch score of 2, reliable with restrictions).
    - *Surrogate: Ethylene Glycol (CAS #107-21-1):* 7-day NOEC (*P. promelas*, fathead minnow) = 15,380 mg/L (weight), 32,000 mg/L (mortality) (Klimisch score of 2, reliable with restrictions).
    - *Surrogate: Ethylene Glycol (CAS #107-21-1):* 7-day NOEC (*Ceriodaphnia dubia*, water

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flea) = 8,590 mg/L (reproduction), 24,000 mg/L (mortality) (Klimisch score of 2, reliable with restrictions).
    - *Surrogate: Ethylene Glycol (CAS #107-21-1):* 8-day NOEC (*S. quadricauda*, green algae) = > 2,700 mg/L (Klimisch score of 2, reliable with restrictions).
- UNEP 2007
    - 24h NOEC (*Chloroacoccales*, green plankton algae) > 1,000 mg/L (Klimisch score of 2, reliable with restrictions).
- U.S. EPA 2017a
    - Diethylene glycol belongs to the ECOSAR Neutral Organics chemical class. The predicted chronic values are 7,690 mg/L in fish, 1,890 mg/L in daphnids, and 1,200 mg/L in green algae (Appendix F).

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): L

Diethylene glycol was assigned a score of Low for persistence based on its classification as rapidly biodegradable based on studies demonstrating that it meets the 28-day but not the 10-day window. GreenScreen® criteria classify chemicals as a Low hazard for persistence when they are rapidly biodegradable (CPA 2018b). The confidence in the score is high as it is based on reliable guideline studies for the target chemical.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists.
    - *Screening:* Not present on any screening lists.
- ECHA 2019a
    - An OECD Guideline 301B study was performed to evaluate the biodegradation potential of diethylene glycol. In this test, aerobic, domestic, non-adapted, activated sludge was exposed to the test substance (purity not reported) at 44 mg/L for 29 days. At 28 days, 70-80% biodegradation was achieved as a measure of CO_2 evolution, and 90-100% biodegradation was achieved as a measure of DOC removal. No additional details were provided; however, the study authors determined the test substance was readily biodegradable. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study as it is a guideline study.
    - An OECD Guideline 301A study was performed to evaluate the biodegradation potential of diethylene glycol. In this test, aerobic, domestic, activated sludge (adaption not specified) was exposed to the test substance (97% purity) at 45 mg/L for 28 days. At 28 days, 90-100% biodegradation was achieved as a measure of DOC removal. The 10-day window was not met; however, the study authors determined the test substance was biodegradable. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study as it is a guideline study.
- U.S. EPA 2017b
    - The BIOWIN modeling Ready Biodegradable Predictor indicates that diethylene glycol is expected to be readily biodegradable. The Level III Fugacity Model (MCI method) predicts 62.6% will partition to water with a half-life of 8.6 days, 28.7% will partition to soil with a half-life of 17.3 days, 8.68% will partition to air with a half-life of 8.56 hours, and 0.111% will partition to sediment with a half-life of 78 days (Appendix G).

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Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
Diethylene glycol was assigned a score of Very Low for bioaccumulation based on a measured BCF of 100 in fish. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when BCF values are ≤100 (CPA 2018b). The confidence in the score is high as it is based on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* Not present on any screening lists.
- ECHA 2019a
  - The bioaccumulation of diethylene glycol was evaluated using a static fish test. 14C-labelled diethylene glycol was administered to fish (*Leuciscus idus melanotus*). A bioconcentration factor (BCF) of 100 was determined. No additional details were provided. ECHA dossier authors assigned a Klimisch score of 2 (reliable with restrictions) for this study as it is a well-documented study that meets generally accepted scientific principles and is acceptable for assessment.
- ECHA 2019a, UNEP 2007
  - Diethylene glycol has log K_{ow} values in the range of -1.98 (measured) to -1.47 (estimated).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Diethylene glycol was assigned a score of Low for reactivity based on its HMIS and NFPA reactivity ratings of 0. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score was reduced due to the lack of measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* Not present on any screening lists.
- ECHA 2019a
  - There are no chemical groups associated with explosive properties present in the molecule.
  - Diethylene glycol is incapable of reacting exothermically with combustible materials on the basis of chemical structure.
- Sigma Aldrich 2018
  - An MSDS for diethylene glycol reports a physical hazard score of 0 under HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives") and NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water").

Flammability (F) Score (vH, H, M, or L): L
Diethylene glycol was assigned a score of Low for flammability based on its flash point of 138-140°C. GreenScreen® criteria classify chemicals as a Low hazard for flammability when adequate data are available and they are not GHS classified (CPA 2018b). The confidence in the score was high as it is based on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* Not present on any screening lists.
- ECHA 2019a
  - Flash point = 138ºC (closed cup test).

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- UNEP 2007
    - Flash point = 140°C (closed cup test).
- HSDB 2009
    - Flash point = 280-290°F (137.8-143.3°C) (open cup test).
- According to GHS criteria (UN 2017), liquids with flash points greater than 93°C are not classified as flammable liquids.

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(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

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APPENDIX B: Results of Automated GreenScreen® Score Calculation for Diethylene Glycol (CAS #111-46-6)

TOXSERVICES TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

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	Diethylene glycol	111-46-6	L	L	*M*	*M*	DG	M	vH	H	*vH*	*H*	L	*L*	*M*	L	L	L	L	vL	*L*	L

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Diethylene glycol	2

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

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Diethylene glycol	2

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												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

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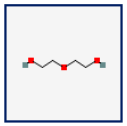
APPENDIX C: Pharos Output for Diethylene Glycol (CAS #111-46-6)



111-46-6

DIETHYLENE GLYCOL

ALSO CALLED [4669-26-5] Diethylene glycol (primary CASRN is 111-46-6), [2126734-27-6] Diethylene glycol (primary...

View all synonyms (72)

Share Profile

Hazards | Properties | Functional Uses | Process Chemistry | Resources

Pharos Hazards View

Download Lists

ENDPOINT	HAZARD LEVEL	HAZARD LIST	HAZARD DESCRIPTION	OTHER LISTS
Developmental	Medium	MAK	Pregnancy Risk Group C	
Reproductive	Medium	GHS - Japan	Toxic to reproduction - Category 2 [H361]	
Endocrine	Medium	TEDX - Potential Endocrine Disruptors	Potential Endocrine Disruptor	
Organ toxicant	High	GHS - Japan	Specific target organs/systemic toxicity following repeated exposure - Category 1 [H372]	+2
	High	GHS - New Zealand	6.9B (oral) - Harmful to human target organs or systems (Cat. 2)	
	Potential Concern	EU - Manufacturer REACH hazard submissions	H373 - May cause damage to organs through prolonged or repeated exposure (unverified)	
Mammalian	Medium	EU - GHS (H-Statements)	H302 - Harmful if swallowed	+3
	Medium	GHS - Australia	H302 - Harmful if swallowed	
	Low	GHS - New Zealand	6.1E (oral) - Acutely toxic	
	Potential Concern	Québec CSST - WHMIS 1988	Class D1B - Toxic material causing immediate and serious toxic effects	

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Restricted list	Potential Concern	Health Canada - Cosmetic Ingredient Hotlist	Ingredients that are Restricted for Use in Cosmetic Products	
Neurotoxicity	Potential Concern	G&L - Neurotoxic Chemicals	Neurotoxic	
Multiple	Potential Concern	EC - CEPA DSL	Inherently Toxic to Humans (iTH)	+1
	Potential Concern	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	

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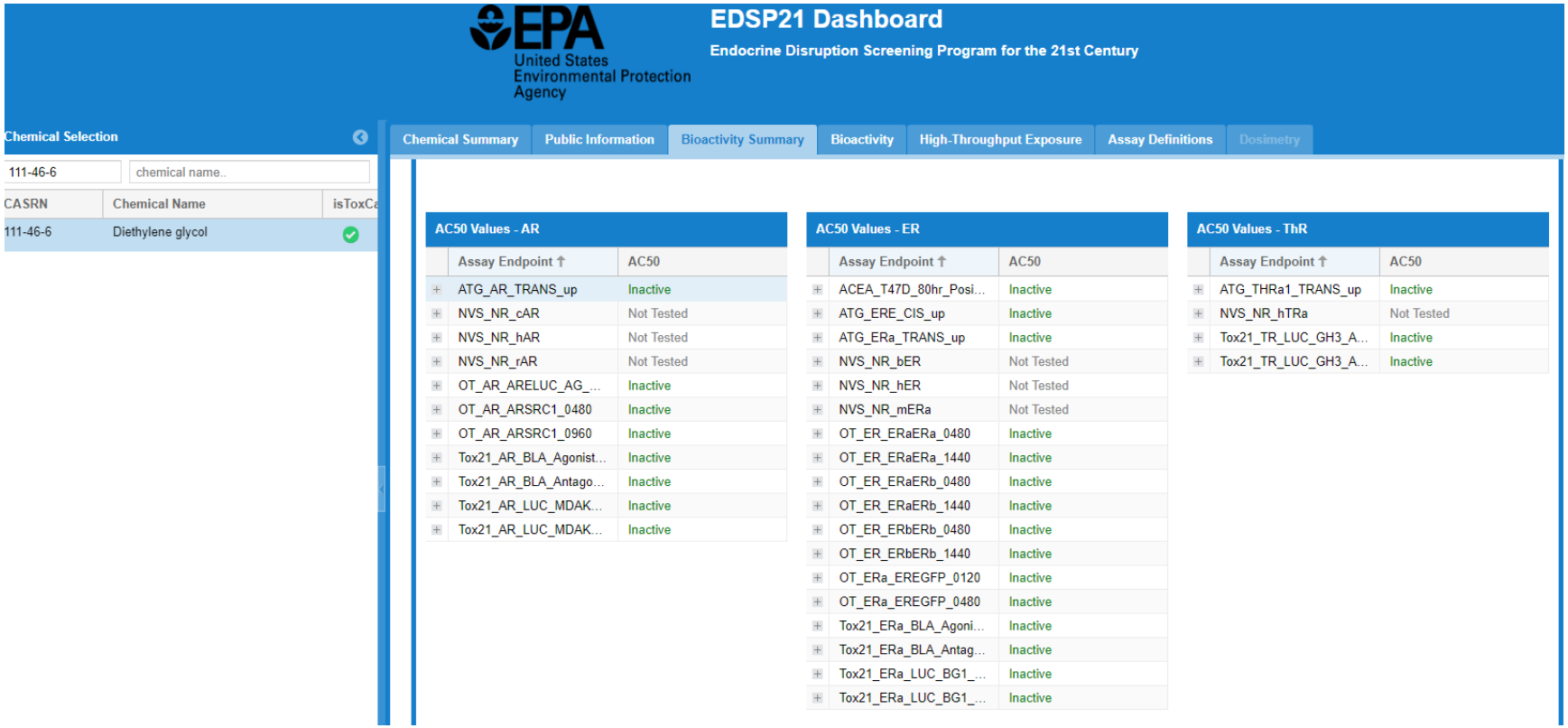
APPENDIX D: EDSP21 Dashboard for Diethylene Glycol (CAS #111-46-6)



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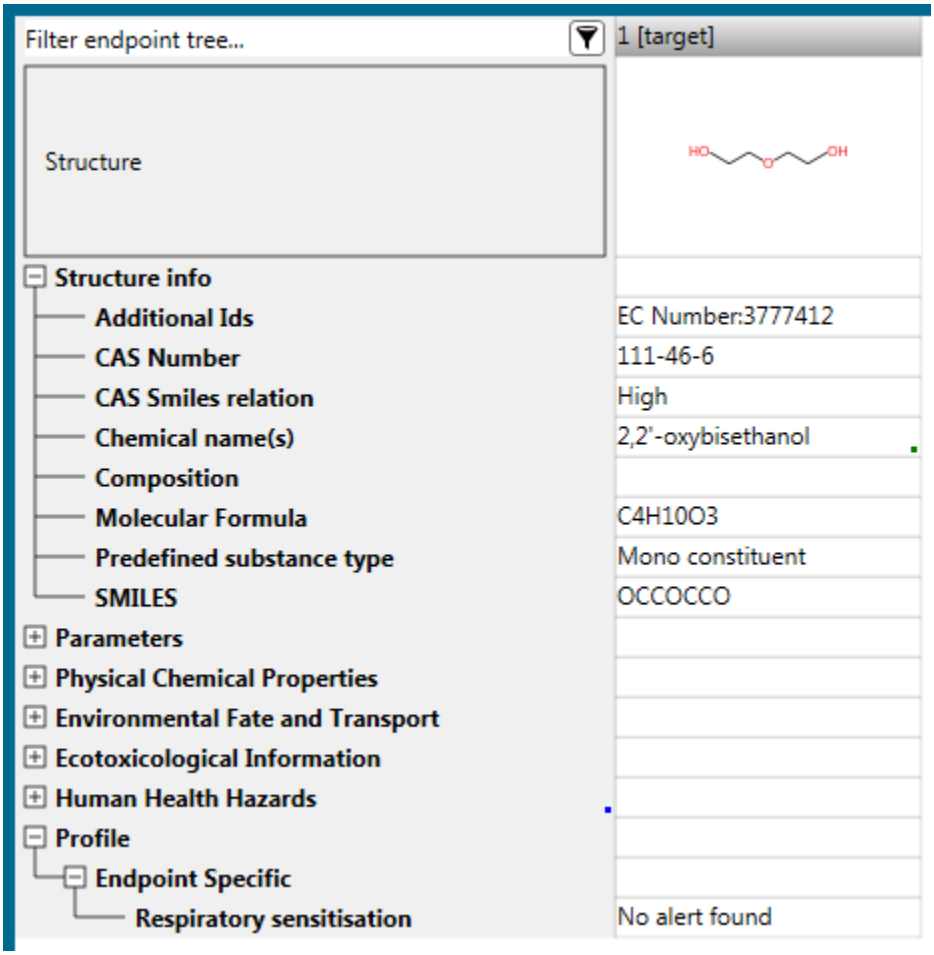
APPENDIX E: OECD Toolbox Respiratory Sensitization Results for Diethylene Glycol (CAS #111-46-6)



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APPENDIX F: ECOSAR Modeling Results for Diethylene Glycol (CAS #111-46-6)

Created on Aug 26, 2019 3:21:01 PM

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
111466	Ethanol, 2,2 -oxybis-	O(CCO)CCO

Structure

Details	
Mol Wt	106.12
Selected LogKow	-1.47
Selected Water Solubility (mg/L)	1000000
Selected Melting Point (°C)	-8
Estimated LogKow	-1.47
Estimated Water Solubility (mg/L)	1000000.06
Measured LogKow	
Measured Water Solubility (mg/L)	1000000
Measured Melting Point (°C)	-10.4

Class Results:	

Neutral Organics

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	114923.05	5	
Daphnid	48h	LC50	47347.79	5	
Green Algae	96h	EC50	9362.91	6.4	
Fish		ChV	7694.62	8	
Daphnid		ChV	1891.04	8	
Green Algae		ChV	1200.28	8	
Fish (SW)	96h	LC50	141701.62	5	

1 / 2

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Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Mysid	96h	LC50	1107964	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Fish (SW)		ChV	1843.61	8	
Mysid (SW)		ChV	268120.16	8	
Earthworm	14d	LC50	422.92	6	

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APPENDIX G: EPISuite Modeling Results for Diethylene Glycol (CAS #111-46-6)

CAS Number: 111466
SMILES : O(CCO)CCO
CHEM : Ethanol, 2,2 -oxybis-
MOL FOR: C4 H10 O3
MOL WT : 106.12
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): -1.47
Boiling Point (deg C) : ------
Melting Point (deg C) : -6.00
Vapor Pressure (mm Hg) : 0.006
Water Solubility (mg/L): 1
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = -1.47

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 215.97 (Adapted Stein & Brown method)
Melting Pt (deg C): 9.00 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 0.00266 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 0.354 (Mean VP of Antoine & Grain methods)
MP (exp database): -10.4 deg C
BP (exp database): 245.8 deg C
VP (exp database): 5.70E-03 mm Hg (7.60E-001 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 1e+006
log Kow used: -1.47 (user entered)
melt pt used: -6.00 deg C
Water Sol (Exper. database match) = 1e+006 mg/L (25 deg C)
Exper. Ref: RIDDICK,JA ET AL. (1986)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 1e+006 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Neutral Organics

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 2.03E-009 atm-m3/mole (2.06E-004 Pa-m3/mole)
Group Method: 1.20E-013 atm-m3/mole (1.21E-008 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 8.378E-004 atm-m3/mole (8.489E+001 Pa-m3/mole)

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VP: 0.006 mm Hg (source: User-Entered)
WS: 1 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: -1.47 (user entered)
Log Kaw used: -7.081 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 5.611
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.6671
Biowin2 (Non-Linear Model) : 0.5764
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.2759 (days-weeks)
Biowin4 (Primary Survey Model) : 3.9438 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.7504
Biowin6 (MITI Non-Linear Model): 0.8799
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.9483
Ready Biodegradability Prediction: YES

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 0.8 Pa (0.006 mm Hg)
Log Koa (Koawin est): 5.611
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 3.75E-006
Octanol/air (Koa) model: 1E-007
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.000135
Mackay model : 0.0003
Octanol/air (Koa) model: 8.02E-006

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 22.3373 E-12 cm3/molecule-sec
Half-Life = 0.479 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 5.746 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.000218 (Junge-Pankow, Mackay avg)
8.02E-006 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):

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Koc : 1 L/kg (MCI method)
Log Koc: 0.000 (MCI method)
Koc : 0.1579 L/kg (Kow method)
Log Koc: -0.801 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -2.3106 days (HL = 0.004891 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.049 (BCF = 0.8937)
Log BAF Arnot-Gobas method (upper trophic) = -0.049 (BAF = 0.8937)
log Kow used: -1.47 (user entered)

Volatilization from Water:
Henry LC: 0.000838 atm-m3/mole (calculated from VP/WS)
Half-Life from Model River: 1.771 hours
Half-Life from Model Lake : 105.7 hours (4.404 days)

Removal In Wastewater Treatment:
Total removal: 27.53 percent
Total biodegradation: 0.07 percent
Total sludge adsorption: 1.36 percent
Total to Air: 26.09 percent
(using 10000 hr Bio P,A,S)

Removal In Wastewater Treatment:
Total removal: 92.51 percent
Total biodegradation: 88.04 percent
Total sludge adsorption: 0.33 percent
Total to Air: 4.15 percent
(using Biowin/EPA draft method)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	8.68	8.56	1000
Water	62.6	208	1000
Soil	28.7	416	1000
Sediment	0.111	1.87e+003	0

Persistence Time: 90.2 hr

Level III Fugacity Model: (MCI Method with Water percents)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	8.68	8.56	1000
Water	62.6	208	1000
water	(62.6)		

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biota (1.06e-007)
suspended sediment (9.38e-005)
Soil 28.7 416 1000
Sediment 0.111 1.87e+003 0
Persistence Time: 90.2 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	8.86	8.56	1000
Water	63.7	208	1000
water	(63.7)		
biota	(1.08e-007)		
suspended sediment	(1.33e-006)		
Soil	27.3	416	1000
Sediment	0.11	1.87e+003	0

Persistence Time: 88.7 hr

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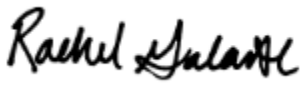
Diethylene Glycol GreenScreen® Evaluation Prepared by:



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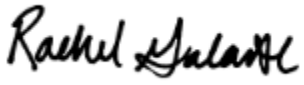
ToxServices LLC

Diethylene Glycol GreenScreen® Evaluation QC'd by:

Jennifer Rutkiewicz, Ph.D.
Senior Toxicologist
ToxServices LLC

Diethylene Glycol GreenScreen® Evaluation Updated by:



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