Chemical Information Profile

for

Ethylene Glycol 2-Ethylhexyl Ether [CAS No. 1559-35-9]

Supporting Nomination for Toxicological Evaluation by the National Toxicology Program

September 2008

National Toxicology Program
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services
Research Triangle Park, NC
http://ntp.niehs.nih.gov/

Data Availability Checklist for Ethylene Glycol 2-Ethylhexyl Ether [1559-35-9]

Abbreviations: H = human; L = *Lepus* (rabbit); M = mouse; R = rat
Note: No judgement of whether the available data are adequate for evaluation of these endpoints in the context of human health hazard or risk assessment has been made.

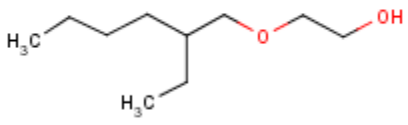
ENDPOINT	H	M	R	L	ENDPOINT	H	M	R	L
ADME					**Developmental Toxicity**				
Absorption					Developmental abnormalities				
Distribution					Embryonic/fetal effects				
Metabolism					Newborn effects				
Excretion					**Carcinogenicity**				
Acute Toxicity (up to 1 week)					Dermal				
Dermal	X			X	Inhalation				
Inhalation					Oral				
Injection					**Anticarcinogenicity**				
Ocular	X				Anticarcinogenic effects				
Oral		X	X		**Genotoxicity**				
Subchronic Toxicity (1 to <26 weeks)					Cytogenetic effects				
Dermal					Microbial gene mutation				
Inhalation					Gene mutation *in vitro*				
Injection					Gene mutation *in vivo*				
Oral					Germ cell effects				
Chronic Toxicity (≥26 weeks)					**Neurotoxicity**				
Dermal					Behavioral activity				
Inhalation					Motor activity				
Injection					**Immunotoxicity**				
Oral					Immunotoxic effects				
Synergism/Antagonism					**Hematotoxicity**				
Synergistic effects					Hematotoxic effects			X	
Antagonistic effects					**Mechanistic Data**				
Cytotoxicity					Target Organs/Tissues				
Cytotoxic effects					Endocrine modulation				
Reproductive Toxicity					Effect on enzymes				
Fertility effects					Modes of action				
Maternal effects					Effect on metabolic pathways				
Paternal effects					**Structure-Activity Relationships**	X	X	X	

The above table provides an overview of the data summarized in this profile. From left to right, column 1 and 6 list the endpoints and columns 2-5 and 7-10 identify the four species (human, rat, mouse, and rabbit) that were considered. An "**X**" is entered in each box that corresponds to an endpoint and species for which data are included in the profile. Blank cells indicate that no data were available in the literature.

Ethylene Glycol 2-Ethylhexyl Ether Nomination Summary

Chemical Name: Ethylene glycol 2-ethylhexyl ether **CAS RN:** 1559-35-9

Formula: $C_{10}H_{22}O_2$ **Molecular Wt.:** 174.28



Basis for Nomination: Ethylene glycol 2-ethylhexyl ether (EGEHE) was nominated by the National Institute of Environmental Health Sciences for toxicological characterization based on the limited amount of toxicological data available and on concern for potential human exposure due to its high production and increasing use. The production volume reported in the U.S. Environmental Protection Agency Inventory Update Reporting rule increased from a range of 10,000 to 500,000 pounds in 1990 to >1 to 10 million pounds in 2002. The application of EGEHE for use in various formulations also appears to have increased (e.g., ink-jet inks, gas supply pipe sealant, electrodeposition coatings for catalytic converters, lens manufacturing cleaning solutions, termite repellent, liquid bleach and dishwashing detergents, flower preservatives, and air fresheners). One study reported that EGEHE was one of 11 chemicals detected in indoor air in the home of a patient with multiple chemical sensitivity (MCS) and that it was a potential contributor to the patient's MCS symptoms. Adverse effects in the kidney, liver, and blood have also been reported. A mouse oral LD_{50} of 3898 mg/kg was reported; somnolence, tremors, and dyspnea of the lungs, thorax, or respiratory tract were observed. Rat oral LD_{50} values ranged from 3080 to 4674 mg/kg. In a subchronic study, rats exhibited somnolence, pigmented or nucleated red blood cells, and changes in erythrocyte cell count. Dermal LD_{50} values of 2120 and >17,640 mg/kg were reported for rabbit and guinea pig, respectively.

A. Chemical Information

Molecular Identification

Chemical Name: Ethylene glycol 2-ethylhexyl ether (EGEHE)
CAS RN: 1559-35-9
Synonyms: Ethanol, 2-[(2-ethylhexyl)oxy]- (7CI, 8CI, 9CI); 2-(2-Ethylhexyloxy) ethanol; Ethylene glycol, mono(2-ethylhexyl) ether
Trade Names: Eastman EEH Solvent; Kyowanol OX
Hill Formula: C10H22O2
Line Formula: $C_4H_9CH.C_2H_5$-CH_2-O-CH_2CH_2-OH
Smiles Notation: CCCCC(CC)COCCO
PubChem CID: 15260 (PubChem, undated)
InChI: 1/C10H22O2/c1-3-5-6-10(4-2)9-12-8-7-11/h10-11H,3-9H2,1-2H3
Molecular Weight: 174.28
Purity of Commercial Products: 82%, 97% [reagent grade] (Sigma-Aldrich, 2008); 99% (Kyowa Hakko Chem. Co. Ltd., 2008)
Additives in Commercial Products: 15 wt % diethylene glycol mono-2-ethylhexyl ether; 1 wt % triethylene glycol mono-2-ethylhexyl ether (Eastman Chem. Co., 2004)
Impurities in Commercial Products: Not available
Mammalian Metabolites: Not available
Biodegradation Products: Not available
Environmental Transformation: Not available

Physical-Chemical Properties

Physical State: clear liquid (Kyowa Hakko Chem. Co. Ltd., 2008)
Specific Gravity or Density Value: 0.88 @ 20/20 ºC (Kyowa Hakko Chem. Co. Ltd., 2008; Prime Tech Ltd., 2005)
Boiling Point: 229 ºC (Kyowa Hakko Chem. Co. Ltd., 2008; Registry, 2005); 235 ºC [EEH solvent] (Eastman Chem. Co., 2004)
Vapor Pressure: 0.0179327 Torr @ 25 ºC [calculated] (Registry, 2005)
Solubility: 0.2% wt. in water @ 20 ºC (Prime Tech Ltd., 2005); 0.1 g/100g @ 20 ºC (Kyowa Hakko Chem. Co. Ltd., 2008)
Log P = Log K_{ow}: 2.738±0.244 [calculated] (Registry, 2005)
Bioconcentration Factor(s) (species): 70.9 @ pH 1-10 [calculated] (Registry, 2005)

B. Exposure Potential

U.S. Annual Production

1986: No reports
1990: 10,000 - 500,000 lb
1994: >500,000 - 1 million lb
1998: >500,000 - 1million lb
2002: >1 - 10 million lb
(U.S. EPA, 2008 [U.S. EPA IUR database; search casno = 1559359])

Worldwide Annual Production

Not available

Production Processes

EGEHE is prepared from the reaction of 2-ethylhexanol and ethylene oxide in the presence of montmorillonite [hydrated sodium calcium aluminum magnesium silicate hydroxide] or hydrotalcite [synthetic aluminum magnesium hydroxycarbonate] as a catalyst (Fujita et al., 1987 pat. appl.; Maruyama et al., 2002 pat. appl.).

Uses

EGEHE is a component of acrylic glossy paints (e.g., Diamond Vogel Paint, 2004 and Duron, Inc., 2002), a replacement for Exxate solvent (Eastman Chem. Co., 2006), and a sealant for slate (Glaze 'N Seal Products, 2002). It is also used in the semiconductor industry (Camenzind et al., 1999). Eastman EEH Solvent (EGEHE, 84-85 wt %) is used in architectural maintenance coatings, cathodic electrodeposition primers, cleaners, floor polishes, original equipment manufacturer and special purpose coatings, and latex paints (as a coalescent) (Eastman Chem. Co., 2008a, 2008b). The following patents/patent applications propose a number of new uses for EGEHE [CAPLUS and TOXCENTER search results]:

- ink-jet inks (Choy, 2003 pat. appl.)
- paste for making plasma display panel electrodes by screen printing (Takada et al., 2004 pat. appl.)
- gas supply pipe sealant (Doi and Sakai, 2002 pat. appl.)
- PVC plasticizer (Gamrath and Weesner, 1951 pat.; Yasuda and Eto, 1990 pat. appl.; Yoshimoto et al., 1991 pat. appl.)
- sunburn treatment and oral hygiene products (Greff, 1998 pat. appl.)
- antioxidant formulations for biodiesel and other fatty acid and acid ester compositions (Carter et al., 2007 pat. appl.)
- automobile cationic electrodeposition coatings (Ikenoue and Kasari, 2002 pat. appl.; Inoue et al., 2004 pat. appl.; Miyazoe et al., 2004 pat. appl.; Nojiri, 2002 pat. appl.)
- hydrophilic modifier for well treatment and drilling fluids (Todd et al., 2006 pat. appl.)
- adsorbent for organic solvent gas recovery (e.g., from painting booths) (Midori and Umehara, 2004 pat. appl.; Takakura, 2000 pat. appl.)
- extractant for organic compounds from aqueous streams (Frank et al., 2005 pat. appl.)
- bactericide and fungicide (Moryama et al., 1993 pat. appl.)
- lens manufacturing cleaning solution (Nishihara and Wada, 2001 pat. appl.)
- termite repellent, wood impregnation (Oda et al., 2000 pat. appl.)
- antimicrobial in fabric-finishing, paper products, shampoos, deodorants, and therapeutic compositions for antiviral and antibacterial effectiveness against rhinovirus, rotavirus, coronavirus, respiratory syncytial virus, and Gram-positive and -negative bacteria and combinations of it (Lynch et al., 2005 pat. appl.; Saud et al., 2004 pat. appl.; Tanaka et al., 1989 pat. appl.)
- vapor-phase corrosion inhibitor (Senkus, 1956 pat.)
- solid detergents, presumably for industrial cleaning (Sugai, 2001 pat. appl.)
- liquid bleach and dishwashing detergent compositions (Hattori and Yomogida, 2008 pat.; Suekuni et al., 2005 pat.)
- cleaning solutions for sliced wafers or plates (Kondo and Shirasawa, 1997 pat. appl.)
- plastic organotin heat stabilizer composition (Tsukahara and Anzai, 1998 pat. appl.)
- cold cleaners (Freon substitute) for aqueous cleaning of metals and electronics (e.g., solder flux removal) (Yamashita and Nishama, 1995 pat. appl.)
- flower preserver compositions (Hashimoto and Hayashi, 2007 pat.)
- air freshener gels (Yamazaki et al., 1995 pat. appl.)
- preparation of 2-cyanoacrylate-based adhesive for living organisms, vaso-occlusion treatment, bone prosthetic, etc. (Abe et al., 2008 pat. appl.)
- marine antifouling coating solvent (Hamilton and Furman, 2007 pat. appl.)
- carbon fiber production solvent (Higashi et al., 2007 pat. appl.)

Occupational Exposure

Exposure Limits (Standards and Criteria): Not available

Exposure to workers is possible from the use of EGEHE-containing products or processes (e.g., electrodeposition composition for automobile coatings, semiconductor industry cleaners, and metal and floor cleaning). [See Uses.]

General Population Exposure

EGEHE was one of 11 chemicals detected in indoor air of a home in Japan where a woman with multiple chemical sensitivity (MCS) resided. Results from a case study of this female subject suggested that the chemicals found in the air may have contributed to the patient's MCS symptoms (Takeuchi et al., 2005). No additional specific exposure information is available.

Foods and Beverages, Cosmetics, etc.: Exposure is possible from the use of cosmetics, sunburn and oral hygiene products, antibacterial textile finishes, electronic products, offgassing, ink-jet printer inks, household and personal paper products (e.g., diapers), and air fresheners that contain EGEHE. [See Uses.]

Ambient Environment: Not available

Environmental Occurrence

Natural Occurrence: Not available

U.S. Environmental Releases: Not available

Concentrations in Environmental Media: Not available

C. Toxicological Information

General Toxicity

Adverse effects on the kidneys, liver, and blood have been reported (Leone s.p.a., 2001). In rabbits, EGEHE produced moderate eye irritation (moderate erythema, slight to moderate edema of the conjunctivae and nictitating membranes, slight opacities of the cornea, and fluorescein staining of the cornea and adnexae) (Anonymous, 1992).

Chemical Disposition, Metabolism, and Toxicokinetics

Not available

Acute Exposures

LC_{50}/LD_{50} Values:	oral LD_{50} = 3898 mg/kg [mouse] (Registry, 2005; RTECS, 1998)
	oral LD_{50} = 3080 mg/kg [rat] (Registry, 2005; RTECS, 1998)
	oral LD_{50} = 4600 mg/kg [rat] (General Paint Corp., 2007)
	oral LD_{50} = 4674 mg/kg [male rat]* (Eastman Chem. Co., 2004)
	dermal LD_{50} = 2120 µL/kg [rabbit] (RTECS, 1998)
	dermal LD_{50} = 2584 mg/kg [rabbit] (Eastman Kodak Co., 1992)
	dermal LD_{50} >17,640 mg/kg [guinea pig]* (Eastman Chem. Co., 2004)
	*data with Eastman EEH Solvent
Route:	oral
Species:	mouse (strain and sex not given)
Dose/Duration:	3898 mg/kg (LD_{50}); duration not provided
Observation Time:	not provided
Effects:	somnolence (general depressed activity); tremors; dyspnea of the lungs, thorax, or respiratory tract
Source(s):	RTECS (1998)
Route:	dermal
Species:	rabbit (New Zealand White, sex not given)
Dose/Duration:	2584 mg/kg (LD_{50}); duration not provided
Observation Time:	not provided

Effects:	anorexia, slight depression, cyanosis, ataxia, and soft feces at low doses; salivation, nasal discharge, iritis, significant depression, labored breathing, and prostration at higher doses *[Note: The summary of the clinical signs of toxicity provided were for a series of glycol ethers. The summary notes that the toxicity signs reported were similar after treatment with all glycol ethers, including EGEHE.]*
Source(s):	Eastman Kodak Co. (1992)

Subchronic Exposures

Route:	oral
Species:	rat (strain and sex not given)
Dose/Duration:	117 g/kg (TD_{Lo}) for 6 weeks intermittently
Observation Time:	not provided
Effects:	somnolence (general depressed activity); pigmented or nucleated red blood cells; changes in erythrocyte cell count
Source(s):	RTECS (1998)

Route:	oral (gavage)
Species:	rat (strain not given; male)
Dose/Duration:	dose not specified (range of 1.5-160 g/kg tested for glycol ether series); 6 weeks
Observation Time:	not provided
Effects:	congestive spleen, kidney, and liver; atrophical thymus *[Note: The summary of the clinical signs of toxicity provided were for a series of glycol ethers. The summary notes that the toxicity signs reported were similar after treatment with all glycol ethers, including EGEHE.]*
Source(s):	Eastman Kodak Co. (1992)

Chronic Exposures

Not available

Synergistic/Antagonistic Effects

Not available

Cytotoxicity

Not available

Reproductive and Developmental Toxicity

In male rats gavaged with EGEHE (dose not specified; range of 1.5-160 g/kg tested for series of glycol ethers) for 6 weeks, testicular atrophy with degenerative spermatozoa was observed (Eastman Kodak Co., 1992). *[Note: The summary of the clinical signs of toxicity provided were for a series of glycol ethers. The summary notes that the toxicity signs reported were similar after treatment with all glycol ethers, including EGEHE.]*

Carcinogenicity

Not available

Anticarcinogenicity

Not available

Genetic Toxicity

Not available

Neurotoxicity

Not available

Immunotoxicity

Not available

Hematotoxicity

In male rats gavaged with EGEHE (dose not specified; range of 1.5-160 g/kg tested for series of glycol ethers) for 6 weeks, blood toxicity that included reduced red blood cells and reduced hemoglobin was observed (Eastman Kodak Co., 1992). *[Note: The summary of the clinical signs of toxicity provided were for a series of glycol ethers. The summary notes that the toxicity signs reported were similar after treatment with all ethers, including EGEHE.]*

D. Mechanistic Data

Target Organs/Tissues

Not available

Endocrine Modulation

Not available

Effect on Enzymes

Not available

Modes of Action

Not available

Structure-Activity Relationships

Due to the limited amount of toxicological data available for EGEHE, results from studies of other ethylene glycol ethers are summarized here.

Congeners: Glycol ether toxicity is attributed to oxidation to aldehyde and alkoxyacetic acids by cytosolic alcohol dehydrogenase and aldehyde dehydrogenase (Lockley et al., 2005 [PMID:15551062]).

ADME: Exposure to glycol ethers was determined in occupationally exposed men by measuring alkoxycarboxylic acid metabolites in the urine. 2-Methoxypropionic acid was the prominent metabolite (5.6 mmol/mol creatinine) followed by phenoxyacetic acid (2.3 mmol/mol creatinine) then other alkoxycarboxylic acids totaling <1 mmol/mol creatinine (Ben-Brik et al., 2004 [PMID:15164289]). In rats, absorption and metabolism of dermally applied ^{14}C-labeled glycol ethers was linearly related to dose. Absorption was ~20-25% and the majority was excreted in the urine as alkoxyacetic and other alkoxycarboxylic acids (Sabourin et al., 1992 [PMID:1397793]).

Toxicity: The NTP has tested a number of ethylene glycol ethers. In Swiss CD-1 mice, ethylene glycol butyl ether (EGBE), monoethyl ether, monoethyl ether acetate, monomethyl ether, and monophenyl ether were reproductive toxicants (NTP, 1997). Adverse effects of EGBE on reproduction and development were only observed at toxic doses. EGBE has moderate acute toxicity, is an eye and skin irritant, and produced harmful effects on the central nervous system, kidneys, and liver in rats. EGBE was not mutagenic in mice or rats *in vivo* and gave conflicting results in human and rodent cells *in vitro* (IPCS, 1998). The NTP lifetime inhalation studies of EGBE in F344/N rats and B6C3F$_1$ mice reported no treatment-related tumors in male rats, an increase in combined benign or malignant pheochromocytomas of the adrenal medulla and one malignant pheochromocytoma at the high dose in female rats, an increase in hemangiosarcomas of the liver in all male mice, and a significant increase in the incidences of forestomach squamous cell papillomas and combined papillomas and carcinomas at the high dose in female mice (HSDB, 2005). Ethylene glycol ethers, their aldehydes, and their acid metabolites were also negative in the Ames test with strains TA98, TA100, and TA102 with or without S9 (Hoflack et al., 1995 [PMID:7531287]).

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Search Strategy

STN International files MEDLINE, AGRICOLA, CABA, EMBASE, ESBIOBASE, BIOTECHNO, IPA, BIOSIS, TOXCENTER, FROSTI, FSTA, and PASCAL were searched simultaneously and CAPLUS was searched separately on July 19, 2008, using the same strategies (synonyms and/or CAS Registry Number) as were used in April 2005 but with limitation to materials published since 2005. In the earlier search, 10 results were from TOXCENTER and 113 results were from CAPLUS. Except for the retrieval in AGRICOLA in the current update search, all results again came from TOXCENTER and CAPLUS. The history of the July 19, 2008, online session is reproduced below. It was noted that the 18 TOXCENTER records (L7) were also in CAPLUS based on the 43 CAPLUS records remaining (L15) after duplicates were removed from the 61 CAPLUS records (L14). This is also apparent based on the difference between the 49 CAPLUS records (L11) and the 6 TOXCENTER records (L8).

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L1           14 S 1559-35-9
L2            4 S 2(W)2(W)ETHYLHEXYLOXY(W)ETHANOL
L3            1 S ETHANOL(W)2(W)2(W)ETHYLHEXYLOXY
L4           11 S (ETHYLENEGLYCOL OR ETHYLENE(W)GLYCOL)(2A)
                (ISOOCTYL OR ISO(W)OCTYL OR ETHYLHEXYL OR ETHYL(W)HEXYL
                OR MONO(W)ETHYLHEXYL)(W)ETHER
L5            0 S EHG AND GLYCOL?
L6           19 S L1-L4
                SET DUPORDER FILE
L7           18 DUP REM L6 (1 DUPLICATE REMOVED)
                ANSWER '1' FROM FILE AGRICOLA
                ANSWERS '2-18' FROM FILE TOXCENTER
L8            6 S L7 AND (2005-2008)/PY
L9            6 SORT L8 1-6 TI

     FILE 'CAPLUS' ENTERED AT 14:47:55 ON 19 JUL 2008
L10         153 S L1
L11          49 S L10 AND (2005-2008)/PY

     FILE 'CAPLUS, AGRICOLA, TOXCENTER' ENTERED AT 14:50:35 ON 19 JUL 2008
L14          61 DUP REM L7 L11 (6 DUPLICATES REMOVED)
                ANSWER '1' FROM FILE AGRICOLA
                ANSWERS '2-18' FROM FILE TOXCENTER
                ANSWERS '19-61' FROM FILE CAPLUS
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L15          43 SORT L14 19-61 TI
                SAVE L15 X223CA/A
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Examination of the 43 titles indicated that most of the publications pertained to applications for ethylene glycol 2-ethylhexyl ether and some potential exposure conditions. Five TOXCENTER and seven CAPLUS records were selected from the titles for retrieval of the full articles. The information in these 12 publications represented uses and potential exposures not previously available for the original dossier. One abstract reported that ethylene glycol 2-ethylhexyl ether was detected in indoor air.