FOREWORD INTRODUCITON

2-(2-(2-Methoxyethoxy)ethoxy)-ethanol

CAS N°: 112-35-6

SIDS Initial Assessment Report

For

SIAM 4

Tokyo, Japan, 20 - 22 May 1996

1. Chemical Name:	2-(2-(2-Methoxyethoxy)ethoxy)-ethanol
2. CAS Number:	112-35-6
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 sponsored by 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 (CMA, 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. The chemical was found of low priority for further work. The United States was asked to revise the SIAR to include quantitative calculations of environmental exposures and toxicity 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:	March, 1996
10. Date of last Update:	April, 2005

11. Comments:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	112-35-6
Chemical Name	Ethanol, 2-[2-(2-methoxyethoxy)ethoxy]
Structural Formula	HO-CH_2CH_2 $OCH_2CH_2OCH2CH2$-OCH3

SHORT SUMMARY WHICH SUPPORTS THE REASONS FOR THE CONCLUSIONS AND RECOMMENDATIONS

Human Health

Ethanol, 2-[2-(2-methoxyethoxy)ethoxy] (TGME) is of low acute toxicity in experimental animals by the oral, dermal or inhalation routes of exposure. The oral and dermal LD_{50} values in rats and rabbits are 11,800 mg/kg and 7,400 mg/kg, respectively. An 8-hr exposure to a concentrated vapor of TGME resulted in no mortality in rats. Although TGME can be absorbed through the skin, acute dermal exposures generally has a minimal irritating effect. Contact with the eyes may produce mild irritation.

The repeated dose oral NOAEL of TGME in rats is 400 mg/kg/day. Systemic effects (other than male reproductive effects) noted at an oral dose of 1,200 mg/kg/day TGME for 91 days are slight hepatocellular centrilobular hypertrophy and increased relative liver weight. At 4,000 mg/kg/day TGME, 19 of 20 animals survived and the survivors exhibited reduced weight gain and food consumption, and microscopic changes in the liver (hepatocellular cytoplasmic vacuolization and/or hypertrophy and cholangiofibrosis). The severity of the lesions was minimal or mild (with the exception of moderate or marked hepatocellular cytoplasmic vacuolization in 4/15 males). In a dermal study, no systemic effects (other than male reproductive effects) were found in rats treated with up to 4,000 mg/kg/day TGME for 91 days.

Although a conventional reproductive toxicity test (i.e., mating study) with TGME has not been performed, results of existing 90-day studies that evaluated reproductive parameters indicate that TGME may cause testicular toxicity at high concentrations. Male rats orally administered 4,000 mg/kg/day TGME for 91 days exhibited testicular toxicity characterized by mild to moderate degeneration and/or minimal to moderate atrophy of the seminiferous tubules (spermatocytes or developing spermatids). In the same study, testicular toxicity was observed in 1/15 males at 1200 mg/kg/day and no testicular effects were noted at 400 mg/kg/day. Similarly, a 91-day repeated-dose dermal toxicity study in rats given 400, 1,200 or 4,000 mg TGME/kg/day showed severe testicular toxicity in 1/10 animals given 4,000 mg/kg/day and minimal decreases in developing germ cells in 1/10 rats given 1,200 mg/kg/day. No testicular effects were seen at 400 mg/kg/day. The NOAELs for reproductive toxicity determined from both the oral and dermal studies are between 400 and 1200 mg/kg/day.

Developmental toxicity experiments conducted with TGME indicate developmental effects at doses > 1,000 mg/kg/day. Effects observed in offspring from rats treated with 1,250 mg/kg/day TGME or rabbits treated with 1,500 mg/kg/day TGME during gestation included skeletal variants and decreased body weight gain.
In vitro and *in vivo* genotoxicity studies (Ames, HGPRT and micronucleus tests) with TGME were negative at concentrations up to 5,000 micrograms/plate and 5,000 mg/kg, respectively, indicating that this material is not genotoxic at these concentrations.

Environment

TGME is completely soluble in water. Its melting point is -44°C and its boiling point is 249.2°C. The vapor pressure is < 0.01 mm Hg at 25°C and specific gravity is 1.05.

TGME released into the atmosphere will photodegrade (estimated atmospheric half life = 3.2 hr). When released to water, TGME has a low potential for bioaccumulation (estimated log K_{ow} is –1.46). Ether groups are generally stable to hydrolysis in water under neutral conditions and ambient temperatures. However, TGME will biodegrade

in wastewater under aerobic conditions.

The Level III fugacity model estimated distributions of 0.0657% in air, 45.9% in water, 53.9% in soil and 0.0765% in sediment indicate a low probability of volatilization and a preference for partitioning to water and soil.
Aquatic toxicity data indicate that TGME exhibits low toxicity to aquatic species. The acute LC_{50} values for fish and Daphnia are > 10,000 mg/l. The EC_{50} for algae is > 500 mg/l and the IC_{50} for microorganisms is > 5,000 mg/l.

Exposure

In the United States, 18,000 to 25,000 tonnes of TGME are manufactured each year. TGME is produced in a closed process as a by-product from the manufacture of lighter (mono- and di-) ethylene glycol monomethyl ethers. Ninety-five percent of U.S. production is used in the formulation of hydraulic brake fluids.
Environmental releases are limited by the enclosed nature of industrial processes and the low volatility of the material. Releases are best characterized as usually occurring in very small amounts, but releases are possible wherever brakes are serviced.

The major known use of TGME is as a component of automotive brake fluids. Although exposure is limited during the formulation of TGME into brake fluids (which is done in closed systems in an industrial setting) greater exposure potential exists in automotive plants and brake service/repair shops, where brake lines and cylinders are filled with fluid, or brake systems are serviced. Exposure is more limited in automotive plants than in local shops by automated processes. Because of its low vapor pressure, inhalation exposures are expected to be insignificant. Occasional consumer exposure via brief dermal contact may occur when car owners top off their brake master cylinders from a container of fluid and possibly spill some liquid.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION

The chemical is currently of low priority for further work due to its low hazard potential for human health and the environment.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 112-35-6
Chemical Name: 2-(2-(2-Methoxyethoxy)ethoxy)-ethanol
Molecular Formula: $C_7H_{16}O_4$
Structural Formula: $HO\text{-}CH_2\text{-}CH_2O\text{-}CH_2CH_2\text{-}O\text{-}CH_2CH_2\text{-}OCH_3$
Molecular Weight: 164.20
Synonyms: Triethylene Glycol Monomethyl Ether
Methoxytriglycol
TGME
TM

1.2 Purity/Impurities/Additives

Degree of Purity: Approximately 90-96% by volume

Major Impurities: Tetraethylene glycol monomethyl ether (CAS No. 23783-42-8)

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

Diethylene glycol monomethyl ether (CAS No. 111-77-3)

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

Essential Additives: Not applicable

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Reference
Melting point	-44ºC	Boatman & Knaak, 2001
Boiling point	249.2ºC	Boatman & Knaak, 2001
Relative density		
Vapour pressure	<0.01 mm Hg (25ºC)	Boatman & Knaak, 2001
Vapour Density	6 (air = 1)	Union Carbide, 2000
Specific Gravity	1.05	Union Carbide, 2000
Water solubility	completely soluble	Union Carbide, 2000
Partition coefficient n-octanol/water (log value)	log K_{ow} = -1.46 (calc.)	EPIWIN (v. 3.10)
Flash Point	118ºC (open cup) 135ºC (open/closed cup)	Boatman & Knaak, 2001 Union Carbide, 2000

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

In the United States, 18,000 – 25,000 tonnes/year are produced according to USITC (1993).

In Sweden, 33-35 tonnes were used in 6 products in 1992 (Wahlstrom, 1994).

In Canada, 1,000 to 10,000 tonnes TGME per year has been produced (Canadian Domestic Substances List, 1986).

TGME is produced as a by-product from the production of lighter (mono and di) ethylene glycol monomethyl ethers in a closed system process. Ethylene oxide and methanol react in the presence of a catalyst to produce a mixture of mono, di, tri, and other heavy ethylene glycol monomethyl ethers. A distillation system removes excess alcohol for recycling and isolates the mono- and di-ether products. The separated heavy ethers are held in storage tanks for subsequent shipment by truck.

The primary industrial use (95%) is as a major raw material (diluent) in the formulation of hydraulic brake fluid. On average, the amount of triethylene glycol ethers found in brake fluids is about 40-60 percent.

Other uses include coatings, printing inks, some specialty chemicals such as glycol ether borate esters, antisudsing agents for finely powdered materials, cleaning products, cutting oils and deicing agents.

Table 2 Use Patterns of TGME (Worldwide and in the United States)

Hydraulic brake fluid	95%
Glycol ether borate esters	1%
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

Monitoring data are not available for this material. However, modeled concentrations using 1990 emissions data and an air dispersion model predicted an annual average of 0.004 $\mu g/m^3$ at the fenceline of the manufacturing plant (Union Carbide, 1991).

2.2.2 Photodegradation

The photodegradation half-life of TGME (for the reaction with hydroxyl radicals estimated using the EPIWIN/AOP model) is 3.2 hours.

2.2.3 Stability in Water

This chemical does not have any hydrolysable functional groups.

2.2.4 Transport between Environmental Compartments

The potential distribution of TGME 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. The Level III-estimated distributions of 0.0657% in air, 45.9% in water, 53.9% in soil and 0.0765% in sediment indicate a low probability of volatilization and a preference for partitioning to water and soil.

2.2.5 Biodegradation

TGME was determined to be biodegradable in a BOD test using nonacclimated domestic sewage organisms (Waggy and Payne, 1974; Waggy, 1987)

Chemicals with low calculated values (log K_{ow} < 3) do not have the potential to bioaccumulate. The calculated log K_{ow} of TGME is –1.46.

2.2.6 Other Information on Environmental Fate

TGME possesses physical properties that suggest that once it enters the aqueous compartment, it tends to remain dissolved in water. A soil/sediment partition coefficient (K_{oc}) of 10 has been estimated for TGME using EPIWIN. This suggests that TGME 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

Since the predominant use for TGME is brake fluids, the automotive industry is expected to have a higher incidence of exposure. Occupational exposure to TGME may occur from the inhalation of aerosols or vapors and from dermal exposure. Routine use of protective clothing, face shields, goggles and chemically-resistant gloves by workers who are sampling process streams and tanks, conducting analytical testing, bulk loading, monitoring process operations, and maintaining equipment will reduce or eliminate exposure.

There are no occupational exposure standards or workplace exposure limits for TGME.

Because no actual monitoring data are available, several worst-case exposure estimates were modeled by US EPA (1995), as indicated in the following sections.

Manufacturing

Occupational exposure during manufacturing is probably minimal because a closed system is likely to be used. Room ventilation and use of PVC-coated gloves are recommended in a Material Safety Data Sheet for TGME as a protective measure. Based on 100% triethylene glycol ether concentration and a worst case assumption that workers do not wear gloves or respirators, dermal

exposure was estimated to range from 1,950 to 3,900 mg/day.[1] Estimated inhalation exposure to TGME during sampling, drumming, filling tankwagons, cleaning, and maintenance was estimated to range from 0.019 to 10.8 mg/day (8-hour time-weighted-average).

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% 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 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. 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 TGME 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 would result in an estimated dermal exposure rate 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.

[1] All dermal estimates in this document are based on an administered dose (i.e., they do not take into account decreased penetration through the skin). However, because toxicity tests are based on administered dose (and also do not consider absorption), dermal exposure that does not consider absorption through the skin is the most appropriate estimate to use when comparing with toxicity values such as NOAELs and LOAELs.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

The *in vitro* rate of penetration of TGME through human epidermis was reported as 0.034 mg/cm^2/hr (Leber et al, 1990).

3.1.2 Acute Toxicity

Acute toxicity has been tested by the oral, inhalation and dermal routes. Smyth et al. (1962) reported an oral LD_{50} of 11.3 ml/kg (11.8 g/kg) for rats, and a dermal LD_{50} of 7.1 ml/kg for rabbits. An 8-hr exposure to a concentrated vapor of TGME resulted in no mortality in rats (Smyth et al., 1962, Carpenter, 1958).

3.1.3 Irritation

Contact of TGME with the eyes may produce slight irritation. Smyth et al. (1962) reported a very small area of corneal necrosis when 0.5 ml of undiluted chemical was applied to the eyes of rabbits.

TGME can be absorbed through the skin, and acute dermal exposures can have an irritating effect. Smyth et al. (1962) reported slight irritation (the least visible capillary injection) when undiluted solution was applied to the uncovered clipped skin of rabbits; however, in tests in which intact rabbit skin was covered, erythema was observed in 4/5 test animals treated with 2.0 g/kg for 24 hr (MBRL, 1977). A study using 20 subjects suggests that the material is slightly irritating to human skin (Palazzolo, 1969).

3.1.4 Sensitisation

No data were found on sensitization.

3.1.5 Repeated Dose Toxicity

In a 13-week drinking water study, TGME was administered to rats at doses of 400, 1,200, and 4,000 mg/kg/day. At 1,200 mg/kg/day and higher, statistically-significant changes in relative liver weight were observed. Histopathological effects included hepatocellular cytoplasmic vacuolization (minimal to mild in most animals) and hypertrophy (minimal to mild) in males at all doses and hepatocellular hypertrophy (minimal to mild) in high-dose females. These effects were statistically significant at 4,000 mg/kg/day. At 400 mg/kg/day, 3 of 15 males exhibited hypertrophy and cytoplasmic vacuolization of the liver (Gill and Negley, 1990; Gill et al., 1998). This incidence was not statistically different from the controls (one control animal exhibited hepatocellular cytoplasmic vacuolization, but no hypertrophy). A NOAEL of 400 mg/kg/day was considered to be appropriate since the effects on the liver at this dose were not significantly different from controls and at this dose level, these effects could possibly be adaptive changes.

Additional effects were also observed in the aforementioned study. Cholangiofibrosis was observed in 7/15 high-dose males; this effect was observed in a small number of bile ducts and was of mild severity (Gill et al, 1998). One high-dose female died on Day 37. In the high-dose group, the testes of 12-15 males exhibited primarily mild to moderate degeneration and/or atrophy of the seminiferous tubules (spermatocytes or developing spermatids). At 1,200 mg/kg/day, one male had

severe seminiferous tubule atrophy and moderate Leydig cell hypertrophy. The testicular effects are described in more detail in Section 3.1.8 below. Significant, small decreases in total test session motor activity were observed in the high-dose animals (as discussed more completely in Section 3.1.9). Males and females treated with the highest dose consumed less food and had lower body weights and body weight gains than control animals. In addition, water consumption was decreased in high-dose females (Gill and Negley, 1990; Gill et al., 1998).

A 91-day dermal study of TGME in rats given 400, 1,200 or 4,000 mg/kg/day showed severe testicular toxicity in 1/10 rats given 4,000 mg/kg/day and minimal decreases in developing germ cells in 1/10 rats given 1,200 mg/kg/day. Decreased numbers of platelets were observed at 4,000 mg/kg/day; these were slightly below the historical control range. Skin irritation was confined to small sections of the treated area (Corley et al., 1990; Gill et al., 1998). The NOAEL was between 400 mg/kg/day and 1,200 mg/kg/day (Anderson 1995). Refer to Section 3.1.8 below for additional information about the testicular effects.

In a 21-day dermal study, TGME was administered to rabbits at 1,000 mg/kg/day. Erythema and edema were observed. In addition, testicular degeneration (scored as trace in severity) was observed in one rabbit given TGME. Testicular effects included spermatid giant cells, focal tubular hypospermatogenesis, and increased cytoplasmic vacuolization (IRDC, 1986). Due to a high incidence of similar spontaneous changes in normal New Zealand White rabbits as reported in Morton et al. (1986a,b), the testicular effects were considered to be unrelated to treatment (see Section 3.4). Thus, the NOAEL for TGME was established at 1,000 mg/kg/day. Findings from this report were considered unremarkable (Anderson, 1995).

A 2-week dermal study also was conducted in rats administered TGME at doses of 1,000, 2,500, and 4,000 mg/kg/day (Yano, 1987). In this study, significantly-increased red blood cells at 4,000 mg/kg/day and significantly-increased urea concentrations in the urine at 2,500 mg/kg/day were observed. A few of the rats given 2,500 or 4,000 mg/kg/day had watery cecal contents and/or hemolyzed blood in the stomach These gross pathologic observations were not associated with any histologic abnormalities in these tissues or alterations in hematologic and clinical chemistry parameters. A few males and females treated with either 1,000 or 2,500 mg/kg/day had a few small scabs or crusts at the test site. These alterations were slight in degree and did not adversely affect the rats.

Conclusion

Oral and dermal studies indicate that at high doses, some systemic effects have been observed. The 90-day oral study found effects in the liver and a NOAEL of 400 mg/kg/day was established for this study. Other effects included cholangiofibrosis and testicular effects. In the 90-day dermal study, the NOAEL was established at 400-1200 mg/kg/day based on testicular effects. Decreased numbers of platelets were also seen at 4000 mg/kg/day. Testicular effects were observed in the 21-day dermal study, but were found to be unrelated to treatment and a NOAEL of 1000 mg/kg/day was chosen. Finally, a 2-week dermal study resulted in increased red blood cells and urea at 2500 mg/kg/day and higher.

3.1.6 Mutagenicity

Negative results were obtained when TGME was tested for genetic mutations in *Salmonella* and Chinese hamster ovary cells (both with and without metabolic activation) (Samson and Gollapudi, 1990; Liscombe and Gollapudi, 1990). In addition, results of a mouse micronucleus test were determined to be negative for chromosomal aberrations (McClintock and Gollapudi, 1990).

3.1.7 Carcinogenicity

No data are available for this endpoint.

3.1.8 Toxicity for Reproduction

Effects on Reproductive Organs

Although studies designed to specifically assess reproductive toxicity have not been performed with TGME, the effect TGME on reproductive organs has been scrutinized. A lower molecular weight glycol ether, ethylene glycol methyl ether (EGME), has been shown to be a testicular toxicant. TGME, as noted below, also exhibits testicular toxicity, generally at higher doses than those at which EGME exhibits such effects.

Although mating studies with TGME have not been performed, the repeated-dose oral and dermal toxicity tests have included examination of reproductive organs. 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). Because it is difficult to determine whether the effects seen at 1,200 mg/kg/day were related to treatment, the NOAEL from the oral study was determined to be between 400 and 1,200 mg/kg/day for testicular effects (Anderson, 1995).

Because effects were seen in many animals at 4,000 mg/kg/day, the effects at 1,200 mg/kg/day may be related to treatment. On the other hand, the testicular effects at 1,200 mg/kg/day may be related to another contributing factor. Specifically, 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 ethylene glycol monomethyl ether (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 (4,000 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 may not be 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 1,200 mg/kg/day in the aforementioned study (Anderson, 1995).

In a 21-day dermal study with 1,000 mg/kg/day TGME in rabbits, testicular degeneration was observed in one rabbit given TGME (IRDC, 1986). 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).

Developmental toxicity

Developmental toxicity data are available for TGME. TGME did not produce developmental toxicity in the rat when administered orally at 1,000 mg/kg/day (highest dose used) from days 7-16 of gestation (Wason et al., 1986; Leber et al., 1990).

In a gavage study, rats were treated with TGME at doses of 0, 625, 1,250, 2,500 or 5,000 mg/kg/day on days 6 to 15 of gestation. Effects noted in the study were increased resorption rate (at 5,000 mg/kg/day), increased incidence of skeletal variations (at 1,250, 2,500 and 5,000 mg/kg/day), decreased fetal body weight (at 2,500 and 5,000 mg/kg/day), and decreased maternal body weight (5,000 mg/kg/day) and food consumption (at 2,500 and 5,000 mg/kg/day). Therefore, the NOAELs for maternal and fetal toxicity were 1,250 and 625 mg/kg/day, respectively (Hoberman, 1990a).

TGME (0, 250, 500, 1,000 or 1,500 mg/kg/day) also has been administered orally to rabbits from days 6 to 18 of gestation (Hoberman, 1990b). In this study, effects on fetal toxicity parameters seen were increased fetal and/or litter incidences of angulated hyoid alae and reversible delays in ossification of the xiphoid in the 1,500 mg/kg/day group. The 1,500 mg/kg dose caused severe maternal toxicity, as exhibited by a high incidence of maternal death, abortion, clinical signs of treatment, gastrointestinal lesions, and reduced gravid uterine weight. There also was one death in the 1,000 mg/kg/day group (which 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. As this weight gain was not considered to be an adverse effect, the NOAEL for maternal toxicity was 500 mg/kg/day. In this study, the authors concluded that the NOAEL for fetal toxicity was 1,500 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, common skeletal abnormalities were considered by the study personnel to be adverse. On this basis, the NOAEL for developmental toxicity in rabbits is the dose that did not produce an increase in any skeletal abnormalities (1,000 mg/kg/day).

In a gavage study, TGME was administered to rats at doses of 300, 1,650, and 3,000 mg/kg/day from gestational day 6 through postnatal day 21 (Bates and de Serres, 1992). At 3,000 mg/kg/day, maternal animals had significantly heavier kidneys than controls. Analysis of pup in-life data revealed no significant effects of treatment on sex ratio or pup survival during any period. Histological examination of weanling and adolescent pups revealed no findings that could be related to treatment. Female pups from the mid- and high-dose groups and male pups from the high-dose group were significantly heavier than their control cohorts at birth. Pups from these same

groups gained significantly less weight in the period from postnatal day 4 to 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. Final body weights of mid and high dose females and mid-dose males were not significantly different from control. 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 offspring from high dose animals. The authors stated that the "significance of the auditory startle observations with regard to the condition of the test animals is not clear." The EPA also concluded that neurotoxicological findings were unremarkable (Anderson, 1995). A no observable effect level (NOEL) for developmental toxicity of 300 mg/kg/day is assigned to this study, based on decreased postnatal weight gains at 1,650 and 3,000 mg/kg/day. The maternal NOAEL is 1,650 mg/kg/day (based on increased maternal kidney weights at 3,000 mg/kg/day).

Conclusion

Studies that have measured effects on reproductive organs show that TGME clearly exhibits testicular effects at 4000 mg/kg/day. In addition, some testicular effects have been observed at 1,000 or 1,200 mg/kg/day; however, given that the effects are minimal and only one animal was affected at this dose in three different studies, it is less clear that the effects at this dose can be clearly attributed to TGME. Based on these studies, NOAELs of between 400 and 1200 mg/kg/day have been established.

The bulk of the evidence on developmental toxicity shows that effects on the fetus are noted at doses of > 1,000 mg/kg/day TGME during gestation. At 1,250 to 1,650 mg/kg/day TGME (in the rat) and 1,500 mg/kg/day (in the rabbit), the developmental effects observed included skeletal variants and decreased body weight gain.

3.1.9 Specific Toxicities (Neurotoxicity)

Treatment with TGME at concentrations up to 4,000 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, 1,650, 3,000 mg/kg/day) on gestation day 6 through postnatal day 21, Bates and de Serres (1992) found that a dose level of 3,000 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 1,650 mg/kg/day.

Conclusion

In summary, some changes in motor activity were observed in adult rats after administration of 4,000 mg/kg TGME per day in drinking water for 90 days. A developmental neurotoxicity study

also found that pups exhibited changes in auditory startle amplitude and decreases in latency to maximum startle at a dose of 3,000 mg/kg/day. These studies suggest that at high doses, some neurological effects are observed, although they were not accompanied by physical changes in the nervous system or behavioral effects.

3.2 Initial Assessment for Human Health

TGME is manufactured in closed systems. The single predominate use is as a component of automotive brake fluid formulations. Formulation is also carried out in closed processes. Workplace exposure during manufacture and processing is minimized through the use of closed processes and low volatility. Due to low vapor pressure, inhalation exposure of TGME will be negligible. The most likely source of potential industrial exposure to TGME is dermal contact when charging or repairing automotive brake systems using brake fluid formulations. 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.

TGME displays low acute toxicity by the oral, inhalation and dermal routes of exposure. All *in vitro* and *in vivo* genotoxicity studies are negative at concentrations up to 5,000 micrograms/plate and 5,000 mg/kg, respectively, indicating that TGME is not genotoxic.

Results of repeated dose studies with TGME suggest that repeated exposure to relatively high doses results in systemic toxicity. The bulk of the evidence suggests that repeated dermal or oral exposure of rats to concentrations of TGME greater than or equal to 1,000 mg/kg/day causes some changes in the liver. Repeated oral administration of 4,000 mg/kg/day TGME causes testicular toxicity. No testicular changes are noted in males treated with 400 mg/kg/day TGME. Testicular effects were observed in single animals at doses of 1,000 and 1,200 mg/kg/day. The occurrence of testicular lesions in a few rats treated dermally with 4,000 mg/kg TGME or orally or dermally with approximately 1,200 mg/kg TGME are different from those observed in rats treated with EGME.

The bulk of the evidence from developmental toxicity experiments conducted with TGME indicates that this material is a developmental toxicant at doses > 1,000 mg/kg/day. Effects observed in offspring from rats treated with 1,250 mg/kg/day TGME or rabbits treated with 1,500 mg/kg/day TGME during gestation included skeletal variants and decreased body weight gain.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

TGME is of low acute aquatic toxicity when tested in fresh and saltwater organisms and it will not adversely affect sewage treatment microorganisms. Experimental data are listed in Table 3. The experimental data can be compared with predicted values using EPIWIN (v 1.30), also listed in Table 2. Predicted toxicity values are based on SARs for neutral organics; MW164.2, log K_{ow} = -1.46, MP = -44°C, BP = 249.2°C, and vapor pressure of 0.01 mm Hg.

Table 3. Experimental and Predicted Aquatic Toxicity Values

Ecotoxicity Effect	Experimental (mg/L)	Predicted (mg/L)
Fish 96-h LC50	> 10,000 (FHM)	218,000
Daphnid 48-h LC50	> 10,000	184,000
Green algal 96-h EC50	> 500 (SS)	94,077
Fish chronic value		16,034
Daphnid chronic value		2,073
Green algal 96-hr chronic value		1,274
Toxicity to sewage microorganisms (IC50)	> 5,000 mg/l	

Note: FHM = fathead minnow; SS = *Scenedesmus subspicatus*

4.2 Terrestrial Effects

No data were located.

4.3 Other Environmental Effects

No data were located.

4.4 Initial Assessment for the Environment

Environmental releases are limited by the enclosed nature of industrial processes and the low volatility of the material. Releases are best characterized as occurring in very small amounts, but they are possible wherever brakes are serviced.

The Level III fugacity model estimated distributions of 0.0657% in air, 45.9% in water, 53.9% in soil and 0.0765% in sediment indicate a low probability of volatilization and a preference for partitioning to water and soil. Ether groups are generally stable to hydrolysis in water under neutral conditions and ambient temperatures. However, TGME will biodegrade in wastewater under aerobic conditions. TGME released into the atmosphere will photodegrade (estimated atmospheric half life = 3.2 hr). When released to water, TGME has a low potential for bioaccumulation (estimated log K_{ow} is –1.46).

Aquatic toxicity data indicate that TGME exhibits low toxicity to aquatic species. The acute LC_{50} values for fish and Daphnia are > 10,000 mg/l. The EC_{50} for algae is > 500 mg/l and the IC_{50} for microorganisms is > 5,000 mg/l.

5 RECOMMENDATIONS

This chemical is currently of low priority for further work due to its low hazard profile for human health and the environment.

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1.0.1 Applicant and Companay Information

Name of Sponsor Country: United States of America

Contact point (name, address, telephone and telefax):

U.S. Environmental Protection Agency

Mr. Oscar Hernandez, Director

Risk Assessment Division (7403M)

1200 Pennsylvania Ave, NW

Washington, DC 20460

Phone: 202-564-7641

e-mail: hernandez.oscar@epa.gov

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

1.0.2 Responder:

American Chemistry Council

Glycol Ethers Panel

1300 Wilson Boulevard

Arlington, VA 22209

Attn: Dr. Susan Lewis

susan_lewis@americanchemistry.com

703-741-5635 (phone)

703-741-6091 (fax)

1. Chemical Identity

1.1 CAS Number: 112-35-6

1.2 Name (give the name supplied by the OECD)

Ethanol, 2-(2-(2-methylethoxyethoxy)ethoxy)-

1.3. Common Synonyms

Triethylene glycol monomethyl ether

Methoxytriglycol

Methyl trioxitol

Polysolve TM

Dowanole TME

Triglycol monomethyl ether

TGME

TM

1.4 Empirical formula

C7H16O4

1.5 Structural formula

HO-CH2CH2O-CH2CH2-O-CH2CH2-OCH3

1.6 Purity of Industrial Product

1.6.1 Degree of purity (percentage by weight/volume)

Approximately 90-96% by volume

1.6.2 Identity of major impurities

Tetraethylene glycol monomethyl ether (CAS No. 23783-42-8)

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

Diethylene glycol monoethyl ether (CAS No. 111-77-3)

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

1.6.3 Essential additives

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

Not applicable.

2.1 Melting or Decomposition Point

Results: -44 ºC

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

GLP: YES [ ]

NO [ ] Not reported**.**

Comments: Freezing Point

Reference: Boatman, R.J. and J.B. Knaak (2001) "Ethers of Ethylene Glycol and Derivatives" in Patty's Industrial Hygiene and Toxicology, 5th ed., Chapter 86, pp 73-270, New York: John Wiley & Sons, Inc.

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

Results: 249.2ºC at 760 mmHg

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

GLP: Yes [ ]

No [ ] Not reported.

Comments: Decomposes

Reference: Boatman, R.J. and J.B. Knaak (2001) "Ethers of Ethylene Glycol and Derivatives" in Patty's Industrial Hygiene and Toxicology, 5th ed., Chapter 86, pp 73-270, New York: John Wiley & Sons, Inc.

2.3 Vapor Pressure

Results: <0.01 mm Hg at 25ºC

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

GLP YES [ ]

NO [ ] Not reported.

Comments:

Reference: Boatman, R.J. and J.B. Knaak (2001) "Ethers of Ethylene Glycol and Derivatives" in Patty's Industrial Hygiene and Toxicology, 5th ed., Chapter 86, pp 73-270, New York: John Wiley & Sons, Inc.

2.4 Partition Coefficient n-Octanol/Water:

Results: log K_{ow} = -1.46

Method: calculated [X]

measured [ ]

GLP: YES [ ]

NO [ ] Not reported.

Analytical Method: Calculated using EPIWIN (v. 3.10) computer estimation software.

Comments (e.g., is the compound surface active or dissociative?): 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

Results: Completely soluble in water at 20ºC.

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

GLP: YES [ ]

NO [ ] Not reported.

Analytical Method: Not reported.

Comments (e.g., the detection limit for insoluble substances):

Reference: Union Carbide Chemicals and Plastics Technology Co., Material Safety Data Sheet.

2.6 Flash Point (liquids)

a) Results: 135ºC closed cup [X] open cup [ ]

Method (e.g., OECD, other including reference to the standard used):

Pensky-Martens Closed Cup, ASTM D 93

GLP: YES [ ]

NO [ ] Not reported.

Comments:

Reference: Union Carbide Chemicals and Plastics Technology Co., Material Safety Data Sheet.

b) Results: 118ºC closed cup [ ] open cup [X]

Method (e.g., OECD, other including reference to the standard used):

GLP: YES [ ]

NO [ ] Not reported.

Comments: data point given as 245ºF

Reference: Boatman, R.J. and J.B. Knaak (2001) "Ethers of Ethylene Glycol and Derivatives" in Patty's Industrial Hygiene and Toxicology, 5th ed., Chapter 86, pp 73-270, New York: John Wiley & Sons, Inc.

c) Results: 135ºC closed cup [ ] open cup [X]

Method: Cleveland Open Cup ASTM D 92:

GLP: YES [ ]

NO [ ] Not reported.

Comments: 275ºF

Reference: Union Carbide Chemicals and Plastics Technology Co., Material Safety Data Sheet.

2.7 Flammability

NO DATA AVAILAB

2.8 pH in Water

NO DATA AVAILABLE

2.9 Other data

(Relative density, surface tension (of aqueous solution), fat solubility, explosivity, oxidizing properties and particle size distribution

Vapor Density (air = 1): 6*

Specific Gravity (H2O = 1): 1.05 (20º/20º)*

Surface Tension: 39.1 dynes/cm**

Comments:

References:*

(1) Union Carbide Chemicals and Plastics Technology Co., Material Safety Data Sheet.

(2) Dow Chemical Co., The Glycol Ethers Handbook, p. 15.

Occupational Exposure

Since the predominant use for TGME is brake fluids, the automotive industry is expected to have a higher incidence of exposure. Occupational exposure to TGME may occur from the inhalation of aerosols or vapors and from dermal exposure. Routine use of protective clothing, face shields, goggles and chemically resistant gloves by workers who are sampling process streams and tanks, conducting analytical testing, bulk loading, monitoring process operations, and maintaining equipment will reduce or eliminate exposure.

Consumer Exposure

The primary use for TGME 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.

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.

18-25 million kg/yr produced in U.S.

Reference: U.S. International Trade Commission. Synthetic Organic Chemicals, U.S Production and Sales, 1993.

3.2 Processes

TGME is produced as a by-product from the production of lighter (mono and di) ethylene glycol monomethyl ethers in a closed process. Ethylene oxide and methanol react in the presence of a catalyst to produce a mixture of mono, di, tri, and other heavy ethylene glycol monomethyl ethers. A distillation system removes excess alcohol for recycle and isolates the mono and di ether products. The separated heavy ethers are held in storage tanks for subsequent shipment by truck.

3.3 Information Concerning Uses

(Including categories and types of uses expressed in percentage terms). Examples of use categories are dyestuffs, intermediates, solvents, adhesives, building material agents, detergents, cleaning agents, fertilizers, plastic agents, surface treatment agents, etc. Types of uses are divided into three: industrial use (open system and closed system), public use and export.

Use Pattern

Approximately 95% is used in the formulation of hydraulic brake fluids for industrial and public use; and approximately 4-5% is used for coatings, printing inks, some specialty chemicals such as glycol ether borate esters, antisudsing agents for finely powdered materials, cleaning products, cutting oils and deicing agents.

Worldwide:	Hydraulic brake fluid	95%
	Glycol ether borate esters	1%
	Coatings	~1%
	Printing inks	~1%
	Antisudsing agents	~1%
	Cleaning products	~1%
	Cutting oils	~1%
	Deicing agents	~1%
In USA:	Hydraulic brake fluid	95%
	Glycol ether borate esters	1%
	Coatings	~1%
	Printing inks	~1%
	Antisudsing agents	~1%
	Cleaning products	~1%
	Cutting oils	~1%
	Deicing agents	~1%

3.4 Options for Disposal.

Mode of disposal (e.g., incineration, release to sewage system) for each category and type of use, if appropriate; recycling possibility

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 and Plastics Technology Co., Material Safety Data Sheet.

3.5 Other Remarks

4.1 Degradability (biotic and abiotic)

4.1.1 Biodegradability

a) Test substance: Triethylene glycol monomethyl ether

Test type: aerobic [X], anaerobic [ ]

Test medium: wastewater

In the case of poorly soluble chemicals, treatment given (nature, conc., etc.):

Not applicable

Test method (e.g., OECD, ISO, other): Biochemical oxygen demand (BOD) method published in APHA.(1955) Standard Methods for the Examination of Water and Wastewater, 16th ed., American Public Health Association,

GLP YES [ ]

NO [ ] Not reported.

Test results: BOD5: 29%

BOD10: 33%

BOD20: 71%

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.

b) Test substance: Triethylene glycol monomethyl ether (>95% purity)

Test type: aerobic [X], anaerobic [ ]

Test medium: activated sludge

In the case of poorly soluble chemicals, treatment given (nature, conc., etc.):

Not applicable

Test method: Modified Zahn-Wellens test. OECD TG 302B (1981)

GLP YES [ ]

NO [ ]

Results:

Time	Percent Elimination	
	150 mg/L	300 mg/L
3 hr	0	0
8 days	13.2	8.2
20 days	33	9.4
21 days	<40	-
29 days	>70	-
31 days	101.4	13.7
34 days		<20
41 days		93.3

Comments: Determination of elimination by DOC measures no sterile control.

Reference: Hoechst AG, 1986, unpublished report No. 86-0223-56

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). If available, information on degradation products, dissociation constants and half-life should be given.

Test substance: Triethylene glycol monomethyl ether

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

GLP YES [ ]

NO [ ] N/A

Results: Predicted half-life is 3.206 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 40.0295 $x10^{-12}$ cm^3/molecule-sec. The HYDROWIN model could not calculate a hydrolysis rate constant for the material.

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.

4.1.4 Identification of Main Mode of Degradability in Actual Use

NO DATA AVAILABLE

4.2 Bioaccumulation

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 = -44 ºC

Boiling Point = 249.2 ºC

Water solubility = 1 x 10^6 mg/L

Vapor pressure = 0.01 mm Hg

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

Results: Environmental distributions:

Air: 0.0657

Water: 45.9

Soil: 53.9

Sediment: 0.0765

Comment: The Koc estimated using the PCKOC Program (v. 1.66) is 10.

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.

4.4 Monitored/Modelled Concentrations (Environment):

Test substance: Triethylene glycol monomethyl ether

Results: 0.004* ($\mu g/m^3$) in air as of 1990

Comment: *Maximum predicted 1990 annual average air concentration at the fenceline of Union Carbide's manufacturing facility, obtained using EPA Industrial Source Complex-Long Term averaging guideline model. This is the only data available for this substance.

Reference: Union Carbide, 1991.

5.l Toxicity to Fish

5.1.1 Results of Acute Tests

a) Test substance: Triethylene glycol monomethyl ether

Test species: Fathead minnow

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

Type of test: static [x], semi-static [ ], flow-through [ ]

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, American Public Health Association

GLP YES [ ]

NO [ ] Not Reported.

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.

b) Test substance: Triethylene glycol monomethyl ether

Test species: fish

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

GLP YES [ ]

NO [ ] N/A

Results: 96-hr LC50 = 218,000 mg/L

Comments: Calculated with a calculated Log Kow of –1.46, a melting point of – 44 degrees C and a molecular weight of 164.2.

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.

5.1.2 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 = 2.28 x 10^5 mg/L, 30 day ChV = 16054mg/L

Comments: Calculated with a calculated Log Kow of –1.46, a melting point of – 44 degrees C and a molecular weight of 164.2.

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

a) Test substance: Triethylene glycol monomethyl ether

Test species: Daphnia magna

Test method (e.g., OECD, other): Bioassay procedures generally followed the techniques recommended in Standard Methods for the Examination of Water and Wastewater, 16th ed., 1985, American Public Health Association.

GLP YES [ ] Not reported.

NO [ ]

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

b) Test substance: Triethylene glycol monomethyl ether

Test species: daphnids

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

GLP YES [ ]

NO [ ] N/A

Results: 48-hr LC50 = 184,000 mg/L

Comments: Calculated with a calculated Log K_{ow} of –1.46, a melting point of – 44 degrees C, and a molecular weight of 164.2.

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.

5.2.2 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 = 2072.9 mg/L

Comments: Calculated with a calculated Log Kow of –1.46, a melting point of – 44.0 degrees C and a molecular weight of 164.2.

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

a) Test substance: Triethylene glycol monomethyl ether

Test species: Scenedesmus subspicatus (Algae)

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

GLP YES [ ]

NO [ ] Not reported

Results: EC50 value (72 hours) > 500 mg/l

Comments: Original reference was not available. Information came from a IUCLID data set produced by the European Chemicals Bureau.

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

b) Test substance: Triethylene glycol monomethyl ether

Test species: Not applicable

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

GLP YES [ ]

NO [ ] N/A

Results: EC50 = 94,077 mg/L

Comments: Calculated with a calculated Log Kow of –1.46, a melting point of –44 degrees C and a molecular weight of 164.2. Prediction using 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.

c) Test substance: Triethylene glycol monomethyl ether

Test species: Not applicable

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

GLP YES [ ]

NO [ ] N/A

Results: 96-hr Chronic value = 1,274 mg/L

Comments: Calculated with a calculated Log Kow of –1.46, a melting point of –44 degrees C and a molecular weight of 164.2.

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.

5.4 Toxicity to other aquatic organisms

5.5 Toxicity to Bacteria

(single species tests such as "Microtox Photobacterium luminescence test" and tests on overall processes such as nitrification or soil respiration are included in this item).

Test substance: Triethylene glycol monomethyl ether

Test species: Not reported.

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

Type of test: static [x], 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^{o}C in the presence of nutrients, buffer, growth substrate and sewage microorganisms.

GLP YES [ ]

NO [ ] Not reported.

Results: IC50 > 5,000 mg/L

Comments: Purity of test material was not noted.

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

*5.6 Toxicity to Terrestrial Organisms

NO DATA AVAILABLE

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

(under this item, studies on absorption, distribution, metabolism and excretion, etc. should be given).

NO DATA AVAILABLE

*6.1 Acute Toxicity

6.1.1 Acute Oral Toxicity

a) Test substance: Triethylene glycol monomethyl ether

Test species/strain: Rat/Wistar

Test method (e.g., OECD, EC, limit test): LD50 and 95% confidence limits calculated by method of Litchfield and Wilcoxon (J. Pharm. & Exp. Therap. (1949).

GLP YES [ ]

NO [ ] Not reported.

Results: LD50 = 12.6 g/kg (10.4 - 15.3 g/kg).

Comments:

Reference: MB Research Laboratories, Inc. (1977) Oral LD50 in Rats. Report to Olin Corp. MB 77-1819

b) Test substance: Triethylene glycol monomethyl ether

Test species/strain: Carworth-Wistar

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

GLP YES [ ]

NO [ ] Not reported.

Results: LD50 = 11.3 mL/kg (11.8 g/kg).

Comments: Groups of five non-fasted rats (4-5 weeks of age; 90-120 g) were intubated with log doses of test compound differing by a factor of 2. Test compound was diluted in either water, corn oil or semi-solid agar (vehicle specific for test compound was not listed). Purity of test material was not noted.

Reference: Smyth, H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A., (1962). Range Finding Toxicity Data, List VI. Am. Ind. Hyg. Assoc., J. 23:95-107.

c) Test substance: Triethylene glycol monomethyl ether

Test species/strain: Carworth Farms-Nelson

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

GLP YES [ ]

NO [ ] Not reported.

Results: LD50 = 11300 mg/kg

Comments: Male rats (5-6 weeks old, 90-120 g) were dosed with 4, 8, or 16 ml/kg test material by stomach intubation. Rats were observed for 14 days. Surviving rats were weighed on day 14. Autopsies were performed on those that died. The method of moving average was used to calculate the LD50 value. Purity of test material was not noted. All rats dosed with 16 ml/kg died within 1 day. None of the other animals died. All animals except 1 dosed with 4 ml/kg gained weight. Autopsies on rats that died revealed congested lungs, mottled livers and kidneys, GI tract irritation, and congested adrenals.

Reference: Carpenter CP. 1958. Range finding tests on methoxytriglycol. Mellon Institute of Industrial Research Report 21-44, dated 6-12-58.

6.1.2 Acute Inhalation Toxicity

a) Test substance: Triethylene glycol monomethyl ether

Test species/strain: Rat/Wistar

Test method (e.g., OECD, EC, limit test): Rats were exposed to 200 mg/L for one hour and observed for 14 days.

GLP YES [ ]

NO [ ] Not reported.

Results: No mortality or toxicity observed. At necropsy, one mottled kidney observed.

LC50: None established.

Comments:

Reference: MB Research Laboratories, Inc. (1977). Report to Olin Corp. unpublished

b) Test substance: Triethylene glycol monomethyl ether

Test species/strain: Rat

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

GLP YES [ ]

NO [ ] Not reported.

Results: All animals survived an 8-hr exposure period to concentrated vapor and had normal weight gains.

LC50: None established.

Comments: Six female rats were exposed to a flowing stream of vapor-ladened air generated by passing 2.5 l/min of dried air at room temperature through a fritted disc immersed to a depth of at least once inch in approximately 50 ml of test material contained in a gas-washing bottle. Rats were exposed from time periods ranging from 15 minutes to 8 hours (until the inhalation period killing about one half of the rats within 14 days was defined). The result is the longest inhalation period which permitted all rats to survive the14-day observation period. Purity of test material was not noted.

Reference:

1) Smyth, H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A., (1962). Range Finding Toxicity Data, List VI. Am. Ind. Hyg. Assoc., J. 23:95-107.

2) Carpenter CP. 1958. Range finding tests on methoxytriglycol. Mellon Institute of Industrial Research Report 21-44, dated 6-12-58.

6.1.3 Acute Dermal Toxicity

Test substance: Triethylene glycol monomethyl ether

Test species/strain: Rabbit/New Zealand White

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

GLP YES [ ]

NO [ ] Not reported.

Results: LD50: = 7.1 ml/kg (7.4 g/kg)

Comments: Male rabbits (3-5 months old) weighing between 2.5 to 3.5 kg were treated with 2.5 ml/kg (N=2), 5 ml/kg (N=4), or 10 ml/kg (N=2) test material according to a variation of the one-day cuff method of Draize and associates (J Pharmacol Exper Ther 82: 377, 1944). Fur was clipped from the entire trunk, and doses were placed beneath an impervious plastic film (VINYLITE sheeting). Animals were immobilized for a 24-hour contact period and the film was removed. Rabbits were then observed for 14 days. The LD50 value and its fiducial range (plus or minus 1.96 standard deviations) was estimated by the method of Thompson (Bacteriol Rev 11: 115, 1947) using the Tables of Weil (Biometrics 8: 249, 1952). Purity of test material was not noted.

Marked erythema of skin was noted after removal of the dressing (doses and number affected was not noted). The two rabbits treated with 10 ml/kg died within 4 days. One of the rabbits treated with 10 ml/kg had internal hemorrhage as evidence by bloody exudate in the peritoneal cavity at autopsy. All other rabbits survived and appeared normal.

Reference:

1) Smyth, H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A., (1962). Range Finding Toxicity Data, List VI. Am. Ind. Hyg. Assoc., J. 23:95-107.

2) Carpenter CP. 1958. Range finding tests on methoxytriglycol. Mellon Institute of Industrial Research Report 21-44, dated 6-12-58.

6.2 Corrosiveness/Irritation

6.2.1 Skin and Eye Irritation

a) Test substance: Triethylene glycol monomethyl 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.

Results: Intact skin: erythema in 4/5 rabbits, edema in 0/5 rabbits.

Abraded skin: erythema in 1/5 rabbits; edema in 1/5 rabbits.

Comments: Observations at necropsy included mottled liver (2), pocked kidneys (2) and bloated large intestine (1).

Reference: MB Research Laboratories, Inc. (1977) Report to Olin Corp., unpublished

b) Test substance: Triethylene glycol monomethyl ether

Test species/strain: Rabbit

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

GLP YES [ ]

NO [ ] Not reported.

Results: Grade of 2 (out of 10); the least visible capillary injection (minimal irritation)

Comments: Undiluted test solution (0.01 ml) was applied uncovered to the clipped belly skin of 5 rabbits. Irritation that occurred within 24 hours was scored in a graded fashion (from 1 to 10), with Grade 1 = no irritation, Grade 2 = the least visible capillary injection, Grade 6 = necrosis when undiluted. Purity of test material was not noted.

Reference:

1) Smyth, H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A., (1962). Range Finding Toxicity Data, List VI. Am. Ind. Hyg. Assoc., J. 23:95-107.

2) Carpenter CP. 1958. Range finding tests on methoxytriglycol. Mellon Institute of Industrial Research Report 21-44, dated 6-12-58.

c) Test substance: Triethylene glycol monomethyl ether

Test species/strain: Human

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

GLP YES [ ]

NO [ ] Not reported.

Results: By 24 hours, erythema scores of 1 or 2 were present in 10/20, and 3/20 subjects, respectively. At 48 hours, erythema scores of 1 or 2 were present in 11/20 and 9/20 subjects, respectively. At 72 hours, more subjects had scores of 2 (13/20), than 1 (7/20). Edema scores were 0 throughout the test. The average total irritation score by 72 hours was 1.65. The material was slightly irritating.

Comments: Twenty human subjects (10/sex, 20-56 years old, 90% Caucasian) were employed in the study. Band-aids (3/8 " x 1-1/2 ") with gauze centers were coated with 0.03 ml of test material just prior to application. Patches were placed on skin for 24 hours, and then removed. The skin site was examined approximately 1 hour after patch removal. After grading, a second patch was applied to the same site. The procedure was repeated for 3 consecutive days.

Erythema and Eschar formation were scored on a basis of 0-4, with 1= barely perceptible erythema, 2= well-defined erythema. 3 = moderate to severe erythema, and 4 = severe erythema to slight eschar formation. Edema was scored on a basis of 0-4, with 1= barely perceptible, 2 = slight (definite raising), 3 = moderate (area raised 1 mm), 4 = severe (raised more than 1 mm and extends beyond area of exposure). The total possible primary irritation score is the sum of the highest erythema and edema scores (8).

Purity of test material was not noted.

Reference: Palazzolo RJ. 1969. Comparative human skin irritation study on five test materials. Industrial Bio-Test Laboratories Report IBT F7445 to Olin Research Center, Dated June 25, 1969.

d) Test substance: Triethylene glycol monomethyl ether

Test species/strain: Rabbit

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

GLP YES [ ]

NO [ ] Not reported.

Results: Grade 1 (out of 10); at most, a very small area of corneal necrosis. Slightly irritating.

Comments: Various volumes and concentrations of test material were applied to rabbit eyes (number of rabbits and time of exposure was not indicated). Eye injury was scored on a 10 point scale according to the degree of corneal necrosis that resulted from instillation of the various concentrations. Grade 1 = very small area of necrosis from 0.5 ml undiluted material, Grade 5 = severe burn from 0.005 ml undiluted material, Grade 10 = severe burn from 0.5 ml of a 1% solution in water or propylene glycol.

Purity of test material was not noted.

Reference:

1) Smyth, H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., and Striegel, J.A., (1962). Range Finding Toxicity Data, List VI. Am. Ind. Hyg. Assoc., J. 23:95-107.

2) Carpenter CP. 1958. Range finding tests on methoxytriglycol. Mellon Institute of Industrial Research Report 21-44, dated 6-12-58.

6.3 Skin Sensitization

NO DATA AVAILABLE

6.4 Repeated Dose Toxicity

6.4.1 Repeated Dose Oral toxicity

a) Test substance: Triethylene glycol monomethyl ether. The purity of the material was at least 98.7%.

Test species/strain: Rat/ Sprague-Dawley CD

Test method (e.g., OECD, other): TSCA Test Guidelines, 40CFR 798, as modified in Section 4 Testing Consent Order for TGME. Reported to be conducted according to OECD TG 408.

GLP YES [x]

NO [ ]

Results: The actual doses attained in the study (time weighted average) were 0, 420, 1240 and 4300 mg/kg/day for males and 0, 420, 1290 and 4100 mg/kg/day for females.

One female in the high dose treatment group (approximately 4000 mg/kg/day) died on Day 37. 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%).

Treatment with triethylene glycol monomethyl ether did not result in any clinical signs of toxicity, alterations in the functional observational battery, or gross microscopic lesions in the nervous system. Significant, small decreases in total test session motor activity were observed in the high-dose treatment group 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."

Increased relative liver weight was observed in males treated with 4000 mg/kg/day (5.229 ± 0.3984) and 1200 mg/kg/day (3.951 ± 0.4191) versus control (3.214 ± 0.1519). Absolute liver weights of males treated with 4000 mg/kg/day were significantly greater than controls (25.926 ± 3.1591 versus 18.978 ± 1.4925). 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.

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). These effects were concluded 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 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). No testicular changes were noted in males treated with 400 mg/kg/day TGME.

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 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 (4200 mg/kg/day) is 4 times greater than the 1000 mg/kg/day limit dose generally recommended for subchronic studies.

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). The summary preparer-assigned NOAEL and LOAEL for testicular effects are 1200 and 4000 mg/kg/day, respectively. The EPA determined that the LOAEL 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).

NOAEL: 400 mg/kg/day

Comments: Male and female rats (8 weeks old, 15/sex/group) 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. The route of administration and maximum dose level was specified in a testing consent order (EPA. 1989. 40 CFR 799, Fed Reg 54:13470-13477). The highest dose level was initially set at 5000 mg/kg/day, but was decreased to 4000 mg/kg/day based on results of a 14-day dose range-finding drinking water study that demonstrated signs of debilitation at levels greater than 4000 mg/kg/day (Gill and Hurley, 1990).

Rats were observed daily for clinical signs and weekly for body weight and water and food consumption. Ten rats/sex/group were observed periodically for behavior (functional observational battery) and motor activity. After 91 days of treatment, tissues of 10 animals/sex/group were fixed in situ, and brains were removed. These animals received complete necropsies, and tissues from 6 animals/sex/group were processed for evaluation of the nervous system by light microscopy. The 5 animals/sex/group not killed and perfused in situ were killed by severing the brachial vessels to permit exsanguination. These animals received complete necropsies, and the liver, kidneys, brain, lungs, adrenals, and testes (males) were weighed. Liver and testes were examined by light microscopy.

Data for continuous variables were analyzed with Levene's test for homogeneity of variance, analysis of variance (ANOVA), and by pooled variance t-tests. If Levene's test indicated heterogeneous variances, groups were analyzed with an ANOVA for unequal variances, followed by separate variance t-tests. Fisher's exact 2 x 2 groups comparisons were used to analyze functional observational battery data. Motor activity counts were log transformed prior to analysis.

Motor activity dose-effects, dose-sex interactions, and time-dose interactions were determined using repeated measures ANOVAs with dose and sex as grouping factors and time as a within-subject factor. Comparisons between treated and control groups were made for total test session activity (the sum of the counts across the 90-min test session) using ANOVA. To reduce the increased false positives associated with repeated significance testing, the correction procedure described by Mantel (Biometrics 36:381-399, 1980) was used when testing for overall significance. The frequency data for anatomic pathology were analyzed as described by Sokal and Rohlf (Biometry, WH Freeman, 1981).

Reference:

(1) 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.

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

b) Test substance: Triethylene glycol monomethyl ether

Test species/strain: Rat/Dawley CD

Test method (e.g., OECD, other): Doses of 0, 0.75, 1.6, 3.9, and 8.0 g/kg/day in drinking water for 14 days

GLP YES [ ]

NO [ ] Data not available

Results: Severely toxic at ≥ 8 g/kg

Mildly to moderately toxic at 4 g/kg

NOAEL: 1.6 g/kg/day

Comments:

Reference: Gill, M.W. and J.M. Hurley (1990). Project Report 52 606, Bushy Run Research Center. (Ref. 6), as cited in Boatman, R.J. and J.B. Knaak (2001) "Ethers of Ethylene Glycol and Derivatives" in Patty's Industrial Hygiene and Toxicology, 5th ed., Chapter 86, pp 73-270, New York: John Wiley & Sons, Inc.

6.4.2 Repeated Dose Dermal Toxicity

a) Test substance: Triethylene glycol monomethyl ether (99.23% TGME prior to start of study and 99.24% TGME after completion of in-life phase of the study, determined by gas chromatography).

Test species/strain: Rat/Sprague-Dawley

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

GLP YES [x]

NO [ ]

Results: There were no indications of systemic toxicity at any dose. Mean body weight and food consumption were comparable to controls throughout the study. There were no treatment-related hematological changes in the interim groups or in males administered test material for 13 weeks. A significant decrease (15%) in platelet counts was noted in females dosed with 4000 mg/kg for 13 weeks when compared to control (1217 +/- 280 x 10^3/cu mm); however, the value (1034 +/- 92 x 10^3/cu mm) was only slightly below the historical control range (1050 to 1262 +/- 93 to 294 x 10^3/cu m) Therefore, it was not considered to be toxicologically significant (Gill et al., Int J Toxicol 17:1-22, 1998). There were no other changes in any hematological parameters (hematocrit, hemoglobin, erythrocyte count, total leukocyte count, and red blood cell indices). There were no changes in clinical chemistries, urinalyses, organ weights, or estrous cyclicity measurements.

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.

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 systemic 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 (0-17 %) for Sprague-Dawley rats.

NOAEL: 4000 mg/kg bw (summary preparer); > 400 and < 1200 mg/kg bw (EPA)

Comments: Triethylene glycol monomethyl ether (TGME) was administered dermally to 8 week-old rats (10/sex/dose level) at 0 (sham control), 400, 1200 or 4000 mg/kg/day for 13 weeks. The route of administration and maximum dose level was specified in a testing consent order (EPA. 1989. 40 CFR 799, Fed Reg 54:13470-13477). The highest dose level (4000 mg/kg/day) represented the maximum amount of test substance that could be retained on the back and sides of the rat as determined in a preliminary 2-week study (Yano et al. 1987. Dow Chemical Company Study ID: K-005610-001, Dated Nov. 25, 1987). 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.

Parameters evaluated throughout the study included clinical and ophthalmic observations, dermal irritation, body weight, food consumption, clinical pathology, estrous cyclicity (daily vaginal smears during study weeks 12 and 13), hematology (just prior to termination), clinical chemistry (just prior to termination), and urinalysis (just prior to dosing and during final week of dosing). Organ weight (standard set), gross pathology and histopathology (control and high dose group) were evaluated upon necropsy. The oocytes, corpora lutea, and follicles from each ovary were evaluated with regard to their normal development. Bone marrow smears were prepared from each animal from the shaft of the femur. The testes and epididymes also were examined microscopically for males in the intermediate- and low-dose groups.

Additional satellite groups of 5 rats/sex/dose level were administered TGME for 30 days for interim hematological (48 hr and 30 days), clinical chemistry (48 hr and 30 days), body weight determinations, clinical observations, and dermal irritation.

For the main study group, the data for continuous variables were evaluated by Bartlett's test for equality of variances. Depending on the outcome of the test, data were analyzed using a parametric or nonparametric analysis of variance (ANOVA), followed by a Dunnett's test (parametric data) or Wilcoxon rank-sum test (nonparametric data) with a Bonferroni correction for multiple comparisons when appropriate. Statistical outliers were identified by a sequential test, but were not excluded from analyses.

For the satellite group, all data (except those for differential leukocyte count and red blood cell parameters) were first tested for equality of variance using Bartlett’s test. Hematologic and clinical chemistry parameters were evaluated during a two-way analysis of variance with the factors of sex and dose. Examinations were first made for a significant sex-dose interaction. If this existed, a one-way ANOVA was preformed separately for each sex. If no sex-dose interaction was identified and a dose effect was identified, or if in the subsequent ANOVA separated by sex a dose-effect was identified, then separate ANOVAs were used for each treatment group with the control. A Bonferroni correction was used to control for multiple comparisons.

Reference:

(1) Gill, M. W. et al. (1998) “Subchronic dermal toxicity and oral neurotoxicity of triethylene glycol monomethyl ether in CD rats.” International Journal of Toxicology 17:1-22.

(2) 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..

b) Test substance: Triethylene glycol monomethyl ether

Test species/strain: Rabbit/New Zealand White

Test Method (e.g., OECD, other): 21-day dermal limit test

GLP YES [x]

NO [ ]

Results: Some hematological and biochemical values from treated animals were different from controls at termination. However, since the same changes were noted in blood samples taken from the animals prior to treatment, they were not considered by the investigators to be related to treatment. No macroscopic skin lesions were observed in treated animals. There were no organ weight variations that could be related to test material administration. Microscopic changes (trace acanthosis and trace to moderate dermatitis) were observed in skin of treated animals. Testicular degeneration (trace in severity) occurred in one rabbit. This lesion was characterized by the presence of spermatid giant cells, focal tubular hypospermatogenesis or cytoplasmic vacuolization. This was not considered to be related to test material by the study investigators since there is a high spontaneous incidence of similar changes in normal New Zealand White rabbits. Based on the results, the investigators concluded that in this study, there was no systemic toxicity induced by treatment with 1000 mg/kg/day test material.

NOAEL: 1 g/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 glutamyl

transpeptidase, 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: International Research and Development Corporation (IRDC). 1986. 21-Day dermal toxicity study in rabbits-limit test on triethylene glycol monobutyl ether, triethylene glycol monoethyl ether and triethylene glycol monomethyl ether. Report dated July 22, 1986.

c) Test substance: Triethylene glycol monomethyl ether

Test species/strain: Rabbit/New Zealand White

Test Method (e.g., OECD, other): 21-day dermal limit test

GLP YES [x]

NO [ ]

Results: Daily applications of 1,000 mg/kg test substance did not produce systemic toxicity in male or female rabbits, including hematological or testicular effects.

NOAEL: 1 g/kg/day

Comments:

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," J. Am. Coll. Toxicol. 9:507. (Ref. 11).

d) Test substance: Triethylene glycol monomethyl ether

Test species/strain: Rat

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

GLP YES [X]

NO [ ]

Results: There were no treatment-related adverse systemic effects. A few males and females treated with either 1000 or 2500 mg/kg/day had a few small scabs or crusts at the test site. These alterations were slight in degree and did not adversely affect the rats.

A number of clinical chemistry, hematological and urinalysis variables were significantly different from control. The lower albumin concentration in females from the 1000 mg/kg/day group and

higher urea nitrogen concentration in males from the 2500 mg/kg/day group were not considered by study personnel to be related to treatment because the effects were not noted at higher concentrations. The lower albumin concentration in males treated with 4000 mg/kg/day also was not attributed to treatment by study personnel because the value was within the range of individual animal values in the control group. A slightly higher alanine aminotransferase activity was also statistically identified in rats from the 4000 mg/kg/day group. As the value was only marginally different from control and was not associated with any histologic changes in the liver, study personnel did not consider this to be related to treatment. A slightly higher red blood cell count and hemoglobin concentration was observed in rats given 4000 mg/kg/day. Since these were only slightly higher than control values, study personnel did not consider them to be related to treatment. A few of the rats given 2500 or 4000 mg/kg/day had watery cecal contents and/or hemolyzed blood in the stomach. These gross pathologic observations were not associated with any histologic abnormalities in these tissues or alterations in hematologic and clinical chemistry parameters. Therefore, they were not attributed by study personnel to be related to treatment.

NOAEL: 4 g/kg/day

Comments: Groups of five rats/sex (200 to 350 g) were dosed with 0, 1000, 2500, or 4000 mg/kg/day of test material on clipped back skin, 6 hours/day for a total of 9 applications during a 12 day period. Test material was held in place with a gauze patch and elastic bandage. Parameters evaluated included clinical observations (including skin evaluations), body weight, feed consumption, clinical chemistry, hematology, urinalysis, fasted body and organ weights, gross pathology, and histopathology.

Reference: Yano BL, Phillips JE, Battjes JE. 1987. Triethylene glycol monomethyl ether: 2-week dermal toxicity study in male and female Sprague-Dawley rats. Dow Chemical Company Study ID: K-005610-001, November 25, 1987

***6.5 Genetic Toxicity**

6.5.1 Bacterial Test

Test substance: Triethylene glycol monomethyl ether (purity: 99.23%)

Test species/strain: Salmonella typhimurium /TA98, TA100, TA1535 and TA1537.

Test method (e.g., OECD, others): Salmonella/mammalian-microsome bacterial mutagenicity assay (Ames test) using a pre-incubation modification of the standard assay, conducted in accordance with EPA TSCA test guidelines.

GLP YES [x]

NO [ ]

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.

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: Triethylene glycol monomethyl ether (purity: 99.23%)

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 [ ]

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.

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 Test in vivo

Test substance: Triethylene glycol monomethyl ether (purity: 99.23%)

Test species/strain: Mice/CD-1 (ICR) BR

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

GLP YES [x]

NO [ ]

Results: One female dose with 1667 mg/kg test material died prior to scheduled necropsy. 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: N/A

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.

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

a) Test substance: triethylene glycol monomethyl ether. 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.

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:

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.

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.

b) Test substance: triethylene glycol monomethyl ether (purity at least 98.7%)

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 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 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

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

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

c) 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.

d) 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.)

a) Neurotoxicity

Test substance: Triethylene glycol monomethyl ether. The purity of the material was at least 98.7%.

Test species/strain: Rat/ Sprague-Dawley CD

Test method (e.g., OECD, other): TSCA Test Guidelines, 40CFR 798, as modified in Section 4 Testing Consent Order for TGME. Reported to be conducted according to OECD TG 408.

GLP YES [x]

NO [ ]

Results: The actual doses attained in the study (time weighted average) were 0, 420, 1240 and 4300 mg/kg/day for males and 0, 420, 1290 and 4100 mg/kg/day for females.

One female in the high dose treatment group (approximately 4000 mg/kg/day) died on Day 37. 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%).

Treatment with triethylene glycol monomethyl ether did not result in any clinical signs of toxicity, alterations in the functional observational battery, or gross microscopic lesions in the nervous system. Significant, small decreases in total test session motor activity were observed in the high-dose treatment group 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."

Additional changes are described in the first record under the repeated dose oral toxicity heading (Section 6.4.1).

Comments: Male and female rats (8 weeks old, 15/sex/group) 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. The route of administration and maximum dose level was specified in a testing consent order (EPA. 1989. 40 CFR 799, Fed Reg 54:13470-13477). The highest dose level was initially set at 5000 mg/kg/day, but was decreased to 4000 mg/kg/day based on results of a 14-day dose range-finding drinking water study that demonstrated signs of debilitation at levels greater than 4000 mg/kg/day (Gill and Hurley, 1990).

Rats were observed daily for clinical signs and weekly for body weight and water and food consumption. Ten rats/sex/group were observed periodically for behavior (functional observational battery) and motor activity. After 91 days of treatment, tissues of 10 animals/sex/group were fixed in situ, and brains were removed. These animals received complete necropsies, and tissues from 6 animals/sex/group were processed for evaluation of the nervous system by light microscopy. The 5 animals/sex/group not killed and perfused in situ were killed by severing the brachial vessels to permit exsanguination. These animals received complete necropsies, and the liver, kidneys, brain, lungs, adrenals, and testes (males) were weighed. Liver and testes were examined by light microscopy.

Data for continuous variables were analyzed with Levene's test for homogeneity of variance, analysis of variance (ANOVA), and by pooled variance t-tests. If Levene's test indicated heterogeneous variances, groups were analyzed with an ANOVA for unequal variances, followed by separate variance t-tests. Fisher's exact 2 x 2 groups comparisons were used to analyze functional observational battery data. Motor activity counts were log transformed prior to analysis. Motor activity dose-effects, dose-sex interactions, and time-dose interactions were determined using repeated measures ANOVAs with dose and sex as grouping factors and time as a within-subject factor. Comparisons between treated and control groups were made for total test session activity (the sum of the counts across the 90-min test session) using ANOVA. To reduce the increased false positives associated with repeated significance testing, the correction procedure described by Mantel (Biometrics 36:381-399, 1980) was used when testing for overall significance. The frequency data for anatomic pathology were analyzed as described by Sokal and Rohlf (Biometry, WH Freeman, 1981).

Reference:

(1) 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.

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

b) Developmental Neurotoxicity

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

Test species/strain: Rat/Sprague-Dawley

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

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:

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 noted that the significance of the auditory startle observations with regard to the conditions of the test animals was not clear. Histopathological assessment of the peripheral and central nervous systems of the pups showed no treatment related lesions in any group.

Comment: Additional fetal data are test conditions are described above in Section 6.7.2.

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

6.10 Biological Monitoring

(including clinical studios, case reports, etc.)

NO DATA AVAILABLE

6.11 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 monomethyl ether (TGME) and ethylene glycol monomethyl ether (EGME) 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 mean steady rate of absorption for triethylene glycol monomethyl ether was 34.0 micrograms/cm2hr (SD +/- 7.73), which was close to 100-fold less than EGME. Test material caused a small change in permeability of the membrane (average damage ratio of 3.36).

Reference:

(1) 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.

(2) Ward RJ, Scott RC. 1986. Triethylene glycol ethers: Absorption through human epidermis in vitro. Imperial Chemical Industries Report No: CTL/P/1600, Oct. 31, 1986.