FOREWORD INTRODUCITON

2-(2-(2-Ethoxyethoxy)ethoxy)-ethanol

CAS N°: 112-50-5

SIDS Initial Assessment Report

For

SIAM 4

Tokyo, Japan, 20 - 22 May 1996

1. Chemical Name:	2-(2-(2-Ethoxyethoxy)ethoxy)-ethanol
2. CAS Number:	112-50-5
3. Sponsor Country:	United States
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	Initially prepared by the Chemical Manufacturer's Association and reviewed and revised by EPA
∉ Name of industry sponsor /consortium	American Chemistry Council (then Chemical Manufacturer's Association)
∉ Process used	See 5.
6. Sponsorship History	
∉ How was the chemical or category brought into the OECD HPV Chemicals Programme ?	This high production volume (HPV) chemical was assigned to the USA in Phase 3 of the OECD HPV voluntary testing program. A SIDS Dossier was prepared by the Chemical Manufacturer's Association and submitted to the National SIDS Contact Point (USA) on September 15, 1992. The SIDS Dossier and Testing Plan were discussed at the 3rd SIDS Review Meeting, September 1993. It was agreed that Acute Toxicity to Algae testing was required but that QSAR values could be used to satisfy this requirement. The SIAR was discussed at the 4th SIAM in May 1996. A majority of participants agreed that the chemical was of low priority for further work and that mutagenicity testing was not required. The United States was asked to revise the SIAR to include quantitative calculations of environmental toxicity and exposure and consumer and occupational exposure information. Those revisions have been made.
7. Review Process Prior to the SIAM:	See 5.
8. Quality check process:	See 5.
9. Date of Submission:	
10. Date of last Update:	April 2005
11. Comments:	

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	112-50-5
Chemical Name	Ethanol, 2-[2-(2-ethoxyethoxy)ethoxy]
Structural Formula	$HO\text{-}CH_2CH_2\ OCH_2CH_2OCH_2CH_2\text{-}OCH_2CH_3$

SUMMARY CONCLUSIONS OF THE SIAR

Analog Justification

Data for ethanol, 2-[2-(2-ethoxyethoxy)ethoxy] or triethylene glycol ethyl ether (TGEE) for some endpoints are either missing or limited. Therefore, triethylene glycol methyl ether (TGME) is used for the genetic, reproductive, neurotoxicity, and algal toxicity endpoints. Use of TGME is justified based on similar structures (i.e., the two chemicals differ by only one methylene group in the terminal alkyl moiety), as well as similarities in physicochemical and environmental fate properties and toxicity. Further, the diffusion rates through human skin are quite comparable. Finally, based on data for monoethylene glycol ethers, TGME is expected to be more toxic than TGEE, so conclusions using TGME will be more conservative.

Human Health

TGEE is of low acute toxicity in experimental animals by the oral, dermal and inhalation routes of exposure. The oral LD50 values are 8,500 and 10,600 mg/kg in male rats and all rats, respectively. In an inhalation study, a 1-hour exposure to 200 mg/L resulted in no deaths. The dermal LD50 from one study is 8,200 mg/kg. TGEE has been shown to be irritating to skin and mildly irritating to eyes of rabbits.

In a 30-day drinking water study in rats, a NOAEL of 750 mg/kg/day was identified. Changes observed at 3,300 mg/kg/day in this study were decreased weight gain, slightly increased blood urea concentrations, and "congestion and cloudy swelling of the liver (6/10) and kidney (1/10)." All animals died at 13,290 mg/kg/day. TGEE produced slight erythema and edema in rats exposed dermally at 1000 mg/kg/day for 21 days. One of five males exhibited testicular effects, which was concluded to be unrelated to treatment.

TGEE did not exhibit developmental toxicity in rats treated with up to 1,000 mg/kg/day (highest dose tested).

TGEE has not been tested for its genetic toxicity either in vivo or in vitro. Based on the lack of genotoxicity of TGME (a compound of similar structure), TGEE is not expected to be genotoxic.

Environment

TGEE is miscible (25 °C) in water and its specific gravity is 1.03 g/cm3 at 20 °C. The vapor pressure is 89.2 hPa at 20 °C. The melting point is -19\°C and the boiling point is 256 °C. Due to a low calculated log Kow (-0.96), TGEE is not expected to undergo bioaccumulation in aquatic organisms.

Upon release to the atmosphere, TGEE is estimated to undergo photodegradation (atmospheric half life = 2.8 hrs). TGEE is readily biodegradable (71% after 20 days) under aerobic conditions tested in fresh water. In Level III Fugacity modeling, mass balances of < 0.001% in air, 45.3% in water, 54.6% in soil and 0.0755% in sediment were estimated and indicate a low probability of volatilization and a preference for partitioning to water and soil.

TGEE is of low acute aquatic toxicity as tested in a variety of freshwater and saltwater species. In *Pimephales promelas*, the 96-hr LC50 is > 10,000 mg/L. In *Daphnia magna*, the 48-hr LC50 is 10,000 mg/L. In algae, the modeled LC50 (using EPIWIN) is also > 10,000 mg/L. Finally, TGEE will not adversely affect sewage treatment microorganisms (IC50 > 10,000 mg/L).

Exposure

TGEE was produced at an estimated 4,072 – 4,538 tonnes in 1990 in the U.S. TGEE is typically prepared by the

reaction of ethanol and ethylene oxide in the presence of a catalyst. Approximately ninety-five percent of TGEE is used as a major raw material (diluent) in the formulation of hydraulic brake fluid.

Human exposure to TGEE may occur during manufacturing and through the use of this material in hydraulic brake fluids. Due to its low vapor pressure, inhalation exposures will be insignificant whereas dermal exposures may be higher.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION

This chemical is currently of low priority for further work.

Human Health: Triethylene glycol ethyl ether possesses properties indicating a hazard for human health (dermal irritation and mild eye irritation). These hazards do not warrant further work as they are related to reversible, transient effects. They should nevertheless be noted by chemical safety professionals and users.

Environment: Triethylene glycol ethyl ether is currently of low priority for further work due to its low hazard profile.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 112-50-5
OECD Name: Ethanol, 2-(2-(2-ethoxyethoxy)ethoxy)-
Molecular Formula: $C_8H_{18}O_4$
Structural Formula: $C_2H_5O(CH_2CH_2O)_2CH_2CH_2OH$
Molecular Weight: 178.2
Synonyms: Triethylene Glycol Monoethyl Ether
Ethoxytriglycol
Ethyltriglycol
TGEE
Poly Solv TE

1.2 Purity/Impurities/Additives

Degree of Purity: Approximately 85 to 99% by volume

Major Impurities: Tetraethylene glycol monoethyl ether (CAS No. 5650-20-4)

Diethylene glycol monoethyl ether (CAS No. 111-90-0)

Diethylene glycol (CAS No. 111-46-6)

Triethylene glycol (CAS No. 112-27-6)

1.3 Physico-Chemical properties

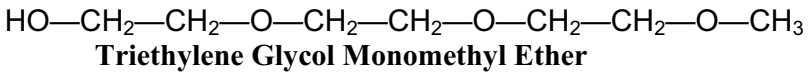
Table 1 Summary of physico-chemical properties

Property	Value	
Melting point	-19ºC	Union Carbide, 1991a
Boiling point	256ºC	Union Carbide, 1991a
Vapour pressure	<0.01 mm Hg (25ºC)	Union Carbide, 1991a
Vapour density	6.16 (air = 1)	Union Carbide, 1991a
Water solubility	completely soluble	Union Carbide, 1991a
Partition coefficient n-octanol/water (log value)	log Kow = -0.96 (calc.)	EPIWIN (v. 3.10)
Flash point	123ºC (closed cup) 135ºC (open cup)	Union Carbide, 1991a Union Carbide, 1991a
Specific gravity	1.025	Union Carbide, 1991a

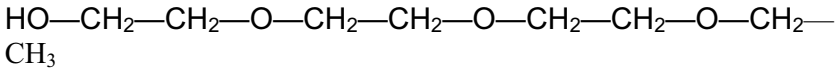
1.4 Analog Justification

Data for triethylene glycol ethyl ether (TGEE) for some endpoints are either missing or limited. Therefore, the close structural analog, triethylene glycol methyl ether (TGME), is used for the genetic, reproductive, neurotoxicity, and algal toxicity endpoints. Figure 1 presents the molecular structures of each compound. Both have similar chemical functionality and differ by only one methylene group in the terminal alkyl moiety.

Figure 1. Chemical Structures of TGEE and TGME



Triethylene Glycol Monomethyl Ether



Triethylene Glycol Monoethyl Ether

A comparison of some physical and chemical properties are presented in Table 2 for these two materials. These values are consistent with the chemicals' similar structures.

Table 2. Comparison of Selected Physicochemical and Environmental Fate Properties of TGEE and TGME

	TGEE	**TGME**
Molecular Weight	178.2	164.2
Boiling Point (^{o}C)	256	249
Water Solubility	Miscible	Miscible
Partition Coefficient (log K_{ow})	-0.96	-1.46
Vapor Pressure (torr, 20^{O}C)	<0.01	<0.01
Specific Gravity (20^{o}/20^{o}C)	1.02	1.05
Biodegradability (BOD_{20})	71%	71%

Although data exist on both of these triethylene glycol ethers for most of the OECD SIDS toxicological end-points (Table 3), more definitive testing has been conducted on TGME.

Table 3. Comparison of Existing Data Set for TGEE and TGME

Environmental Testing	TGEE	TGME
Biodegradability	X	X
Acute Toxicity to Fish	X	X
Acute Toxicity to Daphnids	X	X
Toxicity to Algae		X
ity to Bacteria	X	X
Mammalian Testing		
Acute Oral Toxicity	X	X
Acute Dermal Toxicity	X	X
Acute Inhalation Toxicity	X	X
Skin Sensitization		
Skin Irritation	X	X
Repeated Dose Toxicity	X	X
Reproductive Toxicity		X
Developmental Toxicity	X	X
Neurotoxicity		X
Genotoxicity		
Bacterial Tests		X
Non-Bacterial Tests - *in vitro*		X
Non-Bacterial Tests - *in vivo*		X

A better understanding of the relationship of chemical structure to biological activity can be obtained from a comparison of the acute toxicities and irritancies of these two materials in various species (Table 4). From these data it can be seen that both materials produce quite similar results in comparable tests.

Table 4: Acute Toxicities of TGEE and TGME

	TGEE	**TGME**
Acute Toxicity to Fish (Fathead Minnows, 96-hour LC_{50})	>10,000 mg/l	>10,000 mg/l
Acute Toxicity to Daphnids (48-hour, LC_{50})	>10,000 mg/l	>10,000 mg/l
Acute Oral Toxicity - Rats	10 g/kg	12 g/kg
Acute Dermal Toxicity - Rabbits	8.2 g/kg	7.4 g/kg
Skin Irritation	irritant	irritant

In addition to acute toxicity data, these two materials have been studied side by side in *in vitro* skin absorption, repeated skin application and developmental toxicity screening assays (Leber et al., 1990). Results from these studies are given in Table 4. Although not presented in this document, tests of triethylene glycol butyl ether (TGBE) show comparable results. The results in Table 5 also show the overall lack of toxic response elicited by these congeners. Further, the diffusion rates

through human skin are quite comparable, yet the small magnitude of the values demonstrate that the epidermis affords a considerable barrier to absorption resulting from skin contact.

Use of TGME data for TGEE is also supported based on findings of developmental, reproductive, and neurotoxicity tests of the monoethylene glycol ethers, which show that ethylene glycol methyl ether (EGME) is more toxic than ethylene glycol butyl ether (EGBE) or ethylene glycol ethyl ether (EGEE). Second, limited toxicity for all three triethylene glycol monoethers were found in tests conducted by manufacturers. Based on these findings, EPA decided that testing done with TGME under a Consent Order and a TSCA Section 4 Test Rule were adequate for TGEE and TGBE as well.

Table 5: *In Vitro* Skin Absorption, Repeated Skin Application and Developmental Screening Studies for TGEE and TGME

	TGEE	**TGME**
Human Skin Diffusion Rate ($\sigma g\ cm^{-1}hr^{-1}$)	24	34
21-Day Skin Application (NOAEL-Systemic Toxicity)	1000 mg/kg	1000 mg/kg
Developmental Toxicity (NOAEL-Fetal Effects)	1000 mg/kg (screening study/no effects)	1000 mg/kg (screening study/no effects) 625 mg/kg (increased resorptions/ reduction in mean fetal body weight/ increase in delayed ossification) 300 mg/kg (reduction in mean body weight)

The major use for both of TGME and TGEE is in the formulation of hydraulic brake fluids, –95% of the production volume. In most, if not all of these formulations they are used in combinations with each other.

Given their similar chemical structures, functionality and consistent pattern of physical and chemical properties, it is not surprising that these two triethylene glycol ethers produce very similar patterns of response in biological systems. The fact that in the studies that are directly comparable, both materials demonstrate a relatively low order of overall toxicity and within any one testing procedure results are consistent, lend confidence in the use of TGME as a surrogate for TGEE. Further, the exposure profile for these triglycol ethers is very similar, which should provide confidence in risk evaluation exercises.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The 1990 U.S. production of TGEE is estimated to be 9 to 10 million pounds (4,072 – 4,538 tonnes). Canada's production volume was between 10 and 100 tonnes/year (Canadian Domestic Substances List, 1986, as cited in Taylor, 1996).

Germany does not produce this chemical (Ahlers, 1996).

TGEE is typically prepared in closed, continuous equipment by the reaction of ethanol and ethylene oxide in the presence of a catalyst. The final product is refined by distillation at which point

unreacted alcohol and the mono- and di-ether byproducts are separated. Alternatively, diethylene glycol monoethyl ether may be reacted with ethylene oxide under basic conditions with final purification by distillation.

The primary industrial use of TGEE is 95% as a major raw material (diluent) in the formulation of hydraulic brake fluid.

Other uses include coatings, printing inks, some specialty chemicals, antisudsing agents for finely powdered materials, cleaning products, cutting oils and deicing agents (USEPA, 1995).

Table 5: Use Patterns of TGME (Worldwide and in the United States)

Hydraulic brake fluid	95%
Coatings	~1%
Printing inks	~1%
Antisudsing agents	~1%
Cleaning products	~1%
Cutting oils	~1%
Deicing agents	~1%

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

TGEE can enter the environment through slow escape and evaporation from automotive brake systems. Spills of brake fluids can also occur during brake repair or service in garages and service stations. Typically such spills would be a few drops to under a liter of liquid. Emissions to the atmosphere or surface water occurring via industrial wastes or effluents during manufacture or processing are limited by predominately enclosed processing and low volatility.

2.2.2 Photodegradation

The photodegradation half-life of TGEE (estimated using the EPIWIN/AOP model) is 2.8 hours based on reaction with hydroxyl radicals.

2.2.3 Stability in Water

This chemical does not have any hydrolyzable functional groups.

2.2.4 Transport between Environmental Compartments

The potential distribution of TGEE in the environment has been estimated using the Mackay Level III fugacity modeling approach (EPIWIN). Such modeling estimates relative distribution within different environmental compartments, based on key physical property parameters. A distribution of < 0.001% in air, 45.3% in water, 54.6% in soil and 0.0755 in sediment was estimated using Level III fugacity modeling. This modeling indicates a low probability of volatilization and a preference for partitioning to water and soil.

2.2.5 Biodegradation

Triethylene glycol monoethyl ether is readily biodegradable (BOD Method) under aerobic conditions when tested in fresh water but is only partially degraded when tested in seawater. In fresh water, degradation was calculated to be 71% after 20 days (Waggy, 1987; Price *et al.*, 1974; Bridie *et al*., 1979).

2.2.6 Bioaccumulation

Due to a low estimated value for $\log K_{ow}$ (-0.96, this material is not expected to undergo bioaccumulation.

2.2.7 Other Information on Environmental Fate

TGEE possesses physical properties that suggest that once it enters the aqueous compartment, it tends to remain dissolved in water and will have limited volatilization from water. TGEE is highly soluble in water, has a high boiling point (256 °C) and low vapor pressure (< 0.01 mm Hg at 20 °C).

A soil/sediment partition coefficient (K_{oc}) of 10 has been estimated for TGEE using EPIWIN. This suggests that TGEE has high soil mobility. Thus, it can leach from soil deposits to groundwater, but can also be transported to environments (where aerobic biodegradation can take place).

2.3 Human Exposure

2.3.1 Occupational Exposure

Occupational exposure to TGEE may occur from the inhalation of aerosols or vapors or from dermal exposures. The routine use of protective clothing, face shields and goggles, and chemically resistant gloves at production facilities and at transfer and loading stations will reduce or eliminate exposure to TGEE. Workplace or breathing zone measurements of TGEE concentrations are not available but given the low vapor pressure of this material, inhalation exposure in the workplace should be minimal. Measures employed by the manufacturers of TGEE which are intended to minimize exposure of workers include: manufacture in closed, continuous process vessels; no intermediate drumming of product; transfers of product to tank trucks or railcars employing conservation vents, vapor recovery systems, or vacuum transfer lines. There are no occupational exposure standards or workplace exposure limits for TGEE.

Because no actual monitoring data are available, exposure estimates were modeled by U.S. EPA (1995) using data for triethylene glycol monomethyl ether (TGME). Because these chemicals are used in similar quantities, the results were concluded to be applicable to TGEE.

Manufacturing

Occupational exposure during manufacturing is probably minimal because a closed system presumably is used. Room ventilation and use of PVC-coated gloves are recommended in a Material Safety Data Sheet for TGME as a protective measure. However, a worst-case exposure estimate was determined based on 100% of triethylene glycol ether concentration and the possibility th at workers may not be wearing gloves or respirators. Inhalation exposure to TGME during sampling, drumming, filling tankwagons, cleaning, and maintenance is estimated to range from 0.019 to 10.8 mg/day (8-hour time-weighted-average) and dermal exposure is estimated to range from 1,950 to 3,900 mg/day.

Processing

Some exposure may occur during the formulation of products that contain triethylene glycol ethers (such as brake fluids). No specific information on the processing of these glycol ethers was found, but the glycol ethers would be unloaded or undrummed into storage tanks and then pumped to a mixing tank for blending into the final product. Exposure may also occur during filtration and sampling. Using the dermal and inhalation exposure estimates for 100 percent triethylene glycol ethers noted above under Manufacturing, exposures to products that contain a smaller percentage of triethylene glycol ether can be estimated by multiplying the manufacturing exposure estimates by the actual concentration of glycol in a mixture (e.g., 40-60 per cent for brake fluids). Assuming 60 per cent weight concentration, dermal exposure from processing operations may range from 1,170 to 2,340 mg/day (as a worst-case estimate) and inhalation exposure may range from 0.01 to 6.5 mg/day.

Use

Exposures of automobile repair shop workers to TGME in brake fluid can be estimated. Using the method in USEPA (1991) and assuming one brake job per day, an automobile repair worker's potential dermal dose rate ranges from 260 to 2,340 mg/day for as many as 250 days each year (which translates to 65,000 to 585,000 mg/year). The potential dermal dose rate may increase as additional brake jobs are done during the workday.

For inhalation exposure, two methods were used to estimate airborne TGME concentrations in the workplace. The analogous data method estimates the concentration of TGME in air based on known concentrations of 2-methoxyethanol (2-ME) and the ratio (vapor pressure * mole fractions within the airborne mixture) of each compound. The mass balance method uses the vapor pressure and molecular weight of TGME plus assumptions about how the chemical moves in the air to estimate air concentrations. Airborne TGME levels of 2 ppm (13.3 mg/m^3) and 0.95 ppm (6.4 mg/m^3) were estimated for the analogous data and mass balance methods, respectively. Central tendency inhalation dose rates were estimated as 133 mg/day by the analogous data method, with 2-ME as the analog, and 64 mg/day by the mass balance method. Inhalation dose rates are time-weighted-average exposures during an 8-hour workday. As these worst-case estimates indicate, inhalation exposure is not expected to be significant in any setting.

2.3.2 Consumer Exposure

The primary use for TGEE is in hydraulic brake fluids. Consumer exposure could occur either by inhalation or by dermal absorption. Given the low vapor pressure of this material, inhalation exposure is expected to be minimal.

Assuming a consumer takes two hours to do one brake job per year in an enclosed space, using the EPA methods described under **Occupational exposure,** EPA estimated a dermal exposure rate range of 260 to 2,340 mg/year (0.71 to 6.41 mg/day) and a central tendency inhalation potential dose rate of 16 mg/year (0.044 mg/day) by the mass balance model or 33 mg/year (0.090 mg/day) by the chemical analog model.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

The *in vitro* rate of penetration of TGEE through human epidermis was reported as 0.024 mg/cm^2/h (Leber et al, 1990). The main metabolic pathway for metabolism of TGME and TGEE (and presumably the category members) is oxidation via alcohol dehydrogenase that leads to the formation of an alkoxy acid (Bingham et al., 2001). A second important route of metabolism is oxidation by P-450 mixed function oxidases (O-dealkylation) that lead to the formation of triethylene glycol (TEG). TEG may be oxidized to a carboxylic acid. The principal metabolite of TGME is believed to be 2-[2-(2-methoxyethoxy)ethoxy] acetic acid (Gill et al., 1998).

3.1.2 Acute Toxicity

TGEE is of low acute toxicity in experimental animals by the oral, dermal, or inhalation routes of exposure. Smyth *et al*. (1951) report an oral LD_{50} in rats (unspecified strain) as 10.6 g/kg. More recently, an oral LD_{50} of 8.5 g/kg in male Wistar rats was reported (MB Research Laboratories, 1977a).

Rats exposed by inhalation to TGEE for 1 hr at 200 mg/L survived and appeared normal (MB Research Laboratories, 1977b). Smyth and Carpenter (1948) and Moreno (1976a) report dermal LD_{50} values of 8.2 and > 3.2 g/kg in rabbits, respectively.

3.1.3 Irritation

Results of two skin irritation tests are conflicting; one (MB Research Laboratories, 1977c) suggests that TGEE is irritating to skin and another indicates that it is not (Moreno, 1977). The purity of the material used in these studies is unknown. Necropsy results from the study employing 2.0 g/kg showed mottled liver, white nodules, pocked kidneys, and dark areas in the lungs (MB Research Laboratories, 1977c).

Results of two eye irritation tests indicate that TGEE is mildly irritating to eyes (Smyth and Carpenter, 1948; Moreno, 1976b).

3.1.4 Sensitisation

There are no data available for this endpoint.

3.1.5 Repeated Dose Toxicity

Administration of TGEE dermally to rats (male and female) at 1000 mg/kg, five days/wk for 3 weeks resulted in only slight erythema and edema. No other significant toxicological effects were noted (Leber *et al*., 1990).

Mellon Institute (1945) reports a NOAEL of 750 mg/kg/d in rats administered TGEE in drinking water for 30 days. Effects at higher doses (3,300 and 13,290 mg/kg/d) included mortality, substantially lower water consumption, liver and kidney injury, lowered body weight gain, and high blood urea concentrations.

3.1.6 Mutagenicity

TGEE has not been tested for its mutagenicity either *in vivo* or *in vitro*. Based on the lack of mutagenicity of TGME, TGEE is not expected to be a mutagen. Specifically, negative results were obtained when TGME was tested for genetic mutations in *Salmonella* or Chinese hamster ovary cells (either with or without metabolic activation)(Samson and Gollapudi, 1990; Liscombe and Gollapudi, 1990), or for chromosomal aberrations in a mouse micronucleus test (McClintock and Gollapudi, 1990).

3.1.7 Carcinogenicity

There are no data available.

3.1.8 Toxicity for Reproduction

Effects on Reproductive Organs

Although mating studies with TGEE have not been performed, several of the repeated dose toxicity tests with TGEE and the related material TGME have included examination of reproductive organs. Results of the 30-day drinking water study with TGEE showed that toxicity to reproductive organs did not occur at doses as high as 13,290 mg/kg/d (Mellon Institute, 1945). In a 21-day dermal study with 1,000 mg/kg/day TGEE in rabbits, testicular degeneration was observed in one rabbit given TGEE (Leber, 1990). Testicular effects included spermatid giant cells, focal tubular hypospermatogenesis, and increased cytoplasmic vacuolization. The pathologist grading the lesions stated that "random occurrence of this lesion was suggestive of its spontaneous nature" and was not test-article related. A high incidence of similar changes of spontaneous nature in normal New Zealand White rabbits has been reported by Morton *et al*. (1986a,b). However, an alternate explanation could be that some animals are more sensitive to the effects of TGEE at this dose, since many of the ethylene glycol ethers exhibit testicular and other reproductive effects. Nonetheless, it is true that the triethylene series is much less potent than the ethylene series.

Because only tests of shorter duration are available for TGEE, longer-term oral and dermal data for TGME are also presented. In an oral study, ,male rats treated with 4,000 mg/kg/day TGME in the diet for 91 days exhibited degeneration (12/15) and/or atrophy (5/5) of the seminiferous tubules (spermatocytes or developing spermatids) (Gill and Negley, 1990; Gill *et al*., 1998). These effects were considered to be related to treatment. The severity of the lesions was primarily mild to moderate for degeneration (11/12) and minimal to moderate for atrophy (5/5), indicating that not all tubules were affected and that a limited number of cells was affected within the affected tubules. One male treated with 1,200 mg/kg had severe seminiferous tubule atrophy, a complete loss of cell types in the tubules (except for Sertoli cells) and moderate Leydig cell hypertrophy (not significantly different from controls). The NOAEL was between 400 and 1,200 mg/kg/day for testicular effects (Anderson, 1995).

In a published version (Gill *et al*., 1998) of the aforementioned study, the authors stated that a possible contributing factor in the development of testicular lesions at the high dose was low-level contamination of the test substance with the known testicular toxicant EGME. EGME was present in the test substance at a concentration of 0.02 – 0.04 %, resulting in an EGME dose up to 1.7 mg/kg/day for animals in the high dose group. Given the length of the study, it is possible that EGME contributed to the testicular lesions.

In a 91-day dermal study of TGME in rats, bilaterally-decreased spermatogenesis in seminiferous tubules and decreased spermatozoa in the epididymes (both were graded as severe) were noted in the testes of 1/10 high dose (4000 mg/kg/day) males (Corley *et al*., 1990; Gill *et al*., 1998). The

testes of one male treated with 1,200 mg/kg/day exhibited different testicular changes [bilateral multifocal degeneration of spermatocytes and spermatids (graded as very slight), and multinucleated spermatids]. The incidence of animals with lesions (1/10 in each group) was within the range of historical controls (0-17%).

The degenerative changes in the testes of one mid-dose and one high-dose rat in the 91-day dermal study were not consistent with the types of lesions that have been attributed to EGME. The cell types that are most vulnerable to EGME are the pachytene spermatocytes and round spermatids (Chapin *et al*., 1985). As the dose of EGME is increased, the number and types of cells affected increase up to the point that the germinal epithelium is significantly degenerated and all stages of spermatogenesis are affected (Chapin *et al*., 1985; Miller *et al*., 1983.). In contrast, the testicular effects seen with the high dose animal treated with TGME consisted of a virtually complete lack of mature spermatids beyond stage 12. All other stages, including spermatogonia and spermatocytes, were present and appeared morphologically normal. In the mid-dose rat, the only effects noted consisted of very slight degeneration of spermatocytes and spermatids similar to those seen in historical control animals." The lymphoid tissues and hematological changes that have been reported at doses of EGME that have been associated with testicular changes were unaffected in this study.

Based on severe testicular toxicity in 1/10 rats given 4,000 mg/kg/day and minimal decreases in developing germ cells (1-5% of semineferous tubules affected) in 1/10 rats given 1,200 mg/kg/day, the NOAEL was between 400 and 1200 mg/kg/day in the aforementioned study (Anderson, 1995).

Results of a developmental toxicity study (see below) suggest that treatment with up to 1000 mg/kg/day TGEE by gavage during gestation days 7-16 had no effect on reproduction of females.

Based on the aforementioned data and the expectation that data from TGME are applicable to TGEE, EPA recommended no reproductive toxicity testing for triethylene glycol monoethyl ether (U.S. EPA, 1995).

Developmental Toxicity

TGEE was given to rats in one developmental toxicity study. Administration of TGEE by gavage to pregnant rats at 250 and 1000 mg/kg/day on days 7 through 16 of gestation resulted in no significant changes in clinical conditions or body weights in mothers or adverse effects on the *in utero* development of the conceptus or on viability of the offspring (Leber *et al*., 1990). The NOAEL reported for this study was 1000 mg/kg.

Developmental toxicity studies of TGME show that in some studies, no effects on the fetus are noted at doses of > 1,000 mg TGME/kg/day during gestation (Wason et al., 1986; Leber et al., 1990). Alternately, at 1,250 to 1,650 mg/kg/day TGME (in the rat) and 1,500 mg/kg/day (in the rabbit), developmental effects observed included skeletal variants and decreased body weight gain (Hoberman, 1990a; 1990b). Finally, a NOEL for developmental toxicity of 300 mg TGME/kg/day is assigned to a gavage study in rats, based on decreased postnatal weight gains at 1,650 and 3,000 mg/kg/day (Bates and de Serres, 1992).

Conclusion

In repeated-dose toxicity tests of TGEE, a 30-day drinking water study showed no effects on reproductive organs at doses up to 13,290 mg/kg/day. However, in a 21-day dermal study, testicular effects were seen in one animal at 1,000 mg/kg/day. A longer-term oral (diet) study of TGME (of 90 days) found testicular effects in several animals at 4,000 mg/kg/day and some effects in one animal at 1,200 mg/kg/day. A dermal TGME study of the same length resulted in testicular effects in one animal each at 4,000 and 1,200 mg/kg/day. Since some doses resulted in effects in

only one animal, it is not clear whether the effect was related to treatment or was a random occurrence. However, given that several studies resulted in these effects to a minimal degree, it is possible that some animals show greater sensitivity than others. All effects were seen at fairly high doses.

A single developmental toxicity screening test of TGEE in rats resulted in no effects at doses up to 1,000 mg/kg/day.

3.1.9 Neurotoxicity

Treatment with the related material TGME at concentrations up to 4000 mg/kg/day in drinking water for 90 days did not result in any clinical signs of toxicity, alterations in the functional observational battery, or gross microscopic lesions in the nervous system of rats (Gill and Negley, 1990, Gill *et al*., 1998). Significant, small decreases in total test session motor activity were observed in rats treated with 4,000 mg/kg/day at the Day 60 (males only) and Day 90 (females) evaluation periods. Study personnel stated that "the decreases in motor activity were not considered to be neurotoxicologically significant based on the small magnitude of the changes, the parallel changes in body weights at the evaluation periods, and the lack of corroborative behavioral effects from the functional observational battery evaluations or histological changes in central or peripheral nervous system tissues."

In a developmental neurotoxicity test in which pregnant rats were administered TGME by gavage (0, 300, 1650, 3000 mg/kg/day) on gestation day 6 through postnatal day 21, Bates (1992) found that a dose level of 3000 mg/kg/day resulted in increases in auditory startle amplitude and decreases in latency to maximum startle, but no changes in the habituation process, in the pups of the dosed females. Auditory startle response was assessed on postnatal days 22 and 60. There were no significant effects on measurements of motor activity or active avoidance behavior. Motor activity was assessed for 1 hr in a Figure 8 maze on postnatal days 13, 17, 21, 47, and 58 and learning and memory were assessed with an active avoidance paradigm run on postnatal days 60-64. There were no neurotoxic effects in offspring at maternal doses up to 1650 mg/kg/day.

3.2 Initial Assessment for Human Health

Human exposure to TGEE will occur during manufacturing and through the use of this material in hydraulic brake fluids. Due to the low vapor pressure of TGEE, inhalation exposures will be insignificant. More significant occupational dermal exposures may occur; however, the effects would be mitigated by use of personal protective equipment. Occasional consumer exposure (primarily by the dermal route) may occur when home mechanics top off their master brake cylinders with brake fluids purchased in small containers.

Results from animal testing indicate a low potential for acute or chronic toxicity of TGEE. TGEE is not acutely toxic when administered orally, dermally, or by inhalation. It has been demonstrated to be a skin irritant and a mild eye irritant in rabbits. In a 3-week dermal study, TGEE produced only slight erythema and edema in rats at 1000 mg/kg. A NOAEL of 750 mg/kg/d in rats was determined after TGEE was administered in drinking water for 30 days. TGEE was not teratogenic in rats at 1000 mg/kg, the reported NOAEL for this study.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Data from aquatic toxicity tests suggest that TGEE exhibits low toxicity to aquatic species. In addition, EPIWIN modeling indicates that the EC_{50} value for algae is > 10,000 mg/l. Results from a study with the related material TGME shows an EC_{50} value of > 500 mg/l in algae (BASF, 1989). Based on the available data, TGEE will not adversely affect sewage treatment microorganisms.

Table 7 presents experimental and predicted toxicity values. The predicted values are based on SARs for neutral organics. Input values for the prediction were a molecular weight of 178.23; log K_{ow} –0.96; melting point – 19∀C, boiling point of 256∀C, and vapor pressure of 0.01 mm Hg.

Table 7. Experimental and Predicted Aquatic Toxicity Values

Ecotoxicity Effect	Experimental (mg/L)	Predicted (mg/L)
Fish 96-h LC50	> 10,000 (FHM)	80,054
Daphnid 48-h LC50	> 10,000	69,917
Green algal 96-h EC50		36,862
Fish chronic value (30-day ChV)		6,400
Daphnid chronic value (16-day EC50)		982
Green algal 96-hr chronic value		666
Sewage microorganisms (IC50)	> 10,000	

Note: FHM = fathead minnow

4.2 Terrestrial Effects

No data are available.

4.3 Other Environmental Effects

There are no data available.

4.4 Initial Assessment for the Environment

A qualitative environmental analysis indicates that TGEE has a low potential for an adverse environmental impact. In particular, volatilization from water, adsorption to soil, and bioconcentration within food chains will not be important factors in the environmental fate of TGEE. TGEE will biodegrade in aerobic surface waters and under typical secondary waste treatment conditions. It is also of low aquatic toxicity.

5 RECOMMENDATIONS

Human Health: Triethylene glycol ethyl ether possesses properties indicating a hazard for human health (dermal irritation and mild eye irritation). These hazards do not warrant further work as they are related to reversible, transient effects. They should nevertheless be noted by chemical safety professionals and users.

Environment: Triethylene glycol ethyl ether is currently of low priority for further work due to its low hazard profile.

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SIDS DOSSIER

0. General Information

Name of Sponsor Country United States of America
Contact point (name, address, telephone and telefax)

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Name of Lead Organization: U.S. Environmental Protection Agency

1. Chemical Identity

1.1 CAS Number 112-50-5

1.2 Name (give the name supplied by the OECD)

Ethanol, 2-(2-(2-ethoxyethoxy)ethoxy)-

1.3. Common Synonyms

Triethylene glycol monoethyl ether
Ethoxytriglycol
Ethyltriglycol
TGEE
Poly Solv TE

1.4 Empirical formula

C8H18O4

1.5 Structural formula

HO-CH2CH2O-CH2CH2-O-CH2CH2-OCH2CH3

1.6 Purity of Industrial Product

1.6.1 Degree of purity (percentage by weight/volume)

Approximately 85-99% by volume

1.6.2 Identity of major impurities

Tetraethylene glycol monoethyl ether (CAS No. 5650-20-4)
Diethylene glycol monoethyl ether (CAS No. 111-90-0)
Diethylene glycol (CAS No. 111-46-6)
Triethylene glycol (CAS No. 112-27-6)

1.6.3 Essential additives (stabilizing agents, inhibitors, other additives), if applicable

Not applicable.

2. Physical-Chemical Data

2.1 Melting or Decomposition Point

-19∀C

Method (e.g., OECD, other):

GLP: YES [ ]
NO [ ] Not reported

Comments: Freezing Point

Reference: Union Carbide Chemicals & Plastics Co. Inc.
Solvents & Coatings Materials Division (1991). Material Safety Data Sheet. November 26.

2.2 Boiling Point (including temperature of decomposition, if relevant)

256∀C at 760 mmHg

Method (e.g., OECD, other): Not Reported

GLP: Yes [ ]
No [ ] Not reported.

Comments:

Reference: Union Carbide Chemicals & Plastics Co. Inc. Solvents & Coatings Materials Division (1991) Material Safety Data Sheet. November 26.

2.3 Vapor Pressure

<0.01 mmHg at 20∀C

Method (e.g., OECD, other): Not reported.

GLP YES [ ]
NO [ ] Not reported.

Comments:

Reference: Union Carbide Chemicals & Plastics Co. Inc.
Solvents & Coatings Materials Division. (1991) Material Safety Data Sheet. November 26.

2.4 Partition Coefficient n-Octanol/Water

log Pow = - – 0.96

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [ ] Not reported.

Analytical Method: Calculated using EPISUITE v 3.10, computer software estimation program.

Comments:

Input values were: melting point of – 19∀C and boiling point of 256∀C. Chemicals with log octanol/water coefficients of less than 3 do not have the potential to bioconcentrate.

Reference: U.S. Environmental Protection Agency. 2000. EPIWIN Version 3.10. Computer software developed by EPA's Office of Pollution Prevention and Toxics and Syracuse Research Corporation.

2.5 Water Solubility

100% at 20∀C

Method (e.g., OECD, other): Not reported.

GLP: YES [ ]
NO [ ] Not reported.

Analytical Method: Not reported.

Comments:

Reference: Union Carbide Chemicals & Plastics Co. Inc.
Solvents & Coatings Materials Division. (1991) Material Safety Data Sheet. November 26.

2.6 Flash Point (liquids)

123∀C (Tag closed cup)135∀C (Cleveland open cup)

Method (e.g., OECD, other including reference to the standard used): Not Reported

GLP: YES [ ]
NO [ ] Not reported.

Comments:

Reference: Union Carbide Chemicals & Plastics Co. Inc.
Solvents & Coatings Materials Division. (1991) Material Safety Data Sheet. November 26.

2.7 Flammability (solid/gases)

Method (e.g., OECD, other): Not reported.

GLP: YES [ ]
NO [ ] Not Reported.

Test results: Lower limit: 1.0% by volume in air
Upper limit: 6.5% by volume in air

Comments:

Reference: Union Carbide Chemicals & Plastics Co. Inc. Solvents & Coatings Materials Division. (1991) Material Safety Data Sheet. November 26.2.8

2.8 pH in Water

NO DATA AVAILABLE

Method (e.g., OECD, other):

GLP: YES [ ]
NO [ ]

Comments:

References:

2.9 Other Data

Vapor Density (air = 1): 6.16
Specific Gravity (H2O = 1): 1.025

Comments:

References: Union Carbide Chemicals & Plastics Co. Inc.
Solvents & Coatings Materials Division. 1991. Material Safety Data Sheet. November 26.

3. Source of Exposure

3.1 Production Levels (tonnes per annum)

Information on production levels should be provided in ranges (e.g, 100-1000 tonnes, etc.) per responder or country and the date for which those ranges apply should be given.

Estimated 1990 U.S. production: 9-10 million pounds (4,072-4,538 tonnes).

3.2 Processes

Triethylene glycol monoethyl ether is typically prepared by the reaction of ethanol and ethylene oxide in the presence of a catalyst. The final product is refined by distillation at which point unreacted alcohol and the mono- and di-ether byproducts are separated. Alternatively, diethylene glycol monoethyl ether may be reacted with ethylene oxide under basic conditions with final purification by distillation.

3.3 Information Concerning Uses (including categories and types of uses expressed in percentage terms)

Hydraulic brake fluid (industrial and public use) is the primary use for this compound.

3.4 Options for Disposal

Incinerate in a furnace where permitted under appropriate federal, state and local regulations. In a very dilute solution, this material can be biodegraded in an activated sludge biological waste treatment system.

Reference: Union Carbide Chemicals & Plastics Co. Inc.
Solvents & Coatings Materials Division. 1991. Material Safety Data Sheet.
November 26.

3.5 Other Remarks

4.0 Environmental Fate and Pathways

4.1 Degradability (biotic and abiotic)

4.1.1 Biodegradability

Test substance: Triethylene glycol monoethyl ether

Test type: aerobic [X], anaerobic [ ]

Test medium: (1) freshwater (2) artificial seawater

In the case of poorly soluble chemicals, treatment given (nature, concentration, etc.): Not applicable

Test method (e.g., OECD, ISO, other):

Biochemical oxygen demand (BOD) method published in Standard Methods for the Examination of Water and Wastewater, 13h ed., Am. Public Health Ass'n (1971).

GLP YES [ ]
NO [X] .

Test results:

(1)	BOD5:	8%	(2)	BOD5:	1%
	BOD10:	47%		BOD10:	10%
	BOD15:	63%		BOD15:	12%
	BOD20:	71%		BOD20:	22%

Comments: A modified version of the biochemical oxygen demand (BOD) method published in "Standard Methods for the Examination of Water and Wastewater", 16th edition, Am. Public Health Association, 1985 was used. Nonacclimated domestic sewage organisms were used as seed in the test. The test period was extended to 20 days. Reaeration (if needed) was accomplished by dividing the BOD bottle contents between 2 BOD bottles, sealing, shaking twenty times, returning contents to the original BOD bottle, recording the oxygen level, resealing, and returning the BOD bottle to the incubator. A discussion of these modifications appears in Price et al., "Brine shrimp bioassay and seawater BOD of petrochemicals", J. Water Poll. Control Fed., Jan. 1974. The concentrations of test material and bacteria were not listed in the report. Purity of test material was not noted.

Reference:

(1) Waggy, G.T. (1987) Glycol Ethers-Summary of Available Ecological Fate and Effects Data. Union Carbide Corporation Project Report. November 19.

(2) Waggy, G.T. and J.R. Payne. 1974. Environmental Impact Analysis Product Biodegradability Testing. Union Carbide Corporation Project Report. August 12.

(3) Price, K.S., Waggy, G.T., and R.A. Conway (1974) "Brine shrimp bioassay and seawater BOD of petrochemicals," 46 J. Water Poll. Control Fed. 63.

4.1.2 Sewage Treatment

Information on treatability of the substance

NO DATA AVAILABLE

4.1.3 Stability in Air (e.g., photodegradability) and in Water (e.g., hydrolysis)

Test substance: Triethylene glycol monoethyl ether

Test method or estimation method (e.g., OECD, other): EPIWIN

GLP YES [ ]
NO [ ] N/A

Test results: Predicted half-life is 2.829 hours

Percentage of degradation after certain period: Not reported.

Comment: Half-life was calculated using the AOP Program (v.1.90) in the EPIWIN Suite (v. 3.10). The overall OH rate constant was 45.3733 x 10^{-12} cm^3/molecule-sec. The HYDROWIN model could not calculate a hydrolysis rate constant for the material.

Reference: EPIWIN Suite (v. 3.10)

4.1.4 Identification of main mode of degradability in actual use.

NO DATA AVAILABLE

4.2 Bioaccumulation of Main Mode of Degradability in Actual Use

NO DATA AVAILABLE

4.3 Transport and Distribution (between environmental compartments including estimate of environmental concentrations and distribution pathways)

Method: Calculation of environmental distributions using Fugacity Model (Level III)

Input values: Melting point = -19C
Boiling point = 256C
Vapor pressure = 0.01 mm Hg

Equal emissions to air, water, and soil (1000 kg/hr).

Results: Environmental distributions -

Air:	<0.01
Water:	45.3
Soil:	54.6
Sediment:	0.0755

Comment: The Koc estimated using the PCKOC Program (v. 1.66) is10.

Reference: Episuite (v 3.10) – computer estimation software

4.4 Monitored/Modeled Concentrations (Environment)

Test substance: Triethylene glycol monoethyl ether

Indicate whether the data are measurements or background concentrations or measurements at contaminated sites:

- air: 0. 38 * (σg/m3)

  *Maximum predicted 1989 annual average air concentration at the fenceline of Union Carbide's manufacturing facility, obtained using EPA Industrial Source Complex-Long Term averaging guideline model. No other monitoring data are available.

Reference: Union Carbide Chemical & Plastics Co. Inc. (1991) Air Dispersion Modeling – Seadrift Plant (Ethoxytryglycol) May 23.

5. Ecotoxicological Data

5.l Toxicity to Fish

5.1.1 Results of Acute Tests

Test substance: Triethylene glycol monoethyl ether

Test species: Fathead minnow

Test method (e.g., OECD, other):

- o Type of test: static [X], semi-static [ ], flow-through [ ]
- o Other (e.g., field test) [ ]

Bioassay procedures generally followed the techniques recommended in Standard Methods for the Examination of Water and Wastewater, 13th ed., 1971, Am. Public Health Assoc.

GLP YES [ ]
NO [ ] Not Reported.

Test results:

96-hour LC50: > 10,000 mg/L.

Comments: EPA/ASTM bioassay procedures were followed in obtaining these values. .An initial range-finding test was conducted using 2 fish exposed to concentrations ranging from 10 to 10000 mg/l. Definitive tests were performed with 10 fish (2.5 to 5 cm) per test concentration in vessels containing 18.5 liters of dilution water under minimal controlled aeration (after the first four hours of the test). Fish were exposed for up to 96 hours. The temperature of the water ranged from 71 to 76 degrees F, the pH from 7.2 to 7.6, the total alkalinity from 30-40 mg/l, the total hardness from 30 to 60 mg/l, and the dissolved oxygen from 7.5 to 9.0 mg/l. Purity of test material was not noted.

Reference:

(1) Waggy, G.T. (1987) Glycol Ethers-Summary of Available Ecological Fate and Effects Data. Union Carbide Corporation Project Report. November 19.

(2) Waggy, G.T. and J.R. Payne (1974) Environmental Impact Product Analysis – Acute Aquatic Toxicity Testing. Union Carbide Corporation Project Report. January 25.

Test substance: Triethylene glycol monoethyl ether

Test species: Goldfish

Test method (e.g., OECD, other): APHA, 1971

- o Type of test: static [ ], semi-static [ ], flow-through [ ]
- o Other (e.g., field test) [ ]

GLP YES [ ]
NO [ ] Not Reported.

Test results:
TL_m(24-hr)>5,000 mg/l

Comments:

Reference: Bridie, A.L.,Wolff, C.J.M., and Winter, M. (1979). The acute toxicity of some petrochemicals to goldfish. Water Res. 13(7):623-6.

5.1.2 Results of Long Term Tests (e.g., prolonged toxicity, early life-stage)

Test substance: Triethylene glycol monomethyl ether

Test species: fish

Test method (e.g., OECD, other): ECOSAR

GLP YES [ ]
NO [ ] N/A

Results: 14-day LC50 = 90602.828 mg/L, 30 day ChV = 6400.026mg/L

Comments: Calculated with a calculated Log Kow of –0.96, a water solubility of 1 E 6 mg/L and a molecular weight of 178.23.

Reference: U.S. Environmental Protection Agency. 2000. EPIWIN Version 3.10. Computer software developed by EPA's Office of Pollution Prevention and Toxics and Syracuse Research Corporation.

5.2 Toxicity to Daphnids

5.2.1 Results of Acute Tests

Test substance: Triethylene glycol monoethyl ether

Test species: Daphnia magna

Test method (e.g., OECD, other): EPA/ASTM bioassay procedures were closely followed.

GLP YES [ ] Not reported.
NO [ ]

Test results:

48-hour LC50: > 10,000 mg/L

Comments: Daphnia magna stocks were originally obtained from the EPA laboratory at Duluth, MN. They were maintained at 20-22 degrees C in a series of 600 ml beakers filled with Kanawha River water obtained from the South Side Boat Ramp (Charleston, SC). Daphnia were fed three times a week with a laboratory-prepared food consisting of trout food, yeast and alfalfa powder. Daphnia used in the test were offspring of 20-50

gravid females isolated for 24 hours.

A series of from 5-10 equidistant concentrations based on results of fish toxicity studies (plus control) were tested. Tests were conducted in 250 ml beakers containing 100 ml of test solution (in Kanawha River water) and 5 Daphnia (less than 24 hours old). Tests were run in duplicate. Dissolved oxygen and pH were determined initially and at 48 hours for all test solutions. Total hardness, alkalinity, pH and conductivity of the test and holding water were 55 mg/l as CaCO3, 36 mg/l as CaCO3, 6.7, and 250 micromhos/cm. Mortalities were recorded at 24 and 48 hours. Purity of test material was not noted

Reference: Waggy, G.T. (1987) Glycol Ethers-Summary of Available Ecological Fate and Effects Data. Union Carbide Corporation Project Report. November 19.

5.2.2 Results of Long-term Tests (e.g., reproduction)

Test substance: Triethylene glycol monomethyl ether

Test species: Daphnid

Test method (e.g., OECD, other): ECOSAR

GLP YES [ ]
NO [ ] N/A

Results: 16-day EC50 = 982.159 mg/L

Comments: Calculated with a calculated Log Kow of –0.96, a melting point of –19C, a boiling point of 256C, and a molecular weight of 178.23.

Reference: U.S. Environmental Protection Agency. 2000. EPIWIN Version 3.10. Computer software developed by EPA's Office of Pollution Prevention and Toxics and Syracuse Research Corporation.

5.3 Toxicity to Algae

Test substance: Triethylene glycol monoethyl ether

Test species:

Test method (e.g., OECD, other): QSAR calculation

GLP YES [ ]
NO [ ] Not applicable

Test results: EC50 = 36,900 mg/l, predicted using a calculated Log Kow of –0.96 and a molecular weight of 178.23

Comments: A prediction based on SAR analysis was deemed adequate to satisfy the algal toxicity SIDS endpoint

Reference: U.S. Environmental Protection Agency. 2000. EPIWIN Version 3.10. Computer software developed by EPA's Office of Pollution Prevention and Toxics and Syracuse Research Corporation.

Test substance: Related substance (Triethylene glycol monomethyl ether)

Test species: Scenedesmus subspicatus

Test method (e.g., OECD, other): other

GLP YES [ ]
NO [ ] Not reported

Test results: EC50 > 500 mg/l

Reference: BASF. 1989. Algentest for Methyltriglykol (2/1017/88/t72), dated 15.09.1989.

5.4 Toxicity to Other Aquatic Organisms

Test substance: Triethylene glycol monoethyl ether

Test species: Brine shrimp

Test method (e.g., OECD, other): 24-hour screening test to determine median tolerance level (TL_m)

- Type of test: static [ ], semi-static [ ], flow-through [ ]
- Other (e.g., field test) [ ]

GLP YES [ ]
NO [ ] Not reported.

Test results:

LC50 or EC50 values (acute) TL_m: > 10,000 mg/L

Comments:

Reference: Price, K.S., Waggy, G.T., and Conway, R.A. (1974) “Brine shrimp bioassay and seawater BOD of petrochemicals,” 46 J. Water Poll. Control Fed. 63

5.5 Toxicity to Bacteria

Test substance: Triethylene glycol monoethyl ether

Test species: Not reported.

Single species tests such as “Microtox Photobacterium luminescence test" and tests an overall processes such as nitrification or soil respiration are included in this item.

Test method (e.g., OECD, other):

- Type of test: static [ ], semi-static [ ], flow-through [ ]
- Other (e.g., field observation) [ ]

Determined by turbidity/growth procedures where the median inhibition concentration (IC50) is measured after 16 hours of incubation at 23∀C in the presence of nutrients, buffer, growth substrate and sewage microorganisms. Purity of test material was not noted.

GLP YES [ ]
NO [ ] Not Reported

Test results: IC50 : > 10,000 mg/L

Comments:

Reference: Waggy, G.T. (1987) Glycol Ethers-Summary of Available Ecological Fate and Effects Data. Union Carbide Corporation Project Report. November 19.

5.6 Toxicity to Terrestrial Organisms

5.6.1 Toxicity to Soil-Dwelling Organisms

NO DATA AVAILABLE

5.6.2 Toxicity to Plants

NO DATA AVAILABLE

5.6.3 Toxicity to Birds

NO DATA AVAILABLE

5.7 Biological Effects Monitoring (including biomagnification)

NO DATA AVAILABLE

5.8 Biotransformation and Kinetics in Environmental Species

NO DATA AVAILABLE

6.0 Toxicological Data (oral, dermal and inhalation, as appropriate)

6.1 Acute Toxicity

6.1.1 Acute Oral Toxicity

Test substance: Triethylene glycol monoethyl ether

Test species/strain: Rat/strain not reported

Test method (e.g., OECD, EC, limit test):

Details of test not reported.

GLP YES [ ]
NO [ ] Not Reported.

Test results:

LD50: 10.6 g/kg

Comments: Groups of 10 albino male rats (87-124 g) were given test material by gavage as a dispersion in 1% Tergitol 7 at doses of 7.95, 8.9, 10.0, and 12.6 g/kg (1.4 to 3.0 ml of dispersion containing 0.5 g/ml). Mortality was recorded over 14 days. Body weights were determined at study termination (for survivors). All rats given 7.95 g/kg lived to day 14. The incidence of mortality in the other groups was 1/10 for the 8.9 g/kg group, 6/10 for the 10.0 g/kg group, and 10.10 for the 12.6 g/kg group. All deaths occurred within 5 days. Survivors gained weight and appeared normal histologically. The LD50 value was calculated as 10.61 g/kg, with a range of 9.98 to 11.28 g/kg.

Reference: Smyth et al. (1951) Arch. Ind. Hyg. Occup. Med. 4: 119 plus Smyth, H.F. and C.P. Carpenter (1948) Ind. Hyg. Toxicol. 30: 63. [Cited in Patty's Indust. Hyg. and Toxicol.), 4th Ed. Vol. II D, p. 2859.]

Test substance: Triethylene glycol monoethyl ether

Test species/strain: Rat/Wistar

Test method (e.g., OECD, EC, limit test):

Details of test not reported.

GLP YES [ ]
NO [ ] Not Reported.

Test results:

LD50: 8.5 g/kg

Comments: Rats (200-300 g) were fasted for approximately 18 hours prior to test material administration. Test material was given by intubation at 5.0, 7.12, 10.14, and 14.43 g/kg to groups of 10 animals. Food and water were freely available after treatment.

Rats were observed for toxicity and death for 14 days. The LD50 value and 95% confidence limits were determined by the method of Horn (Biometrics 12:311, 1956).

One rat given 7.12 g/kg died on day 10. Nine out of 10 rats given 10.14 g/kg died by day 3, and all rats given 14.43 g/kg died within 24 hours. Clinical observations included lethargy, ataxia, flaccidity, piloerection, and blood in the urogenital area. Gross necropsy in the high dose group revealed dark lungs and liver, very red intestines, and yellow areas in the intestines.

Reference: MB Research Laboratories, Inc. 1977. Report on Oral LD50 in Rats. EPA Document No. 878216031, Fiche No. OTS0206799. [As cited in TSCATS.]

6.1.2 Acute Inhalation Toxicity

Test substance: Triethylene glycol monoethyl ether

Test species/strain: Rat/Wistar

Test method (e.g., OECD, EC, limit test):

Ten rats (200-250 g, sex not stated) were placed in a 50 liter chamber and exposed to a nominal concentration of 200 mg/liter of test material for one hour. The rats were observed daily over 14 days for signs of toxicity. Body weights were recorded prior to and 14 days after treatment.

GLP YES [ ]
NO [ ] Not Reported.

Test results:

No mortality or toxicity observed. Necropsy observations were normal.

LC50: None established.

Comments:

Reference: MB Research Laboratories, Inc. (1977) Inhalation Toxicity in Rats. Report to Olin Corp

6.1.3 Acute Dermal Toxicity

Test substance: Triethylene glycol monoethyl ether

Test species/strain: Rabbit

Test method (e.g., OECD, limit test):

Details of test not reported.

GLP YES [ ]
NO [ ] Not Reported.

Test results:

LD50: 8.2 g/kg

Comments:

Reference: Smyth, H.F. and C.P. Carpenter. 1948. Ind. Hyg. Toxicol. 30: 63. [Cited in Patty's Indust. Hyg. and Toxicol.), 4th Ed. Vol. II D, p. 2859.]

Test substance: Triethylene glycol monoethyl ether

Test species/strain: Rabbit

Test method (e.g., OECD, limit test):

Ten rabbits (1.9 to 3.2 kg) were clipped free of abdominal hair. Epidermal abrasions were made longitudinally every 2 to 3 cm over the clipped area of 5 rabbits. The abrasions were deep enough to penetrate the stratum corneum, but not deep enough to produce bleeding. A single dose of 2.0 g/kg was applied to the exposed area. The area was covered with gauze and the trunk wrapped with impervious material for 24 hours. The dressing was removed, rabbits were cleaned, and animals were evaluated over 14 days.

GLP YES [ ]
NO [ ] Not Reported.

Test results:

There were no deaths or signs of systemic toxicity

Comments: Purity of test material was not noted.

Reference: Moreno OM. 1976. Report on acute dermal toxicity in rabbits. MB Research Laboratories, Inc. Project Number MB 77-1818, for Olin Corporation. Report Dated August 2, 1977. EPA/OTS Document File 0206799.

6.2 Corrosiveness/Irritation

6.2.1 Skin Irritation

Test substance: Triethylene glycol monoethyl ether

Test species/strain: Rabbit/New Zealand White

Test method (e.g., OECD, other):

2.0 g/kg of test substance was applied to intact and abraded skin and covered for 24 hours. Dermal reactions were evaluated by the Draize technique.

GLP YES [ ]
NO [ ] Not Reported.

Test results:

Intact skin: Erythema observed in 5/5 rabbits, edema observed in 2/5 rabbits.
Abraded skin: Erythema, observed in 5/5 rabbits; edema observed in 2/5 rabbits.

Comments:

Observations at necropsy included mottled liver (1 animal), white nodules (2 animals), pocked kidneys (2 animals) and dark areas on lungs (1 animal).

Reference: MB Research Laboratories, Inc. (1977) Acute Dermal Toxicity in Rabbits. Report to Olin Corp.

Test substance: Triethylene glycol monoethyl ether

Test species/strain: Rabbit

Test method (e.g., OECD, other):

Six rabbits were clipped over the back and sides with an electric clipper. A site to the left of the spinal column was abraded. Abrasions were minor incisions through the stratum corneum that did not disturb the derma or produce bleeding. Test material (0.5 ml) was applied to a surgical gauze (1" square, 2 layers thick). The patches were placed on test sites and secured with adhesive tape. The trunk was wrapped with impervious material. Patches were removed after 24 hours. Dermal reactions were evaluated at 24 and 72 hours in accordance with the Consumer Product Safety Act, Title 16 CFR 1500.41.

GLP YES [ ]
NO [ ] Not Reported.

Test results:

Not irritating. An erythema score of 1 (barely perceptible) was observed in 2 rabbits at 24 hours (intact and abraded skin). All others received erythema scores of 0. The mean erythema score was 0.33. No edema was observed at 24 or 72 hours. The mean primary irritation score was 0.17.

Comments:

Purity of test material was not noted.

Reference: Moreno OM. 1977. Report on primary dermal irritation in rabbits. MB Research Laboratories, Inc. Project number MB 77-1818 for Olin Corporation, Dated August 8, 1977. EPA/OTS File 0206799.

6.2.2 Eye Irritation

Test substance: Triethylene glycol monoethyl ether

Test species/strain: Rabbit

Test method (e.g., OECD, limit test):

Details of test not reported.

GLP YES [ ]
NO [ ] Not Reported.

Test results:

Mild irritation to the eyes.

Comments:

Reference: Smyth, H.F. and C.P. Carpenter. 1948. Ind. Hyg. Toxicol. 30: 63. [Cited in Patty's Indust. Hyg. and Toxicol.), 4th Ed. Vol. II D, p. 2859.]

Test substance: Triethylene glycol monoethyl ether

Test species/strain: Rabbit

Test method (e.g., OECD, limit test):

Six New Zealand white rabbits were used in the study. Test material (0.1 ml) was instilled into the conjunctival sac of one eye of each rabbit on Day 0. The contralateral eye served as a control. Ocular reactions were graded in accordance with the Consumer Product Safety Act, Title 16 CFR 1500.42 at 1, 2, and 3 days after instillation of the test material.

GLP YES [ ]
NO [ ] Not Reported.

Test results:

Mildly irritating. Conjunctival redness, chemosis and/or discharge scores of 1 or 2 were noted at 24 hours in all rabbits. These findings completely resolved in 2 rabbits by 72 hours. Slight redness and discharge was observed in 4 and 2 rats (respectively) at 72 hours. Iris and corneal opacity scores of 0 were observed in all animals at each time point. The total conjunctival score [(redness + chemosis + discharge) x 2] at 24 hours ranged from 2-8 out of a possible 20. The highest overall score was 8 out of a possible 110.

Comments:
Purity of test material was not noted.

Reference: Moreno OM. 1976. Report on rabbit eye irritation. MB Research Laboratories, Inc. Project number MB 77-1818 for Olin Corporation, Dated August 12, 1977. EPA/OTS File 0206799.

6.3 Skin Sensitization

NO DATA AVAILABLE

6.4 Repeated Dose Toxicity

Test substance: Triethylene glycol monoethyl ether

Test species/strain: Rabbit/New Zealand White

Test Method (e.g., OECD, other):

21-day dermal limit test to determine systemic toxicity.

GLP YES [X]
NO [ ]

Test results:

There were no deaths or signs of overt toxicity over the study period. There were no significant differences in body weights or food consumption between treated or control groups. There were no treatment-related hematological or biochemical changes. Mild skin irritation was noted after 2 to 3 weeks of treatment with test material. Testicular degeneration (scored as trace in severity), occurred in one rabbit. This lesion was characterized by the presence of spermatid giant cells, focal tubular hypospermatogenesis, or cytoplasmic vacuolization. The pathologist stated that "random occurrence of this lesion was suggestive of its spontaneous nature and was not test article related." A high incidence of similar changes of spontaneous nature in normal New Zealand White rabbits has been reported by Morton et al. in Vet Pathol 23: 176-183, 1986 and Vet Pathol 23: 210-217, 1986

Dose or concentration at which no toxic effects were observed:

1,000 mg/kg/day

Comments: Rabbits were observed over a 51-52 day pretest period for clinical abnormalities. Prior to randomization, rabbits were fasted (19-23 hours), and blood samples were taken from the central ear artery for control hematological and biochemical evaluations. Healthy rabbits (4- 4.5 months of age) were randomly divided into groups of 5 per sex. Prior to study initiation, hair was removed from the back of each rabbit with an electric clipper. Rabbits were shaved as necessary during the course of the study to prevent the test material from becoming matted in the hair and to facilitate accurate observations.

One group of rabbits was left untreated and the other was treated with 1000 mg/kg test material, five days per week for 3 weeks. Dose volumes were calculated based on the specific gravity of test material (as determined at the study site) and the body weight of animals (determined weekly). Test material was placed on the back using a 5 cc plastic syringe. A glass rod was used to evenly distribute the dose over the test site. Following dosing, test sites (of all animals, including controls) were wrapped with gauze bandaging and Dermiform tape and plastic restraint collars were attached to the rabbits. Collars were removed after 6 hours, and test sites (of all animals, including controls) were washed with tepid tap water and dried with paper towels. All animals were fasted for 19-23 hours before study termination.

Animals were observed once daily for clinical signs and twice daily for mortality. Food consumption was estimated daily based on a visual assessment of remaining food. Body weights were recorded weekly. Rabbits were scored immediately prior to each dosing for dermal irritation in accordance with the Draize method. Blood samples taken from the central ear artery of animals at study termination were analyzed for standard hematological (total and differential leukocyte count, erythrocyte count, hemoglobin, hematocrit, platelet count, reticulocyte count, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration) and biochemical (sodium, potassium, chloride, calcium, phosphorus, total bilirubin, gamma glutamyltranspeptidase, aspartate aminotransferase, alanine aminotransferase, ornithine carbamoyltransferase, urea nitrogen, creatinine, total protein, albumin, globulin, cholesterol and glucose) parameters. All animals were examined grossly upon study termination. Weights of adrenals, brain, kidneys, liver, ovaries and testes were taken. A full complement of tissues was examined microscopically.

Body weights (weeks 1, 2, 3, and 4), clinical pathology parameters and organ weights (absolute and relative) were analyzed using Bartlett's test for homogeneity of variance and analysis of variance (one-way). The treatment groups were

compared to the controls using the appropriate t-statistic (for equal or unequal variance). Dunnett's multiple comparison tables were used to judge the significance of the differences. Total bilirubin data was transformed to ranks and analyzed using a non-parametric test. All tests were two-tailed, with $p < 0.05$ and $p < 0.01$ as levels of significance.

Reference: Leber, A.P., Scott, R.C., Hodge, M.C.E., Johnson, D. and Krasavage, W.J. (1990) "Triethylene Glycol Ethers: Evaluations of In Vitro Absorption Through Human Epidermis, 21-Day Dermal Toxicity in Rabbits, and a Developmental Toxicity Screen in Rats," 9 J. Am. Coll. Toxicol. 507.

Test substance: Triethylene glycol monoethyl ether

Test species/strain: Rat/Male Albino

Test Method (e.g., OECD, other):

Groups of 10 rats (90-120 g) were given doses of test material in the drinking water at concentrations of 0 (control), 0.12, 0.5, 2 and 8% for 30 days. The actual doses received were 0, 180, 750, 3300 and 13290 mg/kg/d. Water consumption and deaths were monitored daily.

GLP YES [X]
NO [ ]

Test results:

Rats receiving the highest dose consumed only 25% of the amount of water as controls. All of them died within 6 to 24 days of exposure (average 13). Necropsy of these animals revealed congestion and cloudy swelling of the liver and cloudy swelling and degeneration of epithelium of the convoluted tubules of the kidneys. None of the other rats died. Rats exposed to 3300 mg/kg/d exhibited decreased weight gain, high blood urea concentrations (4/10), kidney damage (1/10), liver abnormalities (6/10). Animals exposed to 750 or 180 mg/kg/day appeared normal.

Dose or concentration at which no toxic effects were observed:

0.5% (750 mg/kg/day)

Reference: Mellon Institute. 1945. Single Dose and Thirty-Day Dose Toxicity of EthoxyTriglycol. EPA Doc. No. 878216154. Fiche No. OTS0206831. [As cited in TSCATS.]

6.5 Genetic Toxicity

6.5.1 Bacterial Test

Test substance: Related material (triethylene glycol monobutyl ether)

Test species/strain: Salmonella typhimurium; TA1535, TA1537, TA 98, TA100

Test method (e.g., OECD, others):

OECD Guide-line 471 "Genetic Toxicology: Salmonella typhimurium Reverse Mutation Assay"

GLP YES [ ]
NO [ ] No information

Test results:

Standard test: The average number of revertant in the controls for strains TA98, TA100, TA1535, and TA1537 in the absence of S-9 were 23, 114, 16, and 9. Addition of S-9 to strain TA98 increased the control mutation frequency to 34. S-9 had no effect on the frequency of mutations in the other strains. Positive controls induced an average of from 152 revertants in TA1535 to 1690 revertants in TA100. The number of revertants induced by test material was not increased from that of control at any concentration. The average number of revertants in cultures treated with test material (in the absence or presence of S-9) ranged from 109-140 in TA100, 12-21 in TA1535, and 8-11 in TA1537. Similar to control TA98 cultures, the average number of revertants in TA98 cultures treated with test material in the presence of S-9 (33-36) were higher than in the absence of S-9 (19-24).

Preincubation test: The average number of revertant in the controls for strains TA98, TA100, TA1535, and TA1537 in the absence of S-9 were 24, 111, 17, and 8. Addition of S-9 to strains TA98 and TA1535 increased the control mutation frequency to 33 and 23, respectively. S-9 had no
substantial effect on the frequency of mutations in the other strains. Positive controls induced an average of from 94 revertants in TA1537 to 1127 revertants in TA100. The number of revertants induced by test material was not increased from that of control at any concentration. The average number of revertants in cultures treated with test material (in the absence or presence of S-9) ranged from 108-135 in TA100 and 7-11 in TA1537. Similar to control TA98 cultures, the average number of revertants in TA98 and TA1535 cultures treated with test material in the presence of S-9 (35-41 and 18-26, respectively) were higher than in the absence of S-9 (19-24 and 14-18, respectively).

The tests were valid, as positive controls induced at least a two-fold increase in frequency of mutations.

Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: > 5000 micrograms/plate
without metabolic activation: > 5000 micrograms/plate

Concentration of test compound resulting in precipitation:

> 5000 micrograms/plate

Genotoxic effects:	+	?	-
with metabolic activation	[ ]	[ ]	[x]
without metabolic activation	[ ]	[ ]	[x]

Comments:

Standard test: Test tubes containing 2 ml of soft agar, bacteria (0.1 ml of > = 10E8 S. typhimurium TA98, TA100, TA1535, or TA1537), test chemical (0.1 ml of test solution, positive control, or aqua dest. solvent) and either buffer or S-9 mix from Aroclor 1254-

induced, male, Sprague Dawley rats (0.5 ml) were prepared. After mixing, the samples were poured onto minimal glucose agar plates within 30 seconds. Preincubation test: Test tubes containing bacteria (0.1 ml of > = 10E8 S. typhimurium TA98, TA100, TA1535, or TA1537), test chemical (0.1 ml of test solution, positive control, or aqua dest. solvent) and either buffer or S-9 mix from Aroclor 1254-induced, male, Sprague Dawley rats (0.5 ml) were incubated at 37 degrees C for 20 minutes. Supplemented top agar (2 ml) was then added. After mixing, the overlay was poured onto minimal glucose agar plates. Plates were incubated at 37 degrees C for 48 hours in the dark. All dose levels (including positive and negative controls) were assayed in triplicate. The method of colony counting was not specified. Positive controls were 5 micrograms N-methyl-N'-nitro-N-nitroso-guanidine MNNG) for strains TA100 and TA1535, 10 micrograms 4-nitro-o-phenylenediamine for strain TA98, and 100 micrograms 9-aminoacridine chloride monohydrate (AACM) for strain TA 1537 (all in the absence of S-9), and 10 micrograms 2-aminoanthracene (AA) for all strains in the presence of S-9. All positive control chemicals were dissolved in DMSO.

Evaluation Criteria: The test material was considered a mutagen if both the mean number of revertant colonies was at least 2 times higher than the mean of the negative (solvent) control and it induced a reproducible dose-response relationship over several concentrations. If the dose-response was not definitive, it was considered to be a presumptive mutagen. If the reversion rates were between 2 and 3 times that of negative controls, the results were considered equivocal or inconclusive.

The Salmonella stains were periodically checked for deep rough character (rfa), UV sensitivity (uvrB), and ampicillin resistance (R factor plasmid). Histidine auxotrophy was automatically checked in each experiment via the spontaneous mutation rate.

Test material purity was 87.2%.

Reference: BASF AG. 1989. Department of Toxicology, Project No. 40M0573/884365, Dated February 24, 1989.

Test substance: Related material (triethylene glycol monomethyl ether)

Test species/strain: S. typhimurium strains TA98, TA100, TA1535, TA1537

Test method (e.g., OECD, others): Test Standard 40 CFR 798.5265

GLP YES [x]
NO [ ]

Test results: Concentrations up to 5000 micrograms/plate did not cause toxicity or cause an increase in mutagenicity above that of negative controls. The study was valid, as the positive controls induced at least 3 times the number of revertants as the negative controls in each tested strain.

Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: > 5000 micrograms/plate
without metabolic activation: > 5000 micrograms/plate

Concentration of test compound resulting in precipitation:

> 5000 micrograms/plate

Genotoxic effects:	+	?	-
with metabolic activation	[ ]	[ ]	[x]
without metabolic activation	[ ]	[ ]	[x]

Comments:

Test Concentrations: The test material was dissolved in distilled water at stock concentrations of 50, 16.67, 5, 1.667, and 0.5 mg/ml. Concentrations were verified by HPLC to be: 51.4, 18.3, 4.91, 1.75 and 0.523 mg/ml. All positive control solutions (1 mg/ml 2-nitrofluorene, 100 micrograms/ml ICR-191, 30 micrograms/ml 2-anthramine) were prepared in DMSO (with the exception of 250 micrograms/ml sodium azide dissolved in water).

Test: Bacteria (0.1 ml of 10E8 or 10E9 S. typhimurium TA 98, TA100, TA1535, or TA1537), test chemical (0.1 ml of test solution, positive control, or solvent) and either buffer or S-9 mix (0.5 ml) were pre-incubated in sterile 12 x 75 mm tightly-capped culture tubes in a gyratory incubator (300 rpm) at 30 degrees C for 30 minutes. Supplemented top agar (2 ml) was then added, the overlay was poured onto plates, and plates were incubated at 37 degrees C for 2 days. All dose levels (including positive and negative controls) were assayed in triplicate.

Revertant colonies were counted manually or with an automatic colony counter. The counter was calibrated periodically. A correction factor was used to compensate for the area not scanned by the counter (i.e. dish edge) and overlapping colonies.

Evaluation Criteria: The test material was considered a mutagen if both the mean number of revertant colonies was at least 3 times higher than the mean of the negative (solvent) control and it induced a reproducible dose-response relationship over several concentrations. If the dose-response was not definitive, it was considered to be a presumptive mutagen. If the reversion rates were between 2 and 3 times that of negative controls, the results were considered equivocal or inconclusive.

Purity of the test material was 99.23%.

Reference: Samson YE and Gollapudi BB. 1990. Evaluation of triethylene glycol monomethyl ether (TGME) in the Ames Salmonella/mammalian-microsome bacterial mutagenicity assay. Dow Chemical Company Study ID TXT:K-005610-005, Dated March 7, 1990.

6.5.2 Non-bacterial *In Vitro* Test

Test substance: Related material (triethylene glycol monomethyl ether)

Type of cell used: Chinese hamster ovary cell

Test method (e.g., OECD, other): HGPRT assay, Test Standard 40 CFR 798.5300

GLP YES [x]
NO [ ]

Test results:

The mutation frequencies observed in cultures treated with the test chemical in the absence (1.4 to 7.1) and presence of S-9 (0 to 7.1) were not significantly different from the

concurrent negative control values (1.4 to 9.6) and were within the laboratory historical negative control range. The assay was valid, since the positive control chemicals induced significant increased in mutation frequencies in assays with and without S-9 (EMS: 142.0-153.6; 20-MCA: 64.7-86.3).

Lowest concentration producing cell toxicity: > 5000 micrograms

Genotoxic effects:	+	?	-
with metabolic activation	[ ]	[ ]	[x]
without metabolic activation	[ ]	[ ]	[x]

Comments: Indicator cells: The CHO-K1-BH4 cell line was used in the study. Periodic examinations revealed no mycoplasma contamination. Cells were grown as a monolayer in Ham's F-12 nutrient mix supplemented with 5% heat-inactivated, dialyzed fetal bovine serum, 25 mM HEPES, 0.25 micrograms/ml Fungizone, 100 units/ml penicillin G and 0.1 mg/ml streptomycin sulfate. The selection medium used for the detection of mutants was Ham's F-12 nutrient mix without hypoxanthine, and supplemented with 10 micromolar 6-thioguanine, 5% serum, 25 mM HEPES, 2 mM L-glutamine and the antibiotics mentioned above.

Test materials: Test material was dissolved in water and further diluted (1:100) in culture medium. The concentrations of test material in stock solutions (200, 300, 400, 500 mg/ml) were verified by analytical methods. 20-methylchlolanthrene (20-MC) was initially dissolved in DMSO, and further diluted in culture medium. Ethyl methanesulfonate (EMS) was dissolved in culture medium.

Preliminary test : The cytotoxicity of the test material was assessed by determining the ability of the treated cells to form colonies. The cultures (3 per dose level) were treated with test material in the absence or presence of S-9, incubated for up to 7 days, fixed with methanol and stained with crystal violet. The number of colonies/dish was counted and the mean colonies/dish/treatment were expressed relative to the negative control value. The test material was not cytotoxic at up to 5000 micrograms/ml. Based on this result, this was the highest concentration used for the gene mutation assay.

Mutation test: Cells in logarithmic growth phase were trypsinized and plated in medium containing 5% serum at a standard density (200 cells/100 mm dish for toxicity assay and 1 x 10E6 cells/100 mm dish for gene mutation assay) prior to treatment. Approximately 24 hours after plating, the medium was replaced with Ham's medium without serum, S-9 mix prepared from liver homogenate of Aroclor-1254 treated (500 mg/kg) male, Sprague Dawley rats (when applicable) and test material (2000 to 5000 micrograms/ml), positive control (either 621 micrograms/ml EMS or 4 micrograms/ml 20-MC) or water. The total volume of the treatment medium was 10 ml/100 mm dish. The number of dishes treated at each dose level was based on the expected degree of toxicity that would yield at least 1 x 10E6 surviving cells. Cells were treated for 4 hours at 37 degrees C. Exposure was terminated by washing the cells with phosphate-buffered saline. Cells were trypsinized 18-24 hours after termination of the treatment and replated at a density of 1 x 10E6 cells/100 mm dish. This step was repeated on the third and sixth days following treatment. On Day 8, cultures were trypsinized and plated at a density of 2 x 10E5 cells/100 mm dish (5 dishes per treatment) in selection medium for the determination of HGPRT-mutants and 200 cells/60 mm dish (5 dishes/treatment) in Ham's medium without hypoxanthine for determination of cloning efficiency. Dishes were incubated for 7-9 days, fixed with methanol and stained with crystal violet. The mutation frequency per 10E6 clonable cells was calculated as the total

number of mutant colonies/cloning efficiency (number of colonies per number of cells plated).

Statistical analysis: The frequencies of mutants per 10E6 clonable cells were statistically evaluated by pairwise tests (treatment vs. negative control) and by linear and quadratic trend analysis over the dose range.

Purity of the test material was 99.23%

Reference: Liscombe VA, Gollapudi BB. 1990. Evaluation of triethylene glycol monomethyl ether in the Chinese hamster ovary cell/hypoxanthine-guanine-phosphoribosyl-transferase (CHO/HGPRT) forward mutation assay. Dow Chemical Company Study ID TXT:K-005610-006, Dated March 7, 1990

6.5.3 Non-bacterial *In Vivo* Test

Test substance: Related material (triethylene glycol monomethyl ether)

Test species/strain: mouse

Test method (e.g. OECD, other): micronucleus assay, Test Standard 40 CFR 798.5395

GLP YES [x]
NO [ ]

Test Results: One female dose with 1667 mg/kg test material died prior to scheduled termination. The cause of death was not determined.

There were no significant increases in the frequencies of micronucleated polychromatic erythrocytes (MN-PCE) in groups treated with test material (range from 0.2 to 1.6) versus negative controls (range 0.4 to 1.2). The ratios of polychromatic erythrocytes (PCE) to normochromatic erythrocytes (NCE) (% PCE) in test animals (67.3 to 82.0) also were similar to those of negative controls (70.6 to 78.7).

The test was valid as positive controls had significantly more MN-PCE than controls (62.2 in males and 34.6 in females).

Lowest dose producing toxicity:

Effect on Mitotic Index or P/N Ratio: None

Genotoxic effects:	+	?	-
	[ ]	[ ]	[x]

Comments: Test material was dissolved in water and administered to mice (approximately 8 weeks old) by single oral gavage at dose levels of 0 (water), 500, 1667 and 5000 mg/kg body weight (10 ml/kg). A previous study revealed that 5000 mg/kg did not affect survival. Concentrations of test material in dosing solutions were verified by HPLC. Groups of animals (5/sex/dose/termination time) were killed by cervical dislocation 24, 48 and 72 hours after treatment. Mice (5/sex) treated with 120 mg/kg cyclophosphamide and killed after 24 hours of treatment served as positive controls.

Bone marrow samples were obtained from both femurs at termination. Cell smears

were prepared from cell suspensions. The slides were air dried, fixed in methanol and stained in 5% Giemsa. Slides were coded and scored blindly. One thousand polychromatic erythrocytes (PCE) were evaluated from each surviving animal and the frequencies of micronucleated polychromatic erythrocytes (MN-PCE) were recorded. Micronuclei were identified as darkly stained bodies with sharp contours and varying shapes such as round, almond, or ring. The ratio of PCE-NCE (normochromatic erythrocytes) in the bone marrow was determined by examining 100 erythrocytes.

Statistical Analysis: The raw data on the counts of MN-PCE for each animal were transformed by adding 1 to each count and then taking the natural log of the adjusted number. The transformed MN-PCE data and the data on percent PCE were analyzed by a three-way analysis of variance looking only at main effects. Pairwise comparisons between treated vs. negative controls were done (if necessary) by a t-test using Bonferroni correction for multiple comparisons.

Purity of the test material was 99.23%.

Reference: McClintock ML and Gollapudi B. 1990. Evaluation of triethylene glycol monomethyl ether in the mouse bone marrow micronucleus test. Dow Chemical Company Study ID TXT:K-005610-007, Dated March 7, 1990.

6.6 Carcinogenicity

NO DATA AVAILABLE

6.7 Reproductive and Developmental Toxicity

6.7.1 Reproductive Toxicity

Test substance: Related material (triethylene glycol monomethyl ether)

Test species/strain: Rat/Sprague-Dawley

Test method (e.g. OECD, other):

other: Dermal toxicity, 400, 1200, 4000 mg/kg bw, 91 days, 6 hr/day, 5days/week

GLP YES [x]
NO [ ]

Test results: (see below)

NOEL for P generation: 4000 mg/kg bw (summary preparer); > 400 and < 1200 mg/kg bw (EPA)
NOEL for F1 generation: not applicable
NOEL for F2 generation: not applicable

Maternal and paternal general toxicity:

There were no indications of systemic toxicity at any dose. Mean body weight and food consumption were comparable to controls throughout the study.

Reproductive toxicity observed in parental animals (fertility, gestation, reproductive organ toxicity, etc.):

Bilaterally decreased spermatogenesis in seminiferous tubules and decreased spermatozoa in the epididymes (both were graded as severe) were noted in the testes of one high dose male rat. This animal had a complete lack of mature spermatids in greater than 41% of tubules in each testicle, few spermatids beyond stage 12 of development in the seminiferous epithelium, and decreased spermatic elements in the head and tail of greater than 41% of the tubules and ducts in the epididymides. The testes of one male treated with 1200 mg/kg exhibited different testicular changes [bilateral multifocal degeneration of spermatocytes and spermatids from germinal epithelium (graded as very slight), and multinucleated spermatids]. In this rat, all stages of the cycle of the seminiferous epithelium were observed in morphologically normal tubules. The epididymides of this rat had decreased spermatic elements in the head and tail of 1-5% of ducts. Some of the ducts also contained immature spermatids. There were no effects on estrous cyclicity or ovaries of females.

Reproductive toxicity observed in offspring (weights of litter, postnatal growth, viability, etc.):

Not applicable

Comments:

Triethylene glycol monomethyl ether (TGME) was administered dermally o 8 week-old rats (10/sex/dose level) at 0 (sham control), 400, 1200 or 400 mg/kg/day for 13 weeks. Test material was applied to shaved areas of skin on the back and sides of each rat (12 cm2 in area), uniformly spread, and covered with a semiocclusive dressing for 6 hours. After removal of the dressing, the application site was wiped with a dampened towel. Material was applied in this manner daily, 5 days/week for 13 weeks. The oocytes, corpora lutea, and follicles from each ovary were evaluated with regard to their normal development. The testes and epididymes also were examined microscopically for males in the intermediate- and low-dose groups.

Purity of the test material (as determined by gas chromatography) was 99.23 % at the onset of the study and 99.24% at completion of the in-life phase.

Study personnel concluded that the bilateral microscopic testicular changes observed in one high-dose and one mid-dose male rat were unrelated to treatment. Reasons given were that the dissimilarity of the lesions for the two animals suggested that they occurred spontaneously, and the incidence of animals with lesions (1/10 in each group) was well within that of historical controls (0-17%). Study personnel also stated that “the degenerative changes in the testes of one mid-dose and one high-dose rat were not consistent with the types of lesions that have been attributed to 2-methoxyethanol (2-ME). The cell types that are most vulnerable to 2-ME are the pachytene spermatocytes and round spermatids (Chapin et al., Fund Appl. Toxicol 5:182-189, 1985). As the dose of 2-ME is increased, the number and types of cells affected increase up to the point that the germinal epithelium is significantly degenerated and all stages of spermatogenesis are affected (Chapin et al., Fund Appl. Toxicol 5:182-189, 1985; Miller et al., Fund Appl Toxicol 3:49-54, 1983.). In contrast, the testicular effects seen with the high dose animal treated with TGME consisted of a virtually complete lack of mature spermatids beyond stage 12. All other stages, including spermatogonia and spermatocytes, were present and appeared morphologically normal. In the mid-dose rat, the only effects noted consisted of very slight degeneration of spermatocytes and spermatids similar to those seen in historical control animals.”

Study personnel also stated that "the lymphoid tissues and hematologic parameters, which have been reported to be affected at doses of 2-methoxyethanol that have been associated with testicular changes (Miller et al., Fund. Appl. Toxicol. 3:49-54, 1983) were unaffected in this TGME study. Taking all factors into consideration, the testicular lesions observed in this dermal study could not be directly attributed to TGME exposure."

The EPA has determined that based on severe testicular toxicity in 1/10 rats given 4000 mg/kg/day and minimal decreases in developing germ cells (1-5% of seminiferous tubules affected) in 1/10 rats given 1,200 mg/kg/day, the NOAEL for testicular toxicity is between 400 and 1200 mg/kg/day (Anderson, L. Triethylene glycol monomethyl, monoethyl and monobutyl ethers RM1 screening document (draft), Feb. 24, 1995). This value was reached even though it was recognized that the testicular changes in the 1,200 mg/kg/day rat were within historical control limits for Sprague-Dawley rats (0 –1 7 %).

Reference:

(1) Corley RA, Ciesslak, Breslin WJ, Lomax LG. 1990. 13-Week dermal toxicity study in Sprague-Dawley rats. Dow Chemical Company Study ID K-005610-004, Dated September 26, 1990.

(2) Gill MW, Fowler EH, Gingell R, Lomax LG, Corely RA. 1998. Subchronic dermal toxicity and oral neurotoxicity of triethylene glycol monomethyl ether in CD rats. Int J Toxicol 17:1-22.

Test substance: Related material (triethylene glycol monomethyl ether)

Test species/strain: Rat/Sprague-Dawley

Test method (e.g. OECD, other): other: drinking water, 400, 1200, 4000 mg/kg bw, 91 days

GLP YES [x]
NO [ ]

Test results: (see below)

NOEL for P generation: 1200 mg/kg bw (summary preparer); > 400 and < 1200 mg/kg bw (EPA)
NOEL for F1 generation: not applicable
NOEL for F2 generation: not applicable

Maternal and paternal general toxicity:

Males and females treated with the highest dose consumed less food and had lower body weights and body weight gains than control animals. Water consumption decreased in high-dose females (by an average of 17%). Increased relative liver weight was observed in males treated with 4000 mg/kg/day and 1200 mg/kg/day versus control. Absolute liver weights of males treated with 4000 mg/kg/day were significantly greater than controls. Microscopic changes (hepatocellular cytoplasmic vacuolization and/or hypertrophy) were noted in livers of high-dose males (14/15). The severity of these liver lesions was minimal or mild (with the exception of moderate or marked vacuolization for 4 high dose males). Mild

cholangiofibrosis was observed around a small number of bile ducts in high-dose males (7/15). This was not considered by study personnel to be physiologically significant due to the limited number of bile ducts affected and the mild nature of the effect (Gill et al., Int J Toxicol 17:1-22, 1998). Minimal or mild hepatocellular hypertrophy was seen in 10/15 high dose females. Three males treated with 400 mg/kg/day and 4 treated with 1200 mg/kg/day also exhibited minimal-mild hepatocellular cytoplasmic vacuolization and/or cellular hypertrophy (not statistically different from the controls). One control male had mild hepatocellular cytoplasmic vacuolization. None of the females treated with 400 or 1200 mg/kg/day exhibited these changes. Hepatocellular hypertrophy was considered by study personnel to be a possible adaptive change to accommodate increased demand to metabolize the test substance. Based on the results of the study, the summary preparer assigned a NOAEL for effects on the liver of 400 mg/kg/day, and a LOAEL of 1200 mg/kg/day (based on increased relative liver weight of males at this dose).

Reproductive toxicity observed in parental animals (fertility, gestation, reproductive organ toxicity, etc.): The testes of males in the high dose group exhibited degeneration (12/15) and/or atrophy (5/5) of the seminiferous tubules (spermatocytes or developing spermatids). The authors concluded that these effects were related to treatment. The severity of the lesions was primarily mild to moderate for degeneration (11/12) and minimal to moderate for atrophy (5/5), indicating that not all tubules were affected and that a limited number of cells was affected within the affected tubules. One male treated with 1200 mg/kg had severe seminiferous tubule atrophy, a complete loss of cell types in the tubules (except for Sertoli cells) and moderate Leydig cell hypertrophy (not significant from control). This was not considered to be related to treatment because of the lack of a plausible explanation for the unusual dose-response relationship (the effect at this dose was more severe than that of a higher dose) and the low incidence of animals affected at this dose level (Gill et al., Int J Toxicol 17:1-22, 1998) One male treated with 1200 mg/kg had severe seminiferous tubule atrophy and moderate Leydig cell hypertrophy (not significant from control). No testicular changes were noted in males treated with 400 mg/kg/day TGME.

Reproductive toxicity observed in offspring (weights of litter, postnatal growth, viability, etc.): Not applicable

Comments:

Rats were treated with triethylene glycol monomethyl ether (TGME) for 91 days via drinking water at target doses of 0, 400, 1200 and 4000 mg/kg/day. Rats were observed daily for clinical signs and weekly for body weight and water and food consumption. Rats were also observed periodically for behavior (functional observational battery) and motor activity. Gross lesions and organ weights were recorded at necropsy. Microscopic analyses of liver, testes and the nervous system also were performed.

The purity of the test material was at least 98.7%.

The authors state that “a possible contributing factor in the development of testicular lesions at the high dose was low-level contamination of the test substance with the known testicular toxicant 2-methoxyethanol (EGME). EGME was present in the test substance at a concentration of 0.02 – 0.04 %, resulting in a EGME dose up to 1.7 mg/kg/day for animals in the high dose group. Given the length of the study, it is possible that EGME contributed to the testicular lesions. A comparison between the doses of EGME and TGME required to produce testicular toxicity indicated that TGME is 350 times less potent than EGME in producing testicular lesions in the rat.” The dose of TGME that caused testicular toxicity (4000 mg/kg/day) is 4 times greater than the 1000 mg/kg/day limit dose generally recommended for subchronic studies.

The NOEL listed above is for reproductive effects. The summary preparer-assigned NOAEL and LOAEL for testicular effects is 1200 and 4000 mg/kg/day, respectively. By

contrast, the EPA has determined that the NOAEL for testicular effects is between 400 and 1200 mg/kg/day (Anderson, L. Triethylene glycol monomethyl, monoethyl and monobutyl ethers RM1 screening document (draft), Feb. 24, 1995).

Reference: Gill MW and Negley JE. 1990. Triethylene glycol monomethyl ether. Ninety day subchronic drinking water inclusion neurotoxicity study in rats. Bushy Run Research Center, Project Report 52-607, September 21, 1990.

6.7.2 Teratogenicity/Developmental Toxicity

Test substance: Triethylene glycol monoethyl ether

Test species/strain: Rat/Alpk: AP Wistar

Test method (e.g., OECD, other): Modified in vivo Chernoff-Kavlock developmental screening assay.

GLP YES [X]
NO [ ]

Test results:

Doses of 250 and 1000 mg/kg of test substance on days 7-16 of gestation resulted in no adverse effects on the in utero development of the conceptus or on viability or postpartum of offspring.

NOAEL for maternal animals: 1,000 mg/kg/day
NOAEL for offspring: 1,000 mg/kg/day

Maternal general toxicity

No significant changes in clinical conditions or body weights.

Pregnancy and litter data

All treated rats were pregnant and delivered live fetuses.
Foetal data (live/dead, sex, external defects, soft tissue and skeletal defects)
No treatment-related effects on pup viability, mean pup body weights or mean pup body weight gains.

Comments:

Female rats were mated with males of the same strain when they were approximately 11-13 weeks of age. The first day spermatozoa were detected in vaginal smears was counted as Day 1 of gestation. Ten gestating animals per group were dosed with deionized water, 250 mg/kg triethylene glycol monoethyl ether (TGEE), 1000 mg/kg TGEE, 50 mg/kg ethylene glycol monomethyl ether (EGME), or 250 mg/kg EGME. Dose levels of TGEE were selected based on the results of a previous range finding study. EGME was administered at levels known to produce toxicity in the assay. All animals were dosed by gavage from Days 7-16 (inclusive) of gestation with 1 ml of dosing solution per 100 g body weight using a 5 ml glass syringe and stainless steel (16 gauge cannula). Dosing solutions were prepared immediately prior to dosing and stored in a refrigerator until use. The volume given to each animal was adjusted daily according to body weight.

Rats were observed each day for clinical condition and signs of illness. Body weights were recorded on Days 1, 7 through 17, 19, and 22 of gestation and on Day

5 post partum. Litters were weighed and sexed on Days 1 (within 24 hours of birth) and 5 post partum. Dead pups were not weighed. Mortality on Day 1 and Day 5 post partum was recorded. The uteri of females which failed to litter were grossly examined for implantation sites on or shortly after Day 25 of gestation to ascertain if the animals had been pregnant.

Animals which littered and their offspring were killed and discarded without postmortem examination after Day 5 post partum. Maternal body weight gains during treatment and pregnancy, litters produced/number pregnant, number of viable litters on Days 1 and 5, total number of live pups/litter, total number of dead pups/litter, mean total litter size (live and dead pups), survival percentage, number of dead pups per group, mean pup weight (Days 1 and 5), mean pup weight gain and mean % weight gain/litter data from treated and control animals were compared using the Student's t-test. All comparisons were two-tailed.

Reference: Leber, A.P., Scott, R.C., Hodge, M.C.E., Johnson, D. And Krasavage, W.J. (1990) "Triethylene Glycol Ethers: Evaluation of In Vitro Absorption through Human Epidermis, 21-day Dermal Toxicity in Rabbits and a Developmental Toxicity Screen in Rats, 9 J. Am. Coll. Toxicol. 507.

Test substance: Triethylene glycol monomethyl ether (purity 99.98%)

Test species/strain: Rat/ Alpk:AP (Wistar)

Test method (e.g., OECD, other): other: modified Chernoff-Kavlok assay (Schuler et al., Environ Health Persp 57:141-146, 1984)

GLP YES [x]
NO [ ]

Results: NOEL for maternal animals = 1000 mg/kg/day
NOEL for offspring = 1000 mg/kg/day

The EPA concluded that there were no remarkable treatment-related effects in this study (Anderson, L. Triethylene glycol monomethyl, monoethyl and monobutyl ethers RM1 screening document (draft), Feb. 24, 1995).

Maternal general toxicity:

Dams dosed with either dose of TGME appeared normal throughout the study and gained a similar amount of weight as negative controls. Administration of 50 or 250 mg/kg EGME was associated with piloerection. Four animals in the 250 mg/kg EGME group had slight vaginal bleeding between Days 17 and 19 of gestation.

Pregnancy and litter data:

The pregnancy rate was high with 9/10 pregnancies in the negative control group, and 10/10 pregnancies in the groups dosed with TGME. No litters were produced in either EGME group (although implantation sites were present in all animals).

Foetal data (live/dead, sex, external defects, soft tissue and skeletal defects):

Mean pup weights were significantly increased in the 1000 mg/kg TGME group at Days 1 and 5. All other litter parameters in pups from rats treated with TGME were similar to the negative control. The increase in pup weights at 1000 mg/kg TGME was ruled incidental. At the dose levels tested (250 or 1000 mg/kg/day), TGME was

not embryotoxic or teratogenic.

Comments: Female rats were mated with males of the same strain when they were approximately 11-13 weeks of age. The first day spermatozoa were detected in vaginal smears was counted as Day 1 of gestation. Ten gestating animals per group were dosed with deionized water, 250 mg/kg triethylene glycol monomethyl ether (TGME), 1000 mg/kg TGME, 50 mg/kg ethylene glycol monomethyl ether (EGME), or 250 mg/kg EGME. Dose levels of TGME were selected based on the results of a previous range finding study. EGME was administered at levels known to produce toxicity in the assay. All animals were dosed by gavage from Days 7-16 (inclusive) of gestation with 1 ml of dosing solution per 100 g body weight using a 5 ml glass syringe and stainless steel (16 gauge cannula). Dosing solutions were prepared immediately prior to dosing and stored in a refrigerator until use. The volume given to each animal was adjusted daily according to body weight.

Rats were observed each day for clinical condition and signs of illness. Body weights were recorded on Days 1, 7 through 17, 19, and 22 of gestation and on Day 5 post partum. Litters were weighed and sexed on Days 1 (within 24 hours of birth) and 5 post partum. Dead pups were not weighed. Mortality on Day 1 and Day 5 post partum was recorded. The uteri of females which failed to litter were grossly examined for implantation sites on or shortly after Day 25 of gestation to ascertain if the animals had been pregnant.

Animals which littered and their offspring were killed and discarded without postmortem examination after Day 5 post partum. Maternal body weight gains during treatment and pregnancy, litters produced/number pregnant, number of viable litters on Days 1 and 5, total number of live pups/litter, total number of dead pups/litter, mean total litter size (live and dead pups), survival percentage, number of dead pups per group, mean pup weight (Days 1 and 5), mean pup weight gain and mean % weight gain/litter data from treated and control animals were compared using the Student's t-test. All comparisons were two-tailed.

Reference: (1) Leber, A.P. et al (1990) “Triethylene Glycol Ethers: Evaluations of In Vitro Absorption through Human Epidermis, 21-Day Dermal Toxicity in Rabbits and a Developmental Toxicity Screen in Rats” J Amer Col Toxicol 9:507-515.

(2) Wason SM, Hodge MCE, Macpherson A. 1986. Triethylene glycol ethers: An evaluation of teratogenic potential and developmental toxicity using an in vivo screen in rats. Imperial Chemical Industries Report No. CTL/P/1584.

Test substance: Triethylene glycol monomethyl ether

Test species/strain: Rat/CD (SD) BR

Test method (e.g., OECD, other): Oral developmental toxicity studies conducted in accordance with EPA TSCA test guidelines.

GLP YES [x]
NO [ ]

Results: NOAEL for maternal animals 1250 mg/kg/day
NOAEL for offspring 625 mg/kg/day

Maternal general toxicity:

One nonpregnant animal in the high dose group (5000 mg/kg/day) was found dead on

day 13 of presumed gestation. This was considered by the authors to be treatment-related. Significant numbers of rats treated with the high dose exhibited decreased motor activity, excess salivation, ataxia, and impaired righting reflex. Food consumption of high dose animals were reduced over the entire dosage period. Average maternal body weight gains of rats in the high dose group were reduced on days 6-9, 6-12, 12-16, and 6-16 of gestation. Consequently, average body weights of these animals were reduced on days 9, 12, and 16. Average gravid uterine weights of high-dose animals were also reduced.

Food consumption of rats receiving 2500 mg/kg/day was reduced during days 6-16, 6-18, and 12-16. Food consumption and average maternal body weights and body weight gains in rats receiving 1250 mg/kg/day were not significantly different from controls. Therefore, 1250 mg/kg/day was considered by study personnel to be the NOAEL for maternal toxicity.

Pregnancy and litter data:

There was no effect of TGME on the number of pregnant dams or number of copora lutea, implantations, live litter size or fetal sex ratios.

Foetal data (live/dead, sex, external defects, soft tissue and skeletal defects):

Significant increases in embryo-fetal lethality (litter averages for total resorptions (1.6 versus 0.6 in control), late resorptions (0.3 versus 0 in controls), percentage of resorbed conceptuses (12.0 versus 4.4 in control) and dams with at least one resorption (81.8% versus 47.8 in control) occurred in the 5000 mg/kg group. Fetuses from rats treated with 2500 or 5000 mg/kg had lower body weights than controls (3.04 and 2.56 g (respectively) versus 3.32 in controls).

There was no effect of TGME on the incidences or types of gross external or internal soft tissue malformations. Groups given 1250 mg/kg/day and higher doses of TGME had significant increases in the litter and/or fetal incidences of reversible delays in fetal ossification. Fetuses from rats given 2500 or 5000 mg/kg/day also had a significant increase in the incidence of cervical ribs. The NOAEL for developmental toxicity was considered by study personnel to be 625 mg/kg/day.

The authors remarked that the skeletal variations noted were common observations in fetuses with reduced body weights. Since only reversible delays in fetal ossification were observed in the 1250 mg/kg/day group, the actual NOAEL may be close to this concentration.

Comments: Groups of 25 mated female rats (203 to 256 g) were given daily dosages of 4.8 ml of deionized water (control), or 0.6, 1.2, 2.4, and 4.8 ml/kg/day of triethylene glycol monomethyl ether (TGME) by gavage. These doses corresponded to 0, 625, 1250, 2500 or 5000 mg/kg/day. All doses were adjusted daily according to body weights recorded immediately prior to intubation.

Rats were observed at least twice daily during the dosage and postdosage periods for clinical signs, signs of resorption, premature deliveries and death. Body weight and feed consumption were recorded on Day 0 of presumed gestation and from days 6 through 20 of gestation. Rats were euthanized on Day 20 of presumed gestation, and the thoracic and abdominal viscera were examined for gross lesions. The uterus was excised from each rat and weighed. The number and placement of implantations were recorded and sites were categorized as early or late resorptions, or live or dead fetuses. Each ovary was examined for the number of corpora lutea. Fetuses were weighed,

sexed, and examined for external alterations. One-half were examined for soft tissue alterations, and the remaining half were examined for skeletal alterations. Dams that were found dead were necropsied on day of death and subjected to the same procedures described for scheduled termination.

Maternal and fetal incidence data were analyzed using the variance test for homogeneity of the binomial distribution. Maternal body weight and feed consumption data, organ weight data, and litter averages for percent male fetuses, percent dead or resorbed conceptuses per litter, fetal body weights, fetal ossification sites, and percent fetal alterations were analyzed using Bartlett's Test of homogeneity of variances and the analysis of variance (when data were homogeneous). If the analysis of variance was significant, Dunnett's Test was used to identify the statistical significance of individual groups. If data were not homogeneous, the Kruskal-Wallis test was used when less than or equal to 75% ties were present; when more than 75% ties were present the Fisher's Exact Test was used. In cases where the Kruskal-Wallis Test was statistically significant, Dunn's Method of Multiple Comparisons was used to identify the statistical significance of individual groups.

All other Caesarean-sectioning data were evaluated using the procedures previously described for the Kruskal-Wallis Test.

Reference: Hoberman AM. 1990a. Triethylene glycol monomethyl ether (TGME): oral developmental toxicity study in Crl:CD(SD)BR pregnant rats. Argus Research Laboratories, Inc. Study Number 503-005.

Test substance: Triethylene glycol monomethyl ether

Test species/strain: Rabbit/New Zealand white

Test method (e.g., OECD, other): Oral developmental toxicity studies conducted in accordance with EPA TSCA test guidelines.

GLP YES [x]
NO [ ]

Results: NOEL for maternal animals 250 mg/kg/day
NOEL for offspring 1,000 mg/kg/day

Maternal general toxicity:

Eight rabbits treated with the 1500 mg/kg/day dose died, and three aborted. A significant number of rabbits treated with this dose exhibited decreased motor activity, labored breathing, a red substance in the cage pan, dehydration, no feces, ataxia, gastric ulceration, anogenital staining, mottled gallbladders, thin-walled stomach, reddened stomach, and fluid-filled or empty small intestines, and lower average gravid uterine weight. There was one death in the 1000 mg/kg/day group. This was considered to be possibly related to treatment. Rabbits treated with all doses except 250 mg/kg/day gained more weight during the postdosage period than controls, reflecting increased food consumption during this period. Study personnel did not consider this weight gain to be an adverse effect, as it is commonly seen in developmental studies after dosing is terminated.

Based on the data, the investigators concluded that the NOAEL for maternal toxicity was 500 mg/kg/day.

Pregnancy and litter data:

There was no effect of treatment on the number of pregnant rabbits, average number of corpora lutea, implantations, live fetuses, resorptions, or fetal sex ratios. One rabbit in the low dose group aborted. Study personnel did not consider this to be related to test material because it was not dose-dependent.

Foetal data (live/dead, sex, external defects, soft tissue and skeletal defects):

There was no effect of treatment on fetal body weight, or incidences or types of gross external or internal soft tissue malformations. The fetal and/or litter incidences of angulated hyoid alae and reversible delays in ossification of the xiphoid were increased in the 1500 mg/kg/day group.

The authors concluded that the NOAEL for fetal toxicity was 1500 mg/kg/day because the skeletal abnormalities observed at this dose were not unique. However, in a similar study performed by the same laboratory in rats (see previous record), common skeletal abnormalities were considered to be adverse. On this basis, the NOAEL for developmental toxicity in rabbits should be the dose that did not produce an increase in any skeletal abnormalities (1000 mg/kg/day).

Comments: Groups of 20 artificially inseminated female rabbits were given daily dosages of 0 (same volume of deionized water as the highest dose), 250, 500, 1000 or 1500 mg/kg/day of triethylene glycol monomethyl ether (TGME) by gavage. All doses were adjusted daily according to body weights recorded immediately prior to intubation.

Rabbits were observed daily during the course of the study for clinical signs, abortions, premature deliveries and death. Body weights were recorded on Day 0, and Days 6 through 29 of presumed gestation. Food consumption was recorded daily. Rabbits were killed on Day 29 of presumed gestation, and the thoracic and abdominal viscera were examined for gross lesions. The uterus was excised from each animal and weighed. The number and placement of implantations were recorded and sites were categorized as early or late resorptions, or live or dead fetuses. Each ovary was examined for the number of corpora lutea. Fetuses were weighed, sexed, and examined for external and soft tissue or skeletal alterations.

Reference: Hoberman AM. 1990b. Triethylene glycol monomethyl ether (TGME): oral developmental toxicity study in New Zealand White rabbits. Argus Research Laboratories, Inc. Study Number 503-004.

Test substance: Triethylene glycol monomethyl ether (purity 99.2%)

Test species/strain: Rat/Sprague-Dawley

Test method (e.g., OECD, other): other: Developmental Neurotoxicity

GLP YES [x]
NO [ ]

Results: NOEL for maternal animals = 1650 mg/kg bw
NOEL for offspring = 300 mg/kg NOEL (study personnel);
300 mg/kg day NOAEL (EPA)

Maternal general toxicity:

Evaluation of data from the maternal animals revealed no dose- related patterns of clinical signs of toxicity or lethality. Maternal body weights were equivalent across all groups and for all time points. No statistically significant effects on maternal weight gain or food consumption were noted. Necropsy of maternal animals in the high- dose group revealed significantly heavier kidneys than controls. Kidney weights increased in a dose-dependent manner. Necropsy of maternal animals revealed that kidneys from the maternal animals exposed to 3000 mg/kg/day of TGME were significantly heavier than controls.

The authors stated that "TGME administered by gavage to pregnant and lactating CD" (Sprague- Dawley) rats resulted in no overt signs of maternal toxicity". However, they also stated that the increased kidney weights in the high dose animals occurred as a result of exposure to TGME. Based on this comment, a maternal NOAEL of 1650 was assigned by the summary preparer. This is in agreement with the maternal NOAEL derived by the EPA (Anderson, L. Triethylene glycol monomethyl, monoethyl and monobutyl ethers RM1 screening document (draft), Feb. 24, 1995).

Pregnancy and litter data:

The length of gestation was significantly increased in the high-dose group animals compared to control although this finding was "of questionable biological significance since the difference between the groups was smaller than the 14-hour breeding time."

Foetal data (live/dead, sex, external defects, soft tissue and skeletal defects):

Analysis of pup in life data revealed no significant effects for PND 0/4 pup sex ratio or for pup survival during any period. Female pups from the mid- and high-dose groups (6.7 and 6.8 +/- 0.1 g) and male pups from the high- dose group (7.0 and 7.1 +/- 0.1 g) were significantly heavier than their control cohorts on PND O (6.2 and 6.7 +/- 0.1 g for females and males, respectively). Pups from these same groups gained significantly less weight in the period from PND 4 to PND 21. Although born heavier, the male pups from the high-dose group were significantly lighter than the control pups at the end of the study on PND 68 (440.7 +/- 6.0 vs. 462.4 +/- 4.8 g). Final body weights (PND 68) of mid and high dose females and mid-dose males were not significantly different from control.

Evaluation of pup development through the determination of vaginal opening revealed no differences between groups. Male pup development, as gauged by time of testes descent, was significantly advanced in the pups from the mid- and high-dose groups. Necropsy of weanling and adolescent pups revealed no findings that could be related to treatment. Histopathological assessment of the peripheral and central nervous systems of the pups showed no treatment related lesions in any group.

Of the 256 mated animals assigned to this study 33, 27, 28, and 31 litters in the control to high-dose group, respectively, had sufficient pups of both sexes to be used for the behavioral evaluations. Evaluation of the behavioral data generated during the course of this study indicated no dose-related effects on motor activity or active avoidance data. Significant effects on auditory startle response parameters were noted. In particular, the auditory startle amplitude (magnitude of the startle reflex) was increased in male and female pups in the high-dose group on PND 22. Auditory startle amplitude was also increased for male pups on PND 60 and a similar trend of smaller magnitude was observed in PND 60 females. When startle latency (time to maximum startle reflex) was examined, the pups showed no consistent effect on PND 22, but both male and female pups demonstrated a decrease in the startle latency on

PND 68.

The authors arrived at a no observable effect level (NOEL) of "equal to or greater than 300 mg/kg/day" based on decreased postnatal weight gains at 1650 and 3000 mg/kg/day. The reviewer does not believe that a NOAEL can be assigned from this study due to the unclear significance of minor reductions in body weight gains of animals at various time points and changes in startle response at 1650 and 3000 mg/kg. A NOAEL for teratogenicity of 300 mg/kg/day has been derived by the EPA (Anderson, L. Triethylene glycol monomethyl, monoethyl and monobutyl ethers RM1 screening document (draft), Feb. 24, 1995).

Comment: Timed pregnant CD" (Sprague-Dawley) rats, 64 sperm plug-positive females per group, were gavaged with the neat test material, triethylene glycol monomethyl ether (TGME), once daily, on gestational day (GD) 6 through postnatal day (PND) 21 at doses of 0, 300, 1650 or 3000 mg/kg/day. The volume of TGME administered was adjusted based on each animal's most recent body weight. Clinical observations were made at least twice daily during the dosing period and daily otherwise. Maternal body weights were measured on GD 0, 6, 9, 12, 15, 18, 20, and on PND 0, 4, 7, 13, 17, and 21. Food consumption was measured for the intervals GD 0-6, 6-9, 9-12, 12-15, 15-18, 18-20, and PND 0-3, 3-6, 6-9 and 9-12. Maternal animals were allowed to deliver and rear their young. Pups were counted, examined externally, weighed, and sexed on PND 0 and PND 4. After examination on PND 4, litter size was standardized by random culling to either a 4:4 or 5:3 sex ratio. Litters with insufficient numbers of pups were removed from the study after culling. Litters with sufficient numbers of pups remained on study, and pups were examined and weighed on PNDs 7, 13, 17, 21,35, 49, and 68. Male pups were examined daily starting at PND 17 for testicular descent, and females were examined daily starting on PND 30 for vaginal opening. One male and one female pup from each litter were assigned to each of three behavioral tests. Motor activity was assessed for one hour in a Figure-8 maze on PNDs 13, 17, 21, 47, and 58. Auditory startle response was assessed on PNDs 22 and 60, and learning and memory were assessed with an active avoidance paradigm run on PNDs 60-64. Three euthanizations occurred during the course of this study. The first took place after culling and involved those dams that had failed to deliver as well as the dams and pups from litters of insufficient size or sex ratio. The second took place on PND 22 and the third on PND 68.

On PND 22 the dams were evaluated for body weight, liver and kidney weight and the number of uterine implants (metrial glands). On PND 22 and PND 68 one male and one female pup from each litter were weighed and killed. A total of 24 of these pups were perfused *in situ* at each euthanization (PND 22 and PND 68 *i.e.,* 48 animals total) and were examined for histopathologic lesions of the central and peripheral nervous system. The brains of the remaining animals at each termination were removed and separated into the telencephalon, diencephalon, medulla oblongata/pons, and the cerebellum. These sections were all weighed separately.

Data were analyzed using the FREQ, GLM, NPAR1WAY and LIFETEST procedures in the SAS software package, in conjunction with a set of custom-designed analysis procedures.

Reference: Bates HK and de Serres FJ. 1992. Developmental neurotoxicity evaluation of triethylene glycol monomethyl ether (CAS 112-35-6) administered by gavage to time-mated CD rats on gestational day 6 through postnatal day 21. CMA Reference Ge-43.0-DEV/NEU-RTI, dated March 3, 1992.

6.8 Specific Toxicities (neurotoxicity, immunotoxicity, etc.)

Test substance: Related material : Triethylene glycol monomethyl ether

Test species/strain: Rat/Sprague-Dawley

Test method (e.g., OECD, other): Developmental Neurotoxicity Study

GLP YES [X]
NO [ ]

Test results: Evaluation of the behavioral data generated during the course of this study indicated no dose-related effects on motor activity or active avoidance data. Significant effects on auditory startle response parameters were noted. In particular, the auditory startle amplitude (magnitude of the startle reflex) was increased in male and female pups in the high-dose group on PND 22. Auditory startle amplitude was also increased for male pups in the high dose group on PND 60 and a similar trend of smaller magnitude was observed in PND 60 females. When startle latency (time to maximum startle reflex) was examined, the pups showed no consistent effect on PND 22, but both male and female high dose pups demonstrated a decrease in the startle latency on PND 68. Histopathological assessment of the peripheral and central nervous systems of the pups showed no treatment related lesions in any group. There were no neurotoxic effects in offspring at maternal doses up to 1650 mg/kg/day.

Comments: Pregnant rats were administered TGME by gavage (0, 300, 1650, 3000 mg/kg/day) on gestation day 6 through postnatal day 21. Maternal animals were allowed to deliver and rear their young. Pups were counted, examined externally, weighed, and sexed on PND 0 and PND 4. After examination on PND 4, litter size was standardized by random culling to either a 4:4 or 5:3 sex ratio. Litters with insufficient numbers of pups were removed from the study after culling. One male and one female pup from each litter were assigned to each of three behavioral tests. Motor activity was assessed for one hour in a Figure-8 maze on PNDs 13, 17, 21, 47, and 58. Auditory startle response was assessed on PNDs 22 and 60, and learning and memory were assessed with an active avoidance paradigm run on PNDs 60-64. On PND 22 and PND 68 one male and one female pup from each litter were weighed and killed. A total of 24 of these pups were perfused *in situ* at each euthanization (PND 22 and PND 68 *i.e.,* 48 animals total) and were examined for histopathologic lesions of the central and peripheral nervous system. The brains of the remaining animals at each necropsy were removed and separated into the telencephalon, diencephalon, medulla oblongata/pons, and the cerebellum. These sections were all weighed separately.

The analyzed chemical purity of the test material was 99.2%.

Reference: Bates HK and de Serres FJ. 1992. Developmental neurotoxicity evaluation of triethylene glycol monomethyl ether (CAS 112-35-6) administered by gavage to time-mated CD rats on gestational day 6 through postnatal day 21. CMA Reference Ge-43.0-DEV/NEU-RTI, dated March 3, 1992.

6.9 Toxicodynamics, Toxicokinetics

NO DATA AVAILABLE

7. Experience with Human Exposure (give full description of study design, effects of accidental or occupational exposure, epidemiology)

7.1 Biological Monitoring (including clinical studies, case reports, etc.)

NO DATA AVAILABLE

7.2 Other

Absorption through human skin

Human abdominal whole skin (2.54 cmE2) was mounted in a glass diffusion apparatus (at 30 +/- 1 degree C) and the diffusion of triethylene glycol monoethyl ether (TGEE) was monitored during a 12-hr period using gas chromatography (n=6). The integrity of the epidermal membranes was first assessed by measuring permeability of membranes to tritiated water. Epidermal membranes displaying permeability constants greater than 1.5 x 10E-3 cm/hr were deemed to have been damaged during preparation and were rejected. The rate of absorption of TGEE was 24.1 micrograms/ cm2/hr, and the mean damage ratio was 1.37 (no increase in permeability).

Reference: Leber, A.P., Scott, R.C., Hodge, M.C.E., Johnson, D. and Krasavage, W.J., (1990) "Triethylene Glycol Ethers: Evaluations of In Vitro Absorption Through Human Epidermis, 21-Day Dermal Toxicity in Rabbits, and a Developmental Toxicity Screen in Rats" 9 J. Am. Coll. Toxicol. 507.

8. Recommended Precautions, Classification (use, and/or transportation) and Safety Data Sheets.

-- A MSDS is available --

9. Availability of References for Existing Review(s)

-- Available --

10. Name of Responder

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