FOREWORD INTRODUCTION

High Boiling Ethylene Glycol Ethers Category

Triethylene glycol butyl ether, CAS No. 143-22-6
Tetraethylene glycol methyl ether, CAS No. 23783-42-8
Tetraethylene glycol butyl ether, CAS No. 1559-34-8

SIDS Initial Assessment Report

For

SIAM 15

Boston, Massachusetts, 22-24 October 2002

1. Category Name: High Boiling Ethylene Glycol Ethers Category

2. Category Members: Triethylene glycol butyl ether, CAS No. 143-22-6
Tetraethylene glycol methyl ether, CAS No. 23783-42-8
Tetraethylene glycol butyl ether, CAS No. 1559-34-8

3. Sponsor Country: United States
National SIDS Contact Point in Sponsor Country:
U.S. Environmental Protection Agency
Mr. Oscar Hernandez, Director
Risk Assessment Division (7403M)
1200 Pennsylvania Ave., NW
Washington, DC 20460
Phone: 202-564-7641;

4. Shared Partnership with: Industry (ICCA)

5. Roles/Responsibilities of the Partners:

- Name of industry sponsor /consortium

Industry Contact
Dr. Susan A. Lewis
American Chemistry Council
1300 Wilson Boulevard
Arlington VA 22209

- Process used

6. Sponsorship History

- How was the chemical or category brought into the OECD HPV Chemicals Programme ?

In the U.S., TGBE (Triethylene glycol butyl ether, CAS No. 143-22-6), TGME (Triethylene Glycol Methyl Ether, CAS No 112-35-6) and TGEE (Triethylene Glycol Ethyl Ether, CAS No 112-50-5) were evaluated under the Toxic Substances Control Act, Section 4. Upon completion of the recommended testing, both TGME and TGEE were sponsored and reviewed in the OECD/SIDS program (SIAM 4). Both chemicals were determined to be a low priority for further work.

Testing:	No testing:	(x)
	Testing	( )

7. Review Process Prior to the SIAM:

8. Quality check process:

9. Date of Submission:

10. Date of last Update:

11. Comments:

SIDS INITIAL ASSESSMENT PROFILE

High Boiling Ethylene Glycol Ethers Category

CAS No.	143-22-6 23783-42-8 1559-34-8
Chemical Name	Triethylene glycol butyl ether Tetraethylene glycol methyl ether Tetraethylene glycol butyl ether
Structural Formula	$HO(CH_2CH_2O)_nR$ n= 3 or 4; R=methyl or butyl Note: Both tetraethylene glycol methyl ether and tetraethylene glycol butyl ether are available as mixtures with other glycol ethers and some other compounds. Therefore, the molecular and structural formulas for tetraethylene glycol methyl ether and tetraethylene glycol butyl ether presented represent structures for only a portion of the compounds in the methyl and butyl high boiling streams.

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The category contains three structurally related, high boiling glycol ethers:

- Triethylene glycol butyl ether (TGBE; CAS No. 143-22-6);
- Tetraethylene glycol methyl ether (TetraME; CAS No. 23783-42-8); and
- Tetraethylene glycol butyl ether (TetraBE; CAS No. 1559-34-8).

TGBE is available as a relatively pure product, with a purity of ≥85 percent. TetraME and TetraBE are not commercially available as pure compounds, but as components of mixtures that contain glycol ethers of various chain lengths.

Data for these glycol ethers are supplemented with data from compounds that are closely related to the category members in molecular structure, and physicochemical properties, and toxicity. These compounds are:

- Triethylene glycol methyl ether (TGME; CAS No. 112-35-6);
- Triethylene glycol ethyl ether (TGEE; CAS No. 112-50-5);
- Polyethylene glycol methyl ether (MPEG350; CAS No. 9004-74-4);
- Polyethylene glycol butyl ether (CAS No. 9004-77-7); and
- Brake Fluid DOT 4.

TGME and TGEE were both reviewed at SIAM 4. Polyethylene glycol monobutyl ether (CAS No. 9004-77-7) is used only for the melting point. (Details of the composition of category members and analogs are provided in Section 1 and Appendix I of the SIAR.)

Human Health

Based on structural and physical similarities of TetraME and TetraBE with the other glycol ethers, it is likely that they will also exhibit similar toxicity.

Results of several acute toxicity studies are available. The oral LD_{50} values are 5,300 mg/kg and 6.73 ml/kg for TGBE and > 15,000 mg/kg for TetraME. In an inhalation study, an 8-hour exposure to a saturated solution of TGBE resulted in no deaths. Two dermal LD_{50}s were estimated for TGBE: > 2000 mg/kg and 3.54 ml/kg. Data for the surrogate compounds are comparable.

In general, repeated dermal or oral exposures to moderate to high doses of TGBE and the surrogate compounds are well tolerated. In a 21-day dermal study, a systemic toxicity NOAEL of 1000 mg/kg/day (single dose tested) was established for TGBE. The repeated dose oral NOELs or NOAELs of TGME, TGEE and Brake Fluid DOT4 in rats range from 150 to 750 mg/kg/day. Systemic effects (other than reproductive effects) noted at an oral dose of approximately 1,000 mg/kg/day TGME or Brake Fluid DOT4 are reduced weight gain, slight hepatocellular centrilobular hypertrophy, and increased relative liver weight (TGME). All rats survived oral exposure to 3,300 mg/kg/day TGEE for 30 days, and 19/20 survived oral exposure to 4,000 mg/kg/day TGME for 90 days. Changes observed in rats treated orally with 3,300 mg/kg/day TGEE for 30 days were decreased weight gain, slightly increased high blood urea concentrations, and "congestion and cloudy swelling of the liver (6/10) and kidney (1/10)." Rats administered 4,000 mg/kg/day TGME orally for 91 days 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 2-week intravenous toxicity study with 1,000 mg/kg/day MPEG350, there was no effect of treatment on body or organ weights, hematological values, or pathology of the heart, liver, spleen, kidneys, adrenal glands or gonads.

Reproductive toxicity of the surrogate chemicals is limited to high doses. 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. A NOAEL for reproductive toxicity between 400 and 1200 mg/kg/day was derived from this study. 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. A NOAEL between 400 and 1200 mg/kg/day was derived from this study. Results of a 90-day dermal toxicity study found that doses of up to 338 mg/kg/day MPEG350 did not produce toxicity to reproductive organs. In a 21-day dermal toxicity study, testicular degeneration (scored as trace in severity) was observed in one rabbit given 1,000 mg TGEE/kg/day and another treated with 1,000 mg TGME/kg/day. Results of a 2-week study indicate that dermal administration of up to 4,000 mg TGME/kg/day did not produce testicular toxicity.

The bulk of the evidence from developmental toxicity experiments conducted with the category member TGBE and the surrogates TGME, TGEE and Brake Fluid DOT4 indicates that fetal toxicity was not noted at doses < 1,000 mg/kg/day. The single oral exposure study in rats resulted in maternal and developmental NOAELs of 1000 mg/kg/day (highest dose tested). Of the surrogates, TGME has been studied most extensively. In one oral study in rats, the developmental NOAEL for TGME was 625 mg/kg/day based on decreased body weight and skeletal variations, with a maternal NOAEL of 1,250 mg/kg/day based on decreased body weight and food consumption. Another oral study in rats with TGME resulted in developmental and maternal NOAELs of 1000 mg/kg/day (highest dose tested). In an oral study in rabbits with TGME, the developmental NOAEL was 1000 mg/kg/day based on presence of angulated hyoid alae and reversible delays in ossification of the xiphoid. The maternal NOAEL was 500 mg/kg/day based on maternal deaths, abortion, clinical signs of treatment, gastrointestinal lesions, and reduced uterine weight. Finally, the developmental NOAEL for TGEE from an oral study in rats was determined to be 1000 mg/kg/day.

All *in vitro* and *in vivo* genotoxicity studies on the category member TGBE and surrogates (TGME, MPEG350, and Brake Fluid DOT 4) were negative at concentrations up to 5,000 micrograms/plate and 5,000 mg/kg, respectively, indicating that these chemicals are not genotoxic at these concentrations.

Environment

In most cases, measured and predicted environmental fate parameters among category members and surrogates are similar. Ether groups are generally stable to hydrolysis in water under neutral conditions and ambient temperatures. OECD guideline studies indicate ready biodegradability for TGBE and inherent biodegradability for TetraME. However, an APHA comparative biodegradation study of TGME, TGEE and TGBE indicates somewhat slower biodegradation of TGBE. No glycol ethers that have been tested demonstrate marked resistance to biodegradative processes. Due to the structural and physical similarities with the other glycol ethers in the category, TetraBE is likely to be biodegradable. Upon release to the atmosphere by evaporation,

high boiling glycol ethers are estimated to undergo photodegradation (atmospheric half lives = 2.4-2.5 hr). When released to water, the category members undergo biodegradation (47-92% after 8-21 days) and have a low potential for bioaccumulation (log Kow ranges from –1.73 to +0.51).

Based on the structural and physical similarities with TGBE and TGME, it is likely that the toxicity of TetraBE and TetraME to aquatic species will be similar. Aquatic toxicity data indicate that the tri- and tetra ethylene glycol ethers are "practically non-toxic" to aquatic species. For the category member TGBE, the LC_{50} values for fish and *Daphnia*, are 2,400 mg/l, 2,210 mg/l, respectively, and the EC_{50} for algae is > 500 mg/l. No major differences are observed in the order of toxicity going from the methyl- to the butyl ethers.

Exposure

In the United States, three manufacturers produced 20,900 metric tonnes (46 million pounds) of TGBE in 1999. Production is projected to increase slightly to 22,300 metric tonnes (49 million pounds) in the year 2004. In 1998, > 454 – 4,540 metric tonnes (> 1-10 million pounds) of TetraGME and > 4,540 – 22,700 metric tonnes (> 10-50 million pounds) of TetraGBE were produced in the United States. In Western Europe consumption of triethylene glycol ethers was 40,000 metric tonnes (88 million pounds), but this is a total for combined methyl, ethyl and butyl ethers of triethylene glycol. Although Japan may produce significant amounts of TGBE, other regions (including Canada, Mexico, South America and Eastern Europe) do not produce significant commercial amounts of TGBE.

Although inhalation and oral exposure is possible, the most likely route of human exposure to high boiling ethylene glycol ethers (liquids with boiling points ranging between 235-350°C) is via dermal contact. Workplace exposure during manufacture and storage is limited by the enclosed nature of the manufacturing processes and equipment. The major known use of high boiling ethylene glycol ethers is as components of automotive brake fluids. Although exposure is limited during the formulation of these glycol ethers 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. 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. 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.

RECOMMENDATION

The High Boiling Ethylene Glycol Ethers Category is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

The High Boiling Ethylene Glycol Ethers category is currently of low priority for further work based on a low hazard potential.

SIDS Initial Assessment Report

1 IDENTITY OF CATEGORY MEMBERS AND SURROGATES

The High Boiling Ethylene Glycol Ethers Category consists of three members: triethylene glycol butyl ether (CAS No. 143-22-6), tetraethylene glycol methyl ether (CAS No. 23783-42-8) and tetraethylene glycol butyl ether (CAS No. 1559-34-8). These chemicals form a category based on similar structural, physicochemical, and toxicological properties. Triethylene glycol butyl ether (TGBE) is a fairly pure product. However, both tetraethylene glycol methyl ether (TetraME) and tetraethylene glycol butyl ether (TetraBE) are available as mixtures with other glycol ethers and various other compounds (see Table 1). Therefore, the molecular and structural formulas for TetraME and TetraBE presented in Table 1 represent structures for only a portion of the compounds in the methyl and butyl high boiling streams of which they are components. Category members and surrogates are closely related in physicochemical properties. These chemicals are high boiling liquids of low volatility and high water solubility.

Surrogate chemicals used to support the category are: 3,6,9-trioxadecan-1-ol (TGME) (CAS No. 112-35-6), 3,6,9-trioxaundecan-ol (TGEE)(CAS No. 112-50-5), polyethylene glycol methyl ether (MPEG350) (CAS No. 9004-74-4), polyethylene glycol butyl ether (CAS No. 9004-77-7) and the commercial product "Shell brake fluid DOT4" (Table 2). Data from surrogates are used to fill data gaps of category members. The details and references for each study selected are given in the robust summary/dossier sets for each category member.

1.1 Category Justification

Category members are closely related in molecular structure and physicochemical properties and thus, the potential for toxicological effects. All category members and data-rich surrogates are glycol ethers (or contain glycol ethers) that can be represented by the following generic molecular structure:

$$HO(CH_2\ CH_2O)_nR$$

Where n = 2, 3, 4, 5, 6, and higher ethylene units; and R = alkyl (methyl, ethyl, butyl). All category members and data rich surrogates therefore possess a primary alcohol group at one end of the molecule attached to one or more repeating ethylene glycol units. At the other end of the molecule is an ether function where the alkyl group is methyl, ethyl or butyl. All category members thus possess the same functional groups (alcohol or ether) and the members differ from each other only in the number of ethylene glycol units or the identity of the alkyl group. A detailed description of the category members is given in Appendix I. A matrix that shows whether data are present for each SIDS endpoint (see below) is shown in Appendix II.

1.2 Physicochemical Properties

Category members and surrogates are closely related in physicochemical properties. As noted in Section 1.1, they are high boiling liquids of low volatility and high water solubility. This comparison is shown in Table 3.

Table 1. Members of the High Boiling EGE's Category

Chemical Name	Triethylene Glycol Butyl Ether (TGBE)	Tetraethylene Glycol Methyl Ether (TetraME)	Tetraethylene Glycol Butyl Ether (TetraBE)
IUPAC Name	3,6,9-Trioxatridecan-1-ol	3,6,9,12-Tetraoxatridecan-1-ol	3,6,9,12-Tetraoxahexadecane-1-ol
CAS Number	143-22-6	23783-42-8	1559-34-8
Molecular Formula	$C_{10}H_{22}O_4$	$C_9H_{20}O_5$	$C_{12}H_{26}O_5$
Structural Formula	$HO(CH_2CH_2O)_3$-$CH_2CH_2CH_2CH_3$	$HO(CH_2CH_2O)_4CH_3$	$HO(CH_2CH_2O)_4$-$CH_2CH_2CH_2CH_3$
Synonyms	Butoxytriethylene glycol 2-(2-(2 Butoxy ethoxy)ethoxy)ethanol Butoxytriglycol Butyltriglycol Triethylene glycol (mono)butyl ether	Methoxytetraethylene glycol Methyltetraglycol Tetraethylene glycol monomethyl ether	Butoxytetraethylene glycol Butyltetraglycol Tetraethyleneglycol monobutyl ether
Composition (Chemical Name, CAS No. and Percent Composition)	Purity 85-100% of CAS No. 143-22-6 (w/w). Impurities include: Polyethylene glycol butyl ether (9004-77-7); Diethylene glycol butyl ether (112-34-5); Triethylene glycol (112-27-6); Ethylene glycol butyl ether (111-76-2).	Available as High Boiling Methyl Glycol Stream which includes (w/w): Triethylene glycol methyl ether (112-35-6) (10-75%); Tetraethylene glycol methyl ether (23783-42-8) (4-80%); Pentaethylene glycol methyl ether (23778-52-1) (8-20%); Hexaethylene glycol methyl ether (23601-40-3) (1-5%); Ethylene glycol (107-21-1) (<1%); Diethylene glycol (111-46-6) (0-5%); Triethylene glycol (112-27-6) (0-5%).	Available as High Boiling Butyl Glycol Stream which includes (w/w): Diethylene glycol butyl ether (112-34-5) (1-20%); Triethylene glycol butyl ether (143-22-6) (25-75%); Tetraethylene glycol butyl ether (1559-34-8) (20-60%); Pentaethylene glycol butyl ether (1786-94-3) (8-20%); Hexaethylene glycol butyl ether (4403-55-8) (2-10%); Other high molecular weight chains (<4%): Triethylene glycol (112-27-6) (0-5%); Tetraethylene glycol (112-60-7) (0-5%)

Table 2: Identity of the Surrogates

Chemical Name	Triethylene Glycol Methyl Ether (TGME)*	Triethylene Glycol Ethyl Ether (TGEE)*	MPEG350	Shell DOT 4 Brake Fluid**	Polyethylene Glycol Butyl Ether
IUPAC Name	3,6,9-Trioxadecan-1-ol	3,6,9-Trioxaundecan-1-ol	N/A	Shell DOT 4 Brake Fluid	N/A
CAS No.	112-35-6	112-50-5	9004-74-4	N/A	9004-77-7
Molecular Formula	$C_7H_{16}O_4$	$C_8H_{18}O_4$	$C_5H_{12}O_3$ to $C_{31}H_{64}O_{16}$	Mixture	Mixture
Structural Formula	$HO(CH_2CH_2O)_3CH_3$	$HO(CH_2H_2O)_3CH_2CH_3$	$HO(CH_2\ CH_2O)_nCH_3$ Where n = 2-17 ethylene units	N/A	$HO(CH_2\ CH_2O)_n$ $CH_2\ CH_2\ CH_2\ CH_3$ Where n = 2-17 ethylene units
Synonyms	Methoxytriglycol	Ethoxytriglycol	Polyethylene glycol methyl ether		
Composition (Chemical name, CAS No., and Percent Composition)	Purity 90-96% by volume. Also contains: Tetraethylene glycol methyl ether (CAS # 23783-42-8) Diethylene glycol (CAS # 111-46-6)	Purity 85-99% by volume. Also contains: Tetraethylene glycol ethyl ether (CAS No. 5650-20-4) Diethylene glycol ethyl ether (CAS No. 111-90-0) Diethylene glycol (CAS No. 111-46-6) Triethylene glycol (CAS No. 112-27-6)	Contains diethylene glycol methyl ether (EG2) to hepta-decaethylene glycol methyl ether (EG17). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol methyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol methyl ether (CAS No. 112-35-6), and 0.181% diethylene glycol methyl 111-77-3).	Contains Triethylene glycol monomethyl ether borate ester (106008-94-0) (30-50%); Triethylene glycol monobutyl ether borate ester (3-30%); Triethylene glycol monomethyl ether (112-35-6)(20-30%); Triethylene glycol monobutyl ether (143-22-6)(2-10%); Tetraethylene glycol monomethyl ether (23783-42-8) (20-30%),; Tetraethylene glycol monobutyl ether (1559-34-8)(2-10%); minor additives (<1%).	Similar to composition of CAS No.1559-34-8 (See Table 1)

* Reviewed at SIAM 4

**Data for this brake fluid are included in the robust summary sets for the category members, since exposure to the glycol ethers in the category is typically associated with the application of brake fluids. The three category members comprise 24-50% of the brake fluid Shell DOT4. These data therefore help to support the screening information for this category.

Table 3. Physical and Chemical Properties of Category Members and Surrogates*

Category Member	**TGBE**	**TetraME**	**TetraBE**	TGME	TGEE	MPEG350	Brake Fluid DOT4
CAS No.	143-22-6	23783-42-8	1559-34-8	112-35-6	112-50-5	9004-74-4	N/A
Physical form of marketed product	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid	Liquid
Melting point (^{o}C)	-39	-39[2]	-33[a,b]	-44[e]	-19[g]	-5-10[b]	<51.7[h]
Boiling point (^{o}C)	283.2	280-350[2]	332[c]	249.2[e]	256[g]	>200[b]	>260[h]
Density (g/cm^{3})	0.989[1]	1.06[2]	1.004[a,b]	1.05[b]	1.02[e]	1.09[b]	1.06[h]
Vapor pressure (hPa)	<0.01	<0.1[2]	<0.0001[c]	<0.01[e]	<0.01[e]	<0.0001[b]	< 0.01[h]
Partition coefficient (Log K_{ow})	0.51[2]	-1.73[c]	-0.26[c]	-1.46[c]	-0.96[c]	ND	ND
Water solubility (mg/l)	1,000,000[1]	999,999[c]	945,800[c]	Miscible[f]	Miscible[g]	Miscible[b]	Soluble[h]
Flash point (^{o}C)	137.7 - 157.2[1]	161[2]	> 100[2]	135[b]	123[g]	182[b]	121[h]
Autoignition temperature (^{o}C)	203[2]	325[2]	ND	ND	ND	ND	ND

***** Bolded chemicals are category members. Data for polyethylene glycol monobutyl ether are listed under the TetraBE heading (see footnote a)

See robust summaries for details and references for category members

ND = not determined; [1] Material contained 85% TGBE; [2] Original reference was not available. The study was described in a previous IUCLID data set produced for the European Chemicals Bureau and given a reliability rating of 2 (valid with restrictions). This study is assigned a reliability rating of 4 (not assignable) for this submission since it was not reviewed.

[a] Polyethylene glycol monobutyl ether (CAS No. 9004-77-7), composition range similar to that given in Table 1 for CAS No. 1559-34-8.

[b] Dow Chemical Company MSDS; [c] calculated using EPIWIN; [d] Staples et al (1988);[e] Boatman and Knaak (2001);[f] SIDS dossier for CAS No. 112-35-6, dated September 15, 1992;[g] SIDS dossier for CAS No. 112-50-5; dated September 15, 1992.

[h] Shell Chemical Company MSDS

2 GENERAL INFORMATION ON EXPOSURE

Members of the High Boiling Ethylene Glycol Ethers Category (and the surrogates) are manufactured in closed, continuous equipment by the reaction of ethylene oxide with methyl alcohol or butyl alcohol. This reaction can produce glycol ethers of varying chain length depending on the molar ratio of reactants and the temperatures and pressures used in the reaction. Milder conditions and lower molar ratios of ethylene oxide to alcohol will produce the ethylene glycol mono-alkyl ethers. Using more ethylene oxide and higher temperatures and pressures produces diethylene glycol ethers, triethylene glycol ethers, tetraethylene glycol ethers and higher homologues. The products are purified by distillation. Triethylene glycol butyl ether (TGBE) is a relatively pure product (purity 85-100%). The most common chain length of tetraethylene glycol methyl ether (TetraME) and tetraethylene glycol butyl ether (TetraBE), is four ethylene glycol units; however these materials also contain tri-, penta-, hexa- and higher polyethylene glycol units end-capped with a methyl or butyl ether group.

In the United States, 20,900 metric tons (46 million pounds) of TGBE were produced in 1999 by three manufacturers. In the United States in 1998, > 454 - 4,540 metric tons (> 1-10 million pounds) of TetraME and > 4,540 - 22,700 metric tons (> 10-50 million pounds) of TetraBE were produced (U.S. EPA, 1998).

Regions other than Japan and the United States (including Canada, Mexico, South America and Eastern Europe) do not produce significant commercial amounts of TGBE (Chinn et al., 2000). Production is projected to increase slightly to 22.3 thousand metric tons (49 million pounds) by the Year 2004 (Chinn et al., 2000). In Western Europe, consumption of triethylene glycol ethers (total methyl, ethyl and butyl ethers) was 40 thousand metric tons (88 million pounds) (CEH, 2000). The volumes of the individual triethylene glycol ethers were not broken out for Europe. The manufacturing volumes for triethylene glycol ethers in Japan individually or combined are not available

2.1 Production Volumes and Use Pattern

The most significant current use of the category members and surrogates is as components of automotive hydraulic brake fluids (Chinn et al., 2000). No other major uses are reported. Manufacturers transport TGBE in tank cars and tank trucks to processors of brake fluids. The processors blend the TGBE, TetraBE or TetraME in enclosed equipment with other components to produce formulations that meet performance specifications for brake fluids. These formulations may be further treated or blended with additives to make the hydraulic fluids non-corrosive and stable to decomposition during use. A typical brake fluid formulation contains a mixture of glycol ethers and sometimes polyethylene glycols, as well as additives. An example of a brake fluid is Shell DOT 4, which is described in Table 2.

In the United States, the brake fluids must meet Department of Transportation (DOT) standards. One important performance need is low volatility. The resulting brake fluids are sold to vehicle manufacturers and automotive and truck garages in drums or smaller containers for addition to brake systems. Some brake fluids containing high boiling ethylene glycol ethers (typically in pint and quart cans) are sold by automotive stores to consumers.

Triethylene glycol butyl ether (TGBE) also has been used as a plasticizer intermediate (Lewis, 1993); a chemical intermediate for reaction products with aluminum isopropoxide (SRI); and in various solvent applications (Gerhartz, 1985). These reported uses (if still active) are believed by the manufacturers to be minor uses compared to use as brake fluid components.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

The high boiling ethylene glycol ethers typically enter the environment through slow escape and evaporation from automotive brake systems. Spills of brake fluids can also occur during brake repair or service in garages and service stations. Typically such spills would be a few drops to under a liter of liquid. Emissions to the atmosphere or surface water occurring via industrial wastes or effluents during manufacture or processing are limited by predominately enclosed processing and low volatility. TGBE entering the atmosphere from industrial air emissions or evaporation from brake systems may be washed out of the atmosphere by rainfall (Staples et al., 1988). It is likely that the same process will occur with TetraME and TetraBE.

2.2.2 Photodegradation

Estimated photodegradation hydroxyl radical rate constants (Table 4) for category members are in close agreement. Photodegradation half-lives of TGBE, TetraME, and TetraBE (estimated using the EPIWIN/AOP model) have atmospheric photodegradation half-lives of 2.5, 2.4 and 2.0 hours respectively.

2.2.3 Stability in Water

The category members are not expected to hydrolyze readily. No hydrolysis studies could be located, and the EPIWIN/HYDROWIN model cannot predict hydrolysis rates for the ether function [R-O-R, where R=organic alkyl group]. However, ether groups are generally stable to water under neutral conditions and ambient temperatures. The ether function is hydrolyzed by heating in the presence of halogen acids, particularly hydrogen iodide (Fieser and Fieser, 1960).

Volatilization

As can be seen from Table 3, the category members are highly soluble to miscible in water, possess high boiling points (between 249.2-350 °C) and low vapor pressures. The estimated Henry's Law Constants, falling in the narrow range of 3.54 E-14 to 3.67 E-13 m^3* atm/mol at 25^o C (Table 4), point to a limited volatilization potential.

2.2.4 Transport between Environmental Compartments

The potential distribution of TGBE 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 mass balances for category members, shown in Table 4, lend further weight to limited volatilization and a preference for partitioning to water and soil. The ethers in this category possess physical properties that suggest that once they enter the aqueous compartment, they tend to remain dissolved in water. Soil/sediment partition coefficients (Koc) of 10 have been estimated for TGBE, TetraME and TetraBE using the EPIWIN/PCKOCWIN (Table 4). These results suggest that the category members have uniformly high soil mobility. Thus, these products can leach from soil deposits to groundwater, but can also be transported to environments where aerobic biodegradation can take place.

Table 4. Comparison of Environmental Fate Parameters for Category Members and Surrogates[a]

Chemical	Henry's Law Constant[b] (atm-m^3/mole)	Photodegradation OH radical rate constant[b] (cm^3/molecule-sec)	Koc[c]	Predicted Environmental Distribution (Mackay III fugacity model)[b]			
				Air (%)	Water (%)	Soil (%)	Sed. (%)
TGBE 143-22-6	9.52 E-14	51.5 E-12	24 [d]	0.0608	44.7	55.1	0.0766
TetraME 23783-42-8	1.57 E-13	54.0 E-12	10 [b]	2.45 E-9	45.3	54.6	0.0755
TetraBE 1559-34-8	3.67 E-13	63.0 E-12	10 [b]	6.59 E-9	45.1	54.8	0.0755
TGME 112-35-6	3.54 E-14	40.0 E-12	4 [d]	0.0657	45.9	53.9	0.0765
TGEE 112-50-5	4.77 E-14	45.4 E-12	7 [d]	0.0538 x 10^{-6}	45.3	54.6	0.0755
MPEG350 9004-74-4	No data	No data	No data	No data	No data	No data	No data
DOT4 Brake Fluid	No data	No data	No data	No data	No data	No data	No data
Polyethylene glycol monobutyl ether 9004-77-7	No data	No data	No data	No data	No data	No data	No data

[a] Bolded chemicals are category members. See robust summaries for study details and references

[b] Calculated using EPIWIN or earlier Syracuse Research Corporation Interactive Calculation Program. In running EPIWIN, normal defaults were used as inputs, except in those cases where measured values exist for melting point, boiling point, water solubility.

[c] soil/ sediment coefficient

[d] log Koc = 0.544 log K_{ow} + 1.377 [Staples et al. (1988); Howard (1993); Lyman et al. (1982)].

2.2.5 Biodegradation

When released to water, some studies show that biodegradation of category members is reasonably rapid (Table 5). OECD guideline studies indicate biodegradability (> 90%) for TGBE (ready or inherent) and TetraME (inherent). However, the APHA comparative biodegradation study of TGME, TGEE and TGBE indicate slower rates of biodegradation (from 47-71%). Altogether, the data suggest that different study methodologies provide variable results for the tri- and tetraethylene glycol ethers. No category members or surrogates that were tested demonstrate marked resistance to biodegradative processes. Due to the structural and physical similarities with the other glycol ethers in the category, TetraBE is likely to be biodegradable.

Table 5. Comparison of Biodegradation Rate Ranges for Category Members and Surrogates*

Category Member	Biodegradation Rate Ranges
TGBE **143-22-6**	47% after 20 days (APHA) (ready) 88% after 14 day (OECD) (ready)** 92% after 21 days (OECD) (ready)** 100% after 9 days (OECD) (inherent)**
TetraME **23783-42-8**	99% after 8 days (OECD) (inherent)**
TetraBE **1559-34-8**	Data for all chemicals are used
TGME 112-35-6	71% after 20 days (APHA) (inherent)
TGEE 112-50-5	71% after 20 days (APHA) (inherent)
MPEG 350 9004-74-4	No data
DOT4 Brake Fluid	No data
Polyethylene glycol monobutyl ether 9004-77-7	No data

* Bolded chemicals are category members. See robust summaries for study details and references.

**Original reference was not available. The study was described in a previous IUCLID data set produced for the European Chemicals Bureau and given a reliability rating of 2 (valid with restrictions). This study is assigned a reliability rating of 4 (not assignable) for this submission since it was not reviewed

2.2.6 Bioaccumulation

The category members have a limited potential to bioaccumulate (based on log K_{ow}s ranging from –1.73 to +0.51@ 20^{o}C), and predicted bioconcentration factors, log BCF = ca. 0.50 (EPIWIN/BCF Program).

2.3 Human Exposure

The most likely routes of human exposure to category members are via inhalation or dermal contact. While exposure may occur during manufacture or processing, greater exposure potential is associated with use of brake fluids containing category members.

2.3.1 Occupational Exposure

Exposure during manufacture is limited by the use of enclosed equipment, necessitated by the highly hazardous properties of the reactant ethylene oxide. Bulk storage, handling and transport of product further limits exposure potential. Processors use enclosed equipment for the formulation of brake fluids containing category members. Worker exposure is more likely to occur while adding brake fluids containing high boiling ethylene glycol ethers to automotive brake systems, i.e. when charging, servicing and repairing brakes in automotive factories and garages. Dermal contact is an expected exposure route (rather than inhalation), based on the low volatility of the high boiling glycol ethers.

2.3.2 Consumer Exposure

Home automobile mechanics may be occasionally exposed to high boiling glycol ethers in brake fluids when topping off the brake fluid level in the brake master cylinder. Dermal contact through minor spills is a greater source of exposure than inhalation, since high boiling glycol ethers are not volatile and the operation is of short duration.

General population exposure is also possible through inhalation of ambient air containing low concentrations of high boiling ethylene glycol ethers that may be released from industrial processes or through evaporation of brake fluids containing them. Ingestion of drinking water containing category members as contaminants is also possible. No public monitoring studies or data have been identified that report the presence of TGBE, TetraME or TetraBE in ambient air or groundwater.

However, TGBE was listed as a contaminant found in advanced treatment water in lake Tahoe, CA, Pomona CA and Orange County CA (Lucas, 1984).

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Skin Absorption

Available skin absorption data for TGBE (category member), TGME, and TGEE suggest that the rate of absorption in skin of these three glycol ethers is 22 to 34 micrograms/cm^2/hr, with the methyl ether having the highest permeation constant and the butyl ether having the lowest. The rates of absorption of TGBE, TGEE and TGME are at least 100-fold less than EGME, EGEE, and EGBE, their ethylene glycol monoalkyl ether counterparts, which have absorption rates that range from 214 to 2890 micrograms/ cm^2/hr (Ward and Scott, 1986; Boatman and Knaak, 2001). Therefore, an increase in either the chain length of the alkyl substituent or the number of ethylene glycol moieties appears to lead to a decreased rate of percutaneous absorption. However, since the ratio of the change in values of the ethylene glycol to the diethylene glycol series is larger than that of the diethylene glycol to triethylene glycol series (see Boatman and Knaak, 2001), the effect of the length of the chain and number of ethylene glycol moieties on absorption diminishes with an increased number of ethylene glycol moieties. Therefore, although TetraME and TetraBE are expected to be less permeable to skin than TGME and TGBE, the differences in permeation between these molecules may only be slight.

Metabolism

No metabolism data were located for the category members. The main metabolic pathway for metabolism of ethylene glycol monoalkyl ethers (EGME, EGEE, and EGBE) is oxidation via alcohol and aldehyde dehydrogenases (ALD/ADH) that leads to the formation of an alkoxy acid (Boatman and Knaak, 2001). Alkoxy acids are the only toxicologically significant metabolites of glycol ethers that have been detected *in vivo* (Boatman and Knaak, 2001). Methoxy acetic acid (2-MAA), a metabolite of ethylene glycol methyl ether (EGME), is a known testicular toxicant in rats, and butoxyacetic acid (2-BAA), a metabolite of ethylene glycol butyl ether (EGBE), causes hemolysis of rodent red blood cells. The principal metabolite of TGME is believed to be 2-[2-(2-methoxyethoxy)ethoxy] acetic acid (Gill et al., 1998). Although ethylene glycol, a known kidney toxicant, has been identified as an impurity or a minor metabolite of glycol ethers in animal studies,

it does not appear to contribute to the toxicity of glycol ethers (Boatman and Knaak, 2001). Some glycol ethers have been shown to undergo conjugation with sulfate and glucuronic acid, and the alkoxyacetic acid metabolites may conjugate with glycine (rodents) or glutamine (humans). Conjugation is regarded as a pathway of detoxicification (Boatman and Knaak, 2001).

The chemical 2-butoxyethoxyacetic acid (2-BEAA) is the primary metabolite detected in urine after oral administration of diethylene glycol monobutyl ether acetate (DGBEA) (Deisinger and Guest, 1989). However, unmetabolized DGBEA, DGBE or 2-BAA are not primary metabolites of DGBEA. These findings support the hypothesis that 2-[2-(2-methoxyethoxy)ethoxy] acetic acid is the primary metabolite of TGME and suggests that 2-[2-(2-butoxyethoxy)ethoxy]-, 2-[2-[2-(2-methoxyethoxy) ethoxy] ethoxy]- and 2-[2-[2-(2-butoxyethoxy)ethoxy]ethoxy] acetic acids are the primary metabolites of TGBE, TetraME, and TetraBE. These molecules are not likely to be metabolized to any large extent to toxic molecules such as ethylene glycol or the mono alkoxy acids such as 2-MAA or 2-BAA because metabolic breakdown of the ether linkages also has to occur. Although it is possible that some minimal amounts of EGME or 2-MAA may be produced from TGME, the frank teratogenicity shown by EGME is not seen in TGME studies.

3.1.2 Acute Toxicity

The results of the acute studies summarized in Table 6 indicate that tri- and tetraethylene glycol methyl-, ethyl- and butyl ethers generally display low acute toxicity by the oral, inhalation and dermal routes of exposure. Due to the structural and physicochemical similarities of TetraME and TetraBE with the other glycol ethers, it is likely that they have low potential for acute mammalian toxicity.

Signs of toxicity in animals receiving lethal oral doses of TGBE included loss of righting reflex and flaccid muscle tone, coma, and heavy breathing. Animals administered lethal oral doses of TGEE exhibited lethargy, ataxia, blood in the urogenital area and piloerection before death. Signs of toxicity in animals exposed to sublethal concentrations of the category members or surrogates were not reported.

Table 6. Acute Mammalian Toxicity for Category Members and Surrogates

Category member	Acute rat oral LD_{50}	Acute rat inhalation LD_{50}	Acute rabbit dermal LD_{50}
TGBE **143-22-6**	5,300 mg/kg 6.73 ml/kg	All animals survive 8 hr exposure to concentrated vapor	> 2,000 mg/kg[1] 3.54 ml/kg
TetraME **23783-42-8**	> 15,000 mg/kg[4]	Data for surrogate chemicals are used	Data for surrogate chemicals are used
TetraBE **1559-34-8**	Data for all chemicals are used	Data for all chemicals are used	Data for all chemicals are used
TGME 112-35-6	11.3 ml/kg[3]	All animals survive 8 hr exposure to concentrated vapor	7,400 mg/kg
TGEE 112-50-5	8,500 mg/kg 10,600 mg/kg	>200 mg/l[1,2]	8,200 mg/kg
MPEG350 9004-74-4	> 16 ml/kg[1] 22 ml/kg[2]	No data	> 16 ml/kg[1]
DOT 4 Brake Fluid	> 5,000 mg/kg[1]	No data	> 2,000 mg/kg[1]
Polyethylene glycol monobutyl ether 9004-77-7	No data	No data	No data

*Bolded chemicals are category members. Study details and references are found in the robust summaries

LD_{50} = Lethal dose in 50% of animals; NP = not performed

[1] Highest dose used in study; [2] One hour test, [3] Equivalent to 11,800 mg/kg, [4] Original reference was not available. The study was described in a previous IUCLID data set produced for the European Chemicals Bureau and given a reliability rating of 2 (valid with restrictions). This study is assigned a reliability rating of 4 (not assignable) for this submission since it was not reviewed.

3.1.3 Irritation

Available data for TGBE (category member) TGME, TGEE, MPEG-350, and Brake Fluid DOT 4 were reviewed and summarized. Data from studies performed on TetraME (other than the results) were not available. The data indicate that the glycol ethers may cause mild to moderate skin irritation. Whereas MPEG-350 and Brake Fluid DOT 4 do not appear to be particularly irritating to eyes, TGEE and TGBE are highly irritating to the eyes. In addition, TGME may produce slight irritation (Smyth et al., 1962). Due to the structural and physical similarity of TetraBE with the other glycol ethers, it is likely that it also will have slight to moderate potential for skin irritation, but may be more irritating to the eye.

3.1.4 Repeated Dose Toxicity

The no observable effect or adverse effect levels (NOELs or NOAELs, respectively) and lowest observable effect or adverse effect levels (LOELs or LOAELs, respectively) for the category members are summarized in Table 7.

Table 7. Repeated Dose Toxicity for Category Members and Surrogates*

Category Member	Oral Rat (NO(A)EL, LO(A)EL in mg/kg/day)	Dermal (NOAEL, LOAEL in mg/kg/day)
TGBE 143-22-6	Data for surrogate chemicals TGME and TGEE are used	NOAEL = 1,000 (21 day rabbit)[1]
TetraME 23783-42-8	Data for surrogate chemicals are used	Data for surrogate chemicals are used
TetraBE 1559-34-8	Data for surrogate chemicals are used	Data for surrogate chemicals are used
TGME 112-35-6	NOAEL = 400 (91 day) LOAEL = 1200 (91 day)	NOAEL = 400-1200 (91 day rat) NOAEL = 1,000 (21 day rabbit)
TGEE 112-50-5	NOAEL = 750 (30 day) LOAEL = 3,300 (30 day)	NOAEL = 1,000 (21 day rabbit)
MPEG350 9004-74-4	No data	NOAEL =338 (90 day rabbit)[1] NOAEL = 1,250 (28 day rat)
DOT 4 Brake Fluid	NOEL = 150 (28 day rat) LOEL = 1,000 (28 day rat)	No data
Polyethylene glycol monobutyl ether 9004-77-7	No data	No data

* Bolded chemicals are category members. Study details and references are found in the robust summaries

NOAEL = no observable adverse effect level; LOAEL = lowest observable adverse effect level; NP = not performed [1] Highest dose used in study.

Studies in Animals

Dermal

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 3.4 for additional information about the testicular effects.

Rats were administered MPEG350 (a mixture containing methylated glycol ethers predominantly in the C5-C11 range) in two dermal studies. In a 4-week dermal study in which rats were administered 1,250, 2,500, or 5,000 mg/kg/day, all animals exhibited minor, transient irritation. At 5,000 mg/kg/day, the animals exhibited decreased body weight; at 2,500 mg/kg/day, they exhibited decreased body weight gain; and at 1,250 mg/kg/day, they exhibited decreased absolute thymus and testes weights (Gray, 1987; Hermansky and Leung, 1997). Since the systemic effects seen at 1,250 mg/kg were not observed at 2,500 or 5,000 mg/kg/day, 1,250 mg/kg is considered to be the NOAEL. In a 90-day dermal study in rabbits, 338 mg/kg/day resulted in mild acanthosis in three females. Transient dose-related erythema and desquamation of skin was also observed (Carpenter,

1947; Hermansky and Leung, 1997). Since systemic toxicity was not observed at this dose, the NOAEL is 338 mg/kg/day.

In a 21-day dermal study, TGME, TGEE, and TGBE were 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 TGEE and 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 not to be related to treatment (see Section 3.4). Thus, the NOAELs for TGME, TGEE and TGBE were established at 1,000mg/kg/day. Findings from this report were considered unremarkable (Anderson, 1995).

A 2-week dermal study 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.

Oral

In a 13-week drinking water study, TGME was administered to rats at doses of 400, 1,200, and 4,000 mg/kg/day. Statistically-significant changes in relative liver weight were observed at 1,200 mg/kg/day and higher. 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 3.4. Significant, small decreases in total test session motor activity were observed in the high-dose animals, but no other neurological effects were observed. The changes in motor activity were secondary to systemic toxicity. 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).

In another study, rats were treated for 30 days with TGEE at doses of 180, 750, 3,300, and 13,290 mg/kg/day in drinking water. All rats given the highest dose died. Congestion and cloudy swelling of the liver and cloudy swelling and degeneration of the epithelium of the convoluted tubules of the

kidneys were observed at necropsy. Rats treated with 3,300 mg TGEE /kg/day exhibited decreased weight gain, slightly increased blood urea concentrations, and "congestion and cloudy swelling of the liver (6/10) and kidney (1/10)". Animals exposed to 750 or 180 mg/kg/day appeared normal (Smyth, 1945).

In a 28-day gavage study, 25, 150, and 1,000 mg /kg/day of Brake Fluid DOT4 was administered to rats. Food intake of males dosed with 1000 mg/kg/day was slightly reduced for first 2 weeks of treatment. Livers of all 5 males and some females dosed with 1000 mg/kg/day showed slight centrilobular hypertrophy (Taupin, 1993a). None of the controls exhibited this effect. There was no significant effect of treatment on liver weight or on other organs (including ovaries and testes). A NOEL of 150 mg/kg/day was assigned by the investigator.

Intravenous

In a 14-day intravenous toxicity study in rats with 1,000 mg/kg/day MPEG350, there was no effect of treatment on body or organ weights, hematological values, or pathology of the heart, liver, spleen, kidneys, adrenal glands or gonads were weighed, fixed, and processed for microscopic evaluation (NAMSA, 1997). The only effect noted was a significant decrease in aspartate aminotransferase activity in treated animals with respect to the control; this effect was considered not to be related to treatment. Testicular toxicity was not noted in this study.

Conclusion

Results of these studies suggest that repeated exposure to moderate to high doses of the glycol ethers in this category is required to produce systemic toxicity. Due to the structural and physical similarities of TetraME and TetraBE with the other glycol ethers, it is likely that they also will have low to moderate potential for repeated dose mammalian toxicity.

3.1.5 Mutagenicity

Mutagenicity studies have been conducted for TGME, TGBE, MPEG350, and Brake Fluid DOT 4. These include a number of Ames tests, HGPRT assays, chromosomal aberration studies, and an in vivo mouse micronucleus study. All in vitro and in vivo studies were negative at concentrations up to 5,000 micrograms/plate and 5,000 mg/kg, respectively, indicating that the category members are not genotoxic at the concentrations used in these studies. The details of these studies are summarized in the dossiers for the category members.

3.1.6 Carcinogenicity

No information has been identified for category members with respect to this endpoint. The uniformly negative outcomes of various mutagenicity studies performed on category members lessen the concern for carcinogenicity

3.1.7 Toxicity for Reproduction

Although mating studies with either the category members or surrogates have not been performed, several of the repeated dose toxicity tests with the surrogates have included examination of reproductive organs. Results of these studies are summarized in Table 8. Male rats treated with 4,000 mg/kg/day TGME in the diet for 91 days exhibited degeneration (12/15) and/or atrophy (5/5) of the seminiferous tubules (spermatocytes or developing spermatids) (Gill and Negley, 1990; Gill et al., 1998). These effects were considered to be related to treatment. The severity of the lesions was primarily mild to moderate for degeneration (11/12) and minimal to moderate for atrophy (5/5), indicating that not all tubules were affected and that a limited number of cells was affected within

the affected tubules. One male treated with 1,200 mg/kg had severe seminiferous tubule atrophy, a complete loss of cell types in the tubules (except for Sertoli cells) and moderate Leydig cell hypertrophy (not significantly different from controls). The NOAEL was between 400 and 1,200 mg/kg/day for testicular effects (Anderson, 1995).

In a published version (Gill et al., 1998) of the aforementioned study, the authors stated that a possible contributing factor in the development of testicular lesions at the high dose was low-level contamination of the test substance with the known testicular toxicant 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. 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 (4,000 mg/kg/day) is 4 times greater than the 1,000 mg/kg/day limit dose generally recommended for subchronic studies.

In a 91-day dermal study of TGME in rats, bilaterally-decreased spermatogenesis in seminiferous tubules and decreased spermatozoa in the epididymes (both were graded as severe) were noted in the testes of 1/10 high dose (4000 mg/kg/day) males (Corley et al., 1990; Gill et al., 1998). The testes of one male treated with 1,200 mg/kg/day exhibited different testicular changes [bilateral multifocal degeneration of spermatocytes and spermatids (graded as very slight), and multinucleated spermatids]. The incidence of animals with lesions (1/10 in each group) was within the range of historical controls (0-17%).

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

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

Table 8. Reproductive toxicity of category members and surrogates*

Category Member	Animal Treatment	Reproductive System Effects
TGBE 143-22-6	NZ White rabbit, exam of organs Dermal, 1,000 mg/kg, 6 hr/day, 5 days/week for 3 weeks	No testicular toxicity was observed
TetraME 23783-42-8	Data for surrogate chemicals are used	Data for surrogate chemicals are used
TetraBE 1559-34-8	Data for surrogate chemicals are used	Data for surrogate chemicals are used
TGME 112-35-6	SD rat, exam of organs Gavage, 400, 1,200 and 4,000 mg/kg/d for 91 days	NOAEL: >400 and <1,200 mg/kg/d 4000 mg/kg/d: degeneration (12/15) and/or atrophy (5/5) of seminiferous tubules 1,200 mg/kg/d: severe seminiferous tubule atrophy and moderate Leydig cell hypertrophy (N = 1)
	SD rat, exam of organs Dermal, 400, 1,200 and 4,000 mg/kg/d, 6 hr/d, 5 d/wk for 91 days	NOAEL : >400 and <1200 mg/kg/d 4,000 mg/kg/d: severe bilateral testicular toxicity (1/10) 1,200 mg/kg/d: very slight multifocal degeneration of spermatocytes and spermatids (1/10)
	NZ White rabbit, exam of organs Dermal, 1,000 mg/kg, 6 hr/d, 5 d/wk for 3 weeks	Trace testicular degeneration (presence of spermatid giant cells, focal tubular hypospermatogenesis, or cytoplasmic vacuolization) (N = 1)
	SD rat, exam of organs Dermal, 1,000, 2,500, 4,000 mg/kg/d, 6 hr/d, for 12 days	No testicular toxicity was observed
TGEE 112-50-5	Rat, exam of organs Drinking water, 180, 750, 3,300, 13,290 mg/kg/d, 30 days	No testicular toxicity was observed up to 3,300 mg/kg/d (All rats died at 13,290 mg/kg/d)
	NZ White rabbit, exam of organs Dermal, 1,000 mg/kg/d, 6 hr/d, 5 days/week for 3 weeks	Trace testicular degeneration (presence of spermatid giant cells, focal tubular hypospermatogenesis, or cytoplasmic vacuolization) (N=1)
MPEG350 9004-74-4	NZ White rabbit, exam of organs Dermal, ca.169 and 338 mg/kg/d, 6 hr/d, 5 d/wk for 90 days	No testicular toxicity was observed
	SD rat, exam of organs Intravenous, 1,000 mg/kg/d for 14 d	No testicular toxicity was observed
DOT 4 Brake Fluid	SD Rat, exam of organs Gavage, 25, 150, 1,000 mg/kg/d, for 28 days	No testicular toxicity was observed
Polyethylene glycol monobutyl ether 9004-77-7	No data	No data

* Bolded chemicals are category members. Study details and references are found in the robust summaries

NOAEL = no observable adverse effect level

In a 21-day dermal study, with 1,000 mg/kg/day TGME, TGEE, and TGBE in rabbits, testicular degeneration was observed in one rabbit given TGEE and another 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).

In a 90-day dermal toxicity study, doses of up to 338 mg/kg/day of MPEG350 (highest dose used) did not produce toxicity to reproductive organs (Carpenter, 1947; Hermansky and Leung, 1997). Testicular toxicity also was not observed in rats given 1,000 mg/kg/day MPEG350 intravenously for 14 days (NAMSA, 1997), up to 3,300 mg/kg/day TGEE in drinking water for 30 days (Smyth, 1945), up to 4,000 mg/kg/day TGME dermally for 12 days (Yano et al., 1987), or up to 1,000 mg/kg/day of Brake Fluid DOT4 by gavage for 28 days (Taupin, 1993a).

Conclusion

Although studies designed to specifically assess reproductive toxicity have not been performed with the category members or surrogates, such testing is not necessary. The effect of the surrogates 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. In addition, results of repeated dose toxicity tests with TGME clearly show testicular toxicity at an oral dose of 4,000 mg/kg/day four times greater that the limit dose of 1,000 mg/kg/day recommended for repeat dose studies. It should be noted that TGME is 350 times less potent for testicular effects than EGME.

TGBE is not associated with testicular toxicity, TetraME is not likely to be metabolized by any large extent to 2-MAA (the toxic metabolite of EGME), and a mixture containing predominantly methylated glycol ethers in the C5-C11 range does not produce testicular toxicity (even when administered intravenously at 1,000 mg/kg/day).

3.1.8 Developmental Toxicity

Developmental toxicity data are available for TGBE and the surrogates TGME, TGEE, and Brake Fluid DOT4 (Table 9). TGBE, TGME, and TGEE 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 another study, Brake Fluid DOT4 also did not produce developmental toxicity in the rat when administered orally at 1,000 mg/kg/day (highest dose used) from days 7-17 of gestation (Taupin, 1993b).

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 5000 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 (1000 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, 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

In conclusion, the bulk of the evidence shows that effects on the fetus are not noted in treatments with ≤ 1,000 mg/kg/day 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. TGBE, TGEE and Brake Fluid DOT4 did not produce developmental toxicity in the rat when administered orally at 1,000 mg/kg/day (highest dose used) (Wason et al., 1986; Leber et al., 1990; Taupin, 1993b). Based on the similarities in structure and toxicological profile of all the category members, it is also expected that TetraBE and TetraME may result in similar effects.

Table 9. Developmental toxicity of category members and surrogates*

Category Member	Animal Treatment	Developmental Effects
TGBE **143-22-6**	Wistar rat, 25 0 and 1,000 mg/kg/d by gavage, Days 7-16 of gestation	NOAEL (maternal) = 1,000 mg/kg/d NOAEL (developmental) = 1,000 mg/kg/d
TetraME **23783-42-8**	Data for surrogate chemicals are used	Data for surrogate chemicals are used
TetraBE **1559-34-8**	Data for surrogate chemicals are used	Data for surrogate chemicals are used
TGME 112-35-6	Wistar rat, 250 and 1,000 mg/kg/d by gavage, Days 7-16 of gestation	NOAEL (maternal) = 1,000 mg/kg/d NOAEL (developmental) = 1,000 mg/kg/d
	SD rat, 625, 1,250, 2,500, 5,000 mg/kg/d by gavage, Days 6 to 15 of gestation	NOAEL (maternal) = 1,250 mg/kg/d NOAEL (developmental) = 625 mg/kg/d Maternal - decreased body weight (5,000 mg/kg/d), food consumption (2,500 and 5,000 mg/kg/d) Fetal- lethality, resorptions, reduced bw, cervical ribs (5,000 mg/kg/d); reduced bw, cervical ribs (2,500 mg/kg/d); delays in ossification (1,250 mg/kg/d)
	SD Rat, 300, 1,650, 3,000 mg/kg/day, Day 6 of gestation through Postnatal Day 21	NOAEL (maternal) = 1,650 mg/kg/d NOEL (developmental) = 300 mg/kg/d Maternal - increased kidney weight (3,000 mg/kg/d) Fetal- decreased postnatal weight gain (1,650 and 3,000 mg/kg/d)
	NZ White rabbit, 250, 500, 1,000, 1,500 mg/kg/d, Days 6 to 18 of gestation	NOAEL (maternal) = 500 mg/kg/d NOEL (developmental) = 1,000 mg/kg/d Maternal – increased lethality at 1,000, 1,500 mg/kg/d Fetal – increased skeletal variants at 1,500 mg/kg/d
TGEE 112-50-5	Wistar rat, 250 and 1,000 mg/kg/d by gavage, Days 7-16 of gestation	NOAEL (maternal) = 1,000 mg/kg NOAEL (developmental) = 1,000 mg/kg
MPEG350 9004-74-4	No data	No data
DOT 4 Brake Fluid	SD rat, 25, 150, 1,000 mg/kg/d, Days 7-17 of gestation	NOAEL (maternal) = 1,000 mg/kg/d NOAEL (fetal) = 1,000 mg/kg/d
Polyethylene glycol monobutyl ether 9004-77-7	No data	No data

* Bolded chemicals are category members. Study details and references are found in the robust summaries

NOAEL = no observable adverse effect level; NOEL = no observable effect level; bw = body weight

3.2 Initial Assessment for Human Health

The members of the category and their surrogates generally display low acute toxicity by the oral, inhalation and dermal routes of exposure. However, TGBE is severely irritating to eyes. All *in vitro* and *in vivo* genotoxicity studies are negative at concentrations up to 5,000 micrograms/plate and 5000 mg/kg, respectively, indicating that the high boiling glycol ethers are not genotoxic.

Results of repeated dose studies with TGME, TGEE, TGBE, MPEG350 and Brake Fluid DOT4 suggest that repeated exposure to relatively high doses of the glycol ethers in this category results in systemic toxicity. The bulk of the evidence suggests that repeated dermal or oral exposure of rats to concentrations of TGME or Brake Fluid DOT4 greater than or equal to 1000 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 1000-1200 mg/kg/day TGME and in a single animal at a dose of 1000 mg/kg/day TGEE. 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 TGBE, TGME, TGEE and Brake Fluid DOT4 indicate that these materials are not developmental toxicants 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.

Due to the structural and physical similarities of TetraME and TetraBE with the other glycol ethers, members of this category are expected to exhibit similar low reproductive and developmental toxicity.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute toxicity studies in fish and Daphnia have been performed on TGBE (category member), TGME, TGEE, TetraME, and MPEG350. Data for TGBE, TGME, and TGEE were reviewed. Data from studies performed on TetraME and MPEG350 (other than the LC_{50} values) were not available. Available data for the toxicity of TGBE (category member) and TGME to algae were reviewed and utilized. ECOSAR values (fish) for TGBE, TetraME and TetraBE have been estimated using EPIWIN. The ECOSAR program does not provide numerical LC50/EC50 values for daphnia and algae. Presumably they would be high based on negative Log Pow values.

Table 10 demonstrates the comparative aquatic toxicity of category members and surrogates to aquatic species. The data suggest that trimethyl, -ethyl and –butyl ethers and MPEG350 are "practically non-toxic" to aquatic species. The LC_{50} values for fish, Daphnia, and algae are ≥ 2,400 mg/l, ≥ 2,210 mg/l, and > 500 mg/l, respectively. No major differences are observed in the order of toxicity going from the methyl- to the butyl ethers. Due to the structural and physical similarities of TetraME and TetraBE with the other glycol ethers in the category, it is likely that these glycol ethers are also of low toxicity to aquatic species. The ECOSAR predicted values for fish, obtained using EPIWIN, are roughly consistent with the measured data.

The toxicity of TGBE, TetraME, TGEE and TGME to bacteria also has been tested. In sewer microorganisms exposed to TGBE, TGEE and TGME for 16 hours, the LD50 values were > 5,000, >10,000 and >5,000 mg/l, respectively. The concentration of TetraME required to cause inhibition of respiration of activated sludge is reportedly > 12,500 mg/kg for 3 hours.

Table 10. Comparative Aquatic Toxicity of Category Members and Surrogates*

Chemical	Fish Acute Toxicity LC_{50} (mg/l)[a]	Daphnia Acute Toxicity LC_{50} (mg/l)[b]	Algae Acute Toxicity EC_{50} (mg/l)[c]
TGBE 143-22-6	2,400 197 (7 days) 5,499 (14 day)[d]	2,210	>500
TetraME 23783-42-8	> 10,000[e] 496,000 (14 day)[d]	Data for surrogate chemicals are used	Data for TGBE and TGME are used
TetraBE 1559-34-8	31,259 (14 day)[d]	Data for all chemicals are used	Data for TGBE and TGME are used
TGME 112-35-6	>10,000	> 10,000	> 500[e]
TGEE 112-50-5	>10,000	> 10,000	No data
MPEG350 9004-74-4	>10,000	>10,000	No data
DOT 4 Brake Fluid	No data	No data	No data
Polyethylene glycol monobutyl ether 9004-77-7	No data	No data	No data

*Bolded chemicals are category members. Study details and references are found in the robust summaries

[a] Lethal concentration in 50% (96 hr unless otherwise stated); [b] Lethal concentration in 50% 48 hr

[c] Inhibition of fluorescence in 50%, 72 hr; [d] estimated using ECOSAR

[e] Original reference was not available. The study was described in a previous IUCLID data set produced by the European Chemicals Bureau and given a reliability rating of 2 (valid with restrictions). This study is assigned a reliability rating of 4 (not assignable) for this submission since it was not reviewed.

NP = not performed

4.2 Terrestrial Effects

No data is available for this endpoint.

4.3 Initial Assessment for the Environment

Environmental fate parameters, such as Log K_{ow}s, photodegradation rates, Henry's Law constants and MacKay Level III fugacity predicted percentages of these chemicals in air, water, soil and sediment, are all consistent within the category. These parameters suggest that category members have limited tendency to volatilize, and tend to partition to water and soil. Category members and their surrogates are resistant to water hydrolysis at neutral ambient conditions, but are biodegradable.

Aquatic toxicity data indicate that the tri- and tetra ethylene glycol ethers are "practically non-toxic" to aquatic species. No major differences are observed in the order of toxicity going from the methyl- to the butyl ethers. Due to the structural and physical similarities of TetraBE and TetraME with TGBE and TGME, it is likely that these materials also have low hazard potential for aquatic organisms

5 RECOMMENDATIONS

The chemicals in the High Boiling Ethylene Glycol Ethers category are currently of low priority for further work due to their low hazard potential.

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APPENDIX 1: DETAILED DESCRIPTION OF CATEGORY MEMBERS AND SURROGATES

Category members and surrogates are closely related structurally, and can be represented by the following generic molecular structure:

$$HO(CH_2\ CH_2O)_n\ R$$

Where n = 2, 3, 4, 5, 6, and higher; and R = alkyl (methyl, ethyl, butyl)

Whereas the triethylene glycol ethers are relatively pure products, commercially available tetraethylene glycol ethers exist primarily in the form of mixtures of tri-, tetra-, penta-, hexa- and higher ethylene glycol ethers of varying chain length. Commercial tetraethylene glycol methyl ether (CAS No. 23783-42-8) is very similar in composition to polyethylene glycol methyl ether (MPEG350)(CAS No. 9004-74-4), which is a mixture of di-, tri-, tetra-, penta-, hexa-, and higher ethylene glycol methyl ethers. The difference in these materials rests with the mean number of ethylene glycol units in the chain, and the mean molecular weight. For MPEG 350 (methylated polyethylene glycol or polyethylene glycol methyl ether) the 350 signifies the average molecular weight of the individual glycol ethers making up the product. The molecular weight of 350 corresponds to the mixture having an average ethylene glycol chain length of approximately 7.23 units.

$$HO(CH_2CH_2O)_nCH_3$$

n = 2-17

Polyethylene glycol methyl ether (MPEG350)

Because of the close similarity of composition between commercial tetraethylene glycol methyl ether (CAS No. 23782-42-8) and polyethylene glycol methyl ether, these two materials will have very similar physical, environmental and toxicological properties. Any difference between these two materials is due to the relative concentrations of individual ethers of varying chain length. Data for MPEG350 have been used in the High Boiling Ethylene Glycol Ether Category to characterize TetraME.

Likewise, commercial tetraethylene glycol butyl ether (CAS No. 1559-34-8) is very similar in composition to polyethylene glycol butyl ether (CAS No. 9004-77-7), which is a mixture of di-, tri-, tetra-, penta-, hexa-, and higher ethylene glycol butyl ethers. The difference in these materials also rests with the mean number of ethylene glycol units in the chain, and the mean molecular weight.

$$HO(CH_2CH_2O)_nCH_2CH_2CH_2CH_3$$

n = 2-17

Polyethylene glycol butyl ether

Because of the close similarity of composition between commercial tetraethylene glycol butyl ether (CAS No. 1559-34-8) and polyethylene glycol butyl ether (CAS No. 9004-77-7), these two materials will have very similar physical, environmental and toxicological properties. Any difference between these two materials is due to the relative concentrations of individual ethers of varying chain length.

APPENDIX II: TEST PLAN MATRIX FOR HIGH BOILING ETHYLENE GLYCOL ETHERS CATEGORY

	143-22-6 (TGBE)	**23783-42-8 (TetraME)**	**1559-34-8 (Tetra BE)**	112-35-6 (TGME)	112-50-5 (TGEE)	9004-74-4 (MPEG 350)	Brake Fluid DOT 4
ENDPOINT							
PHYSICAL CHEMISTRY							
Melting point	**Y**	**Y**	**Y[1]**	NA	NA	NA	NA
Boiling point	**Y**	**Y**	**E**	Y	Y	Y	Y
Density	**Y**	**Y**	**Y[1]**	Y	Y	Y	Y
Vapor Pressure	**Y**	**Y**	**E**	Y	Y	Y	Y
Water Solubility	**Y**	**E**	**E**	Y	Y	Y	Y
Kow	**Y**	**E**	**E**	E	E	NA	NA
ENVIRONMENTAL FATE							
Photodegradation	**E**	**E**	**E**	E	E	NA	NA
Stability in Water	**E**	**E**	**E**	E	E	NA	NA
Biodegradation	**Y**	**Y**	**C**	Y	Y	NA	NA
Transport between Environmental Compartments (Fugacity)	**E**	**E**	**E**	E	E	NA	NA
ECOTOXICITY							
Acute Toxicity to Fish	**Y**	**Y**	**E,C**	Y	Y	Y	NA
Acute Toxicity to Aquatic Invertebrates	**Y**	**C**	**C**	Y	Y	Y	NA
Toxicity to Aquatic Plants	**Y**	**C**	**C**	Y	E,C	NA	NA
TOXICOLOGICAL DATA							
Acute Toxicity	**Y**	**Y**	**C**	Y	Y	Y	Y
Repeated Dose Toxicity	**Y**	**C**	**C**	Y	Y	Y	Y
Genetic Toxicity-Mutation	**Y**	**C**	**C**	Y	C	Y	Y
Genetic Toxicity-Chromosomal Aberrations	**C**	**C**	**C**	Y	C	NA	Y
Toxicity to Reproduction	**C**	**C**	**C**	Y	C	NA	NA
Developmental Toxicity	**Y**	**C**	**C**	Y	Y	NA	Y
OTHER TOXICITY DATA							
Irritation (NR)	**Y**	**Y**	**C**	Y	Y	Y	Y
Pharmacokinetics (NR)	**Y (A)**	**NR**	**NR**	Y (A)	Y (A)	NR	NR

Bolded Entries are Category Members

Y = adequate experimental data; NA = not applicable; E = Endpoint fulfilled via estimation;

C = endpoint fulfilled by category approach; NR = not required; A = absorption; [1]polyethylene glycol butyl ether

TRIETHYLENE GLYCOL BUTYL ETHER
CAS No. 143-22-6

SIDS Dossier (including robust summaries)

Existing Chemical	:	ID: 143-22-6
CAS No.	:	143-22-6
EINECS Name	:	2-(2-(2-butoxyethoxy)ethoxy)ethanol
EINECS No.	:	205-592-6
TSCA Name	:	Ethanol, 2-[2-(2-butoxyethoxy)ethoxy]-
Molecular Formula	:	C10H22O4

Producer related Part

Company	:	American Chemistry Council's Ethylene Glycol Ether Panel CEFIC's Oxygenated Solvents Producers Association Kyowa Hakko Kogyo Co., Ltd. Mitsubishi Chemical Corporation NIPPON NYUKAZAI CO. LTD
Creation date	:	29.07.2001

Substance related Part

Company	:	American Chemistry Council's Ethylene Glycol Ether Panel CEFIC's Oxygenated Solvents Producers Association Kyowa Hakko Kogyo Co., Ltd. Mitsubishi Chemical Corporation NIPPON NYUKAZAI CO. LTD
Creation date	:	29.07.2001

Printing date	:	02.12.2002
Revision date	:	02.12.2002
Date of last Update	:	02.12.2002
Number of Pages	:	58
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5

1.0.1 OECD AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

Substance type : organic
Physical status : liquid
Remark : Impurities include polyethylene glycol butyl ether (CAS No. 9004-77-7);
Diethylene glycol butyl ether (CAS No. 112-34-5);
Triethylene glycol (CAS No. 112-27-6);
Ethylene glycol butyl ether (CAS No.111-76-2)
Purity : 85-100 % w/w

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

3,6,9-Trioxatridecan-1-ol
26.09.2001

Butoxytriethylene glycol
26.09.2001

Butoxytriglycol
26.09.2001

Butyl 260
26.09.2001

Butyl triethoxol
26.09.2001

Butyltriglycol
26.09.2001

Butyltriglykol
26.09.2001

Poly-Solv TB
25.09.2001

TGBE
25.09.2001

Triethylene glycol monobutyl ether
26.09.2001

Triglycol monobutyl ether
26.09.2001

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

Production during the last 12 months	:	
Import during the last 12 months	:	
Quantity produced	:	10 000 - 50 000 metric tons in 1999.
Remark	:	About 20,900 metric tons (46 million pounds) were manufactured in the U.S. in 1999. About 40,000 metric tons of combined triethylene glycol methyl-, ethyl- and butyl- ethers were consumed in Western Europe in 1999. About 6,600 metric tons of all other E-Series (ethylene glycol) glycol ethers were produced in Japan in 1999, excluding mono- and di- ethylene glycol ethers and their acetates.
Reliability	:	(1) valid without restriction

14.10.2001 (16)

1.6.1 LABELLING

1.6.2 CLASSIFICATION

Remark	:	The material (100%) was recently given a classification of R41 (risk of serious injury to eyes) in Europe. The EU has not classified this material for the environment.
Reliability	:	(2) valid with restrictions

14.10.2001 (19)

1.7 USE PATTERN

Type	:	industrial
Category	:	basic industry: basic chemicals
Remark	:	The principal global end use is in the formulation of hydraulic brake fluids.
Reliability	:	(1) valid without restriction

14.10.2001 (16)

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.9 SOURCE OF EXPOSURE

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	= -39 ° C
Sublimation	:	no
Method	:	other
Year	:	2000
GLP	:	no data
Test substance	:	A mixture containing 85% (w/w) triethylene glycol monobutyl ether (CAS. No. 143-22-6), <= 12% polyethylene glycol monobutyl ether (CAS No. 9004-77-7), <= 4 % diethylene glycol monobutyl ether (CAS No. 112-34-5), <= 1.8 % triethylene glycol (CAS No. 112-27-6), <= 0.2 % ethylene glycol monobutyl ether (CAS No. 111-76-2)
Source	:	Dow Chemical Company MSDS for butoxytriglycol (#771), dated 6/27/2000.
Reliability	:	(2) valid with restrictions. Details on how value was obtained are unknown
Flag	:	Critical study for SIDS endpoint.

Value	:	= -35 ° C
Decomposition	:	no at ° C
Sublimation	:	no
Method	:	other
Year	:	2001
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Supportive study for SIDS endpoint.

Value	:	= -48 ° C
Decomposition	:	no at ° C
Sublimation	:	no
Method	:	other
Year	:	1998
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions. Details on how value was obtained are unknown.
Flag	:	Supportive study for SIDS endpoint.

(41)

2.2 BOILING POINT

Value	:	= 283.2 ° C at 1013 hPa
Decomposition	:	ambiguous
Method	:	other
Year	:	2000
GLP	:	not applicable
Test substance	:	A mixture containing 85% (w/w) triethylene glycol monobutyl ether (CAS. No. 143-22-6), <= 12% polyethylene glycol monobutyl ether (CAS No. 9004-77-7), <= 4 % diethylene glycol monobutyl ether (CAS No. 112-34-5), <= 1.8 % triethylene glycol (CAS No. 112-27-6), <= 0.2 % ethylene glycol monobutyl ether (CAS No. 111-76-2)
Remark	:	Boiling point determined by extrapolation.
Source	:	Dow Chemical Company MSDS for butoxytriglycol (#771), dated 6/27/2000.

Reliability : (2) valid with restrictions. Details on how value was obtained are unknown
Flag : Critical study for SIDS endpoint.

2.3 DENSITY

Value : = 0.989 at 21° C
Method : other
Year : 2000
GLP : no data
Test substance : A mixture containing 85% (w/w) triethylene glycol monobutyl ether (CAS. No. 143-22-6), <= 12% polyethylene glycol monobutyl ether (CAS No. 9004-77-7), <= 4 % diethylene glycol monobutyl ether (CAS No. 112-34-5), <= 1.8 % triethylene glycol (CAS No. 112-27-6), <= 0.2 % ethylene glycol monobutyl ether (CAS No. 111-76-2)
Source : Dow Chemical Company MSDS for butoxytriglycol (#771), dated 6/27/2000.
Reliability : (2) valid with restrictions. Details on how value was obtained are unknown
Flag : Critical study for non-required endpoint.

Type : density
Value : = .99 - 998 g/cm3 at 20° C
Method : other
Year : 1994
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for non-required endpoint.

(8)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : < .01 hPa at 20° C
Decomposition :
Method : other (measured)
Year : 2000
GLP : no data
Test substance : A mixture containing 85% (w/w) triethylene glycol monobutyl ether (CAS. No. 143-22-6), <= 12% polyethylene glycol monobutyl ether (CAS No. 9004-77-7), <= 4 % diethylene glycol monobutyl ether (CAS No. 112-34-5), <= 1.8 % triethylene glycol (CAS No. 112-27-6), <= 0.2 % ethylene glycol monobutyl ether (CAS No. 111-76-2)
Source : Dow Chemical Company MSDS for butoxytriglycol (#771), dated 6/27/2000.
Reliability : (2) valid with restrictions. Details on how value was obtained are unknown
Flag : Critical study for SIDS endpoint.

Value : 0.000592 mm Hg (0.0007789 hPa) @ 25 degrees C
Method : other: calculated

GLP : not applicable
Test substance : as prescribed by 1.1 - 1.4
Remark : Value was calculated in 2001 by the EPIWIN program using the methods of Antoine and modified Grain.
Reliability : (2) valid with restrictions. Data were obtained by modeling.
Flag : Supportive study for SIDS endpoint.

Value : < .01 hPa at 20° C
Decomposition :
Method : other: calculated
Year : 2001
GLP : not applicable
Test substance : as prescribed by 1.1 - 1.4
Reliability : (2) valid with restrictions. Data were obtained by modeling.
Flag : Supportive study for SIDS endpoint.

Value : = .1 hPa at 20° C
Decomposition :
Method : other
Year : 1994
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study should is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for SIDS endpoint.

(8)

Value : = .02 hPa at 50° C
Decomposition :
Method : Other
Year : 1994
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for SIDS endpoint.

(8)(10)

2.5 PARTITION COEFFICIENT

Log pow : = .51 at 25° C
Method OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year : 1988
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Critical study for SIDS endpoint.

(3)

Log pow : = .02 at unknown temperature
Method other (calculated)
Year : 2001
GLP : not applicable
Test substance : as prescribed by 1.1 - 1.4
Source : The Log Pow was calculated using the Syracuse Research Corporation Log Kow Interactive Calculation Program.
Reliability : (2) valid with restrictions. Data were obtained by modeling.
Flag : Supportive study for SIDS endpoint.

Log pow : ca. .5 at unknown temperature
Method : other (calculated)
Year : 1994
GLP : not applicable
Test substance : as prescribed by 1.1 - 1.4
Remark : A Log Kow of 0.02 was estimated in 2001 by the EPIWIN program based on SMILES.

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for SIDS endpoint.

(8)

Log pow : = .62 at unknown temperature
Method other (calculated): Increment method of Rekker with Computer program from the Firm CompuDrug Ltd.
Year : 1989
GLP : not applicable
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for SIDS endpoint.

(5)

Log pow : = .969 at unknown temperature
Method other (calculated): according to Leo/Hansch using Computer program CLOGP3
Year : 1989
GLP : not applicable
Test substance : as prescribed by 1.1 - 1.4
Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for SIDS endpoint.

(33)

2.6.1 WATER SOLUBILITY

Value : = 1000 g/l at 20 ° C
Qualitative : miscible
Pka : at 25 ° C

PH : at and ° C
Method : other
Year : 2000
GLP : no data
Test substance : A mixture containing 85% (w/w) triethylene glycol monobutyl ether (CAS. No. 143-22-6), <= 12% polyethylene glycol monobutyl ether (CAS No. 9004-77-7), <= 4 % diethylene glycol monobutyl ether (CAS No. 112-34-5), <= 1.8 % triethylene glycol (CAS No. 112-27-6), <= 0.2 % ethylene glycol monobutyl ether (CAS No. 111-76-2)
Source : Dow Chemical Company MSDS for butoxytriglycol (#771), dated 6/27/2000.
Reliability : (2) valid with restrictions. Details on how value was obtained are unknown
Flag : Critical study for SIDS endpoint.

Value : ca. 580 g/l at 25 ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Method : other(calculated)
Year : 2001
GLP : not applicable
Test substance : as prescribed by 1.1 - 1.4
Remark : Water solubility calculated using EPIWIN/WSKOW (v1.40). Program was based on an estimated Log Kow of 0.02.
Source :
Reliability : (2) valid with restrictions. Data were obtained by modeling.
Flag : Supportive study for SIDS endpoint.

Value : at ° C
Qualitative : miscible
Pka : at 25 ° C
PH : at and ° C
Method : other
Year : 1994
GLP : no data

Test substance : as prescribed by 1.1 - 1.4
Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for SIDS endpoint.

(8)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : = 157.2 ° C
Type :
Method : Cleveland Open Cup (ASTM D92)
Year : 2000
GLP : no data
Test substance : A mixture containing 85% (w/w) triethylene glycol monobutyl ether (CAS. No. 143-22-6), <= 12% polyethylene glycol monobutyl ether (CAS No. 9004-77-7), <= 4 % diethylene glycol monobutyl ether (CAS No. 112-34-5), <= 1.8 % triethylene glycol (CAS No. 112-27-6), <= 0.2 % ethylene glycol monobutyl ether (CAS No. 111-76-2)

Source	:	Dow Chemical Company MSDS for butoxytriglycol (#771), dated 6/27/2000.
Reliability	:	(2) valid with restrictions. Details on how value was obtained are unknown
Flag	:	Critical study for non-required endpoint.

Value	:	= 137.7 ° C
Type	:	
Method	:	Pensky-Martens Closed Cup (ASTM D93)
Year	:	2000
GLP	:	no data
Test substance	:	A mixture containing 85% (w/w) triethylene glycol monobutyl ether (CAS. No. 143-22-6), <= 12% polyethylene glycol monobutyl ether (CAS No. 9004-77-7), <= 4 % diethylene glycol monobutyl ether (CAS No. 112-34-5), <= 1.8 % triethylene glycol (CAS No. 112-27-6), <= 0.2 % ethylene glycol monobutyl ether (CAS No. 111-76-2)
Source	:	Dow Chemical Company MSDS for butoxytriglycol (#771), dated 6/27/2000.
Reliability	:	(2) valid with restrictions. Details on how value was obtained are unknown
Flag	:	Critical study for non-required endpoint.

Value	:	= 144 ° C
Type	:	
Method	:	other: DIN 51 758
Year	:	1994
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag	:	Supportive study for non-required endpoint.

(8)

2.8 AUTO FLAMMABILITY

Remark	:	Ignition temperature: 203 degrees C (DIN 51 794)
Type	:	
Method	:	other
Year	:	1990
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag	:	Critical study for non-required endpoint.

(9)

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Remark	:	Explosive limits in air: 0,8-3,8 Vol. %
Type	:	
Method	:	other
Year	:	1994
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag	:	Critical study for non-required endpoint.

(8)

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

Year	:	1994
Remark	:	Hazardous reactions in presence of air/ Keep away from oxygen (forms peroxides).
Reliability	:	(1) valid without restriction. Ethers are known to form peroxides in the presence of oxygen.

(8)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	other
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Direct photolysis		
Rate constant	:	51.5*10^-12 cm3/(molecule*sec)
Halflife t1/2	:	= 2.5 hour(s)
Degradation	:	% after
Quantum yield	:	
Deg. Product	:	
Method	:	other (calculated)
Year	:	2002
GLP	:	not applicable
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	A hydroxyl radical abstraction rate constant of 51.5 E-12 was estimated using the EPIWIN model based on SMILES and chemical bond calculations. The same program estimates a half-life of .208 days or 2.490 hours assuming a 12-hr day of sunlight.
Remark	:	The photodegradation half life and hydroxyl radical rate constant were calculated using the EPIWIN AOP (v1.90) program, based on the molecular structure of the substance. This program assumes that the atmospheric hydroxyl radical will abstract a hydrogen atom from a carbon-hydrogen linkage, and considers the contributions of each carbon-hydrogen bond in the molecule as well as the relative probability that a hydrogen atom will be abstracted from each given carbon-hydrogen bond, in arriving at an overall rate constant. This program is based on the work of Atkinson, who has demonstrated that this approach provides rate constants for relatively simple, common organic compounds that correlate well with measured rate constants. The photodegradation half-life assumes pseudo first order kinetics with a constant specified concentration of hydroxyl radical.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint.

Type	:	air
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	
Rate constant	:	4.6*10^-11 cm3/(molecule*sec)
Degradation	:	% after
Deg. Product	:	
Method	:	other (calculated)
Year	:	1998
GLP	:	not applicable
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag	:	Supportive study for SIDS endpoint.

(1)

Type	:	other
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Method	:	other (calculated)

Year : 1985
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : Could undergo free radical oxidations to peroxides in sunlit waters. No further details given.

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for SIDS endpoint.

(22)

3.1.2 STABILITY IN WATER

Deg. Product :
Method : other(calculated)
Year : 1975
GLP : not applicable
Test substance : as prescribed by 1.1 - 1.4
Remark : No removal from water by aeration for 4 hours, as determined by TOD analysis. Aeration test method, Environmental Research Lab., The Dow Chemical Co.

Reliability : (2) valid with restrictions. This experimental determination correlates with generally recognized behaviors of ether that they do not hydrolyze in water at ambient temperatures unless strongly forced by an external chemical agent, such as boiling hydriodic acid.
Flag : Critical study for SIDS endpoint.

(20)

Deg. Product :
Method : other
Year : 1985
GLP : not applicable
Test substance : as prescribed by 1.1 - 1.4
Remark : Expected to reside primarily in aquatic environments in which it has a relatively short half-life due to biodegradation. Based on water solubility, expected to undergo primary biodegradation in aerobic surface waters and complete biodegradation in anaerobic environments at moderate rates with half-lives of 1-3 weeks. No further details given.

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for SIDS endpoint.

(22)

Deg. Product :
Method : other (calculated)
Year : 2002
GLP : not applicable
Test substance : as prescribed by 1.1 - 1.4
Remark : Hydrolysis rate constants cannot be estimated for ethers by the EPIWIN HYDROWIN program. This substance, which contains primarily ether linkages, is not anticipated to hydrolyze readily in water at neutral pHs.
Source : The EPIWIN HYDROWIN (v1.67) Program.
Reliability : (3) invalid

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	other
Media	:	water - air
Air (level III)	:	0.0608
Water (level III)	:	44.7
Soil (level III)	:	55.1
Biota (level II / III)	:	
Soil (level II / III)	:	
Method	:	Other(calculated)
Year	:	2002
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remarks	:	Measured values used as program inputs were vapor pressure (0.075 mm Hg), melting point (-39 degrees C), log Kow (0.51), water solubility (1,000,000 mg/l, and boiling point (283 degrees C).
Result	:	The EPIWIN Fugacity Level III model predicts a mass amount of 0.0766% to partition to sediment. The half-lives in hours are air (4.98), water (360), soil (360) and sediment (1.44E+3). The EPIWIN HENRY (v3.10) model estimates a Henry's Law Constant of 9.52E-14 atm-m3/mol at 25 degrees C (Bond Estimate). The EPIWIN PCKOC (v1.66) program estimates a Koc (soil-sediment partition constant) of 10. Calculation methods of Howard and Lyman estimate a Koc of 24. The EPIWIN BCF (v2.14) program estimates a log BCF (Bioconcentration Factor) of 0.50. The methods of Howard and Lyman calculate a BCF of 24.
Source	:	Fugacity Model III calculations were performed by the EPIWIN program.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint.

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	other, community waste water, not acclimated.
Concentration	:	10mg/l related to test substance related to
Contact time	:	
Degradation	:	= 88 % after 14 day
Result	:	
Deg. Product	:	
Method	:	OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year	:	1993
GLP	:	no data

Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Critical study for SIDS endpoint

(25)

Type : aerobic
Inoculum : other: Klaeranlagen-Ablauf
Concentration : 20mg/l related to DOC (Dissolved Organic Carbon)
related to
Contact time :
Degradation : = 92 % after 21 day
Result :
Kinetic of test substance : 7 day = 28 **%**

14 day = 88 **%**
21 day = 92 **%**
%
%
Deg. Product :
Method : OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year : 1992
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Critical study for SIDS endpoint

(26)

Type : aerobic
Inoculum : other: Belebtschlamm, communal
Concentration : 500mg/l related to Test substance
related to
Contact time :
Degradation : = 100 % after 9 day
Result :
Deg. Product :
Method : OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year : 1993
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for SIDS endpoint

(25)

Type : aerobic
Inoculum : other: Michigan Divisions Wastewater Treatment Plant secondary effluent
Deg. Product :

Method : other: APHA, American Water Works Association and Water Pollution Control Federation, Standard methods for the examination of water and wastewater, 13th edition
Year : 1971
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : Degradation: reported as BOD5 = 0.02 parts/part = 1% TOD
BOD10= 0.8 p/p = 43% TOD
BOD20= 1.2 p/p = 65% TOD
presumably, therefore, 1% degradation after 5 days, 43% after 10 days and 65% after 20 days.
related to COD

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for SIDS endpoint

(20)

Type : aerobic
Inoculum : other: microorganisms, mixed culture
Contact time :
Degradation : = 24 % after 20 day
Result :
Kinetic of test substance : 5 day = 0 **%**
10 day = 5 **%**
20 day = 24 **%**
%
%
Deg. Product :
Method : other: BSB-Test (BSB des THSB)
Year : unknown
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for SIDS endpoint

(21)

Type : aerobic
Inoculum :
Deg. Product :
Method : other: Clifford, D.A., Automatic measurements of TOD: A new instrumental method. 23rd Annual Purdue Industrial Waste Conference. Purdue University, Lafayette, Indiana
Year : 1968
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : TOD = 1.86 parts oxygen/part formulation

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for SIDS endpoint

(20)

Type : aerobic
Inoculum : other bacteria: BASF-Belebtschlamm
Concentration : 400mg/l related to
related to
Contact time :
Degradation : = 77 % after 6 day
Result :
Deg. Product :
Method : other: Standversuch (TOC)
Year : 1980
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : Substance is well eliminated – biologically decomposable.

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for SIDS endpoint

(7)

Type : aerobic
Inoculum : other: non-acclimated sewage microorganisms
Contact time :
Degradation : = 47 % after 20 day
Result :
Deg. Product : not measured
Method : other: as described in "Standard Methods for the Examination of Water and Wastewater, 16th ed., USPHA, Washington, D.C., 1985).
Year : 1987
GLP : no data
Test Substance : as prescribed by 1.1 - 1.4
Remark : Biological oxygen demand (BOD) of triethylene glycol monomethyl ether (CAS No. 112-35-6) and triethylene glycol monoethyl ether (CAS No. 112-50-5) were also tested in this study. The BOD of both of these chemicals (71% after 20 days) was higher than that of triethylene glycol monobutyl ether. The concentration of test material and bacteria were not listed in the report.
Result : The calculated theoretical oxygen demand was 2.10 mg/mg. After 10 and 20 days of incubation, the percent biooxidation was 5 and 47% (respectively).
Test condition : 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.
Reliability : (2) valid with restrictions. Purity of test material was not noted.
Flag : Supportive study for SIDS endpoint.
02.10.2001

(44)

3.6 BOD5, COD OR BOD5/COD RATIO

BOD5
Method : other: APHA, American Water Works Association and Water Pollution Control Federation, Standard methods for the examination of water and wastewater, 13th edition, NY
Test substance : as prescribed by 1.1 - 1.4
GLP : no data
Method : other
Year : 1971
COD : = 1830 mg/g substance
RATIO BOD5 / COD
BOD5/COD : = .01
Remark : BOD5 = 20 mg O2/g

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for non-required endpoint.

(20)

BOD5
Method : other: BSB-Test, conducted according to DIN 38409/51
Test substance : as prescribed by 1.1 - 1.4
Year : Unknown
GLP : no data
Concentration : related to
BOD5 : mgO2/l
COD
Method : other: CSB-Test according to DIN 38409/41
Year :
GLP : no data
COD : = 1952 mg/g substance
RATIO BOD5 / COD
BOD5/COD : = .16
Result : BSB5 =311 mg/g

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for non-required endpoint.

(6)

COD
Method : other: Alkaline potassium permanganate test method, Environmental Research Lab., The Dow Chemical Co.
Test substance : as prescribed by 1.1 - 1.4
Year : 1975
GLP : no data
COD : mg/g substance
Remark : COD = 1.5 parts oxygen/part formulation

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag : Supportive study for non-required endpoint.

(20)

COD

Method	:	other: American Public Health Association, American Water Works Assoc. and Water Poll. Control Fed.1971, Stand. Methods for the examination of water and wastewater, 13th ed. NY
Test substance	:	as prescribed by 1.1 - 1.4
Year	:	1971
GLP	:	no data
COD	:	Mg/g substance
Remark	:	COD = 1.83 parts oxygen/part formulation
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag	:	Supportive study for non-required endpoint.

(20)

3.7 BIOACCUMULATION

Species	:	other
Exposure period	:	At degree C
Concentration	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Bioconcentration in fish and other aquatic life should not be significant due to high water solubility.
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag	:	Supportive study for non-required endpoint.

(20)

Species	:	other
Exposure period	:	At degree C
Concentration	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	unlikely to bioaccumulate.
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission (since it was not reviewed).
Flag	:	Supportive study for non-required endpoint.

(27)

Elimination	:	
Method	:	other
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Log Pow values from 0.51 (experimentally determined and) and 0.62 were calculated. These values would suggest very low bioaccumulation potential.
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a

reliability rating of 4 for this submission (since it was not reviewed).

Flag : Supportive study for non-required endpoint.

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	= 2400
Method	:	other: as described in Standard Methods for the Examination of Water and Wastewater, 13th edition, 1971.
Year	:	1974
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Toxicity of triethylene glycol monomethyl ether (CAS No. 112-35-6) and of triethylene glycol monoethyl ether (CAS No. 112-50-5) were also tested in this study. LC50 values for both chemicals were > 10000 mg/l.
Result	:	The 24-hr, 48-hr and 96-hr LC50 values were 2400 mg/l
Test condition	:	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.
Reliability	:	(2) valid with restrictions. Purity of test material was not noted
Flag	:	Critical study for SIDS endpoint.

03.10.2001 (43)

Type	:	
Exposure period	:	14 days
Unit	:	mg/l
LC50	:	5498
Method	:	estimated using EPIWIN ECOSAR
Year	:	2002
GLP	:	No
Test substance	:	100% triethylene glycol monobutyl ether (CAS No. 143-22-6)
Remarks	:	Measured values used as program inputs were vapor pressure (0.0075 mm Hg), melting point (-39 degrees C), water solubility (1,000,000 mg/l), Log Kow (0.51), and boiling point (283 degrees C).
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.

Type	:	static
Species	:	Leuciscus Idus (Golden Orfe)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	> 2150 and < 4640
Method	:	DIN 38 412
Year	:	1989
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4. Purity was 87.2%
Result	:	The 24-hr, 48-hr and 96-hr LD50 values were > 2150 and < 4640 mg/l. All fish exposed to 4640 mg/l died within 4 hours. No deaths were observed at 2150 mg/l. Apathy and tumbling were noted at 2150 mg/l. No symptoms of toxicity were observed at 1000 mg/l.
Test condition	:	Ten fish/group were exposed to 0, 1000, 2150, 4640 or 10000 mg/l test material in glass aquariums (30 cm x 22 cm x 24 cm) containing 10 liters of water (2.8 g fish/liter water) after a 3 day acclimation period. Food was

withdrawn 1 day before and during exposure. The average length and weight of fish were 6.7 cm and 2.8 g, respectively. The water had a total hardness, acid capacity, ratio Ca/Mg, ratio Na/K, pH and temperature of 2.5 mmol/l, 0.8 mmol/l, 4:1, 10:1, 8.0, and 20 degrees C. Water was continuously aerated with oil-free air.

Reliability : (2) valid with restrictions. Purity of test material was not high.
Flag : Supportive study for SIDS endpoint.
30.11.2001 (12)

Type : semistatic
Species : Poecilia reticulata (Fish, fresh water)
Exposure period : 7 day
Unit : mg/l
Analytical monitoring : no
LC50 : = 197
Method : other
Year : 1981
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : The molecular weight of the test material (206 g/mole) was used to convert the log LC50 (in micromoles/liter) to the LC50 (in mg/l).
Result : The log of the LC50 was calculated to be 2.98 micromoles/l
Test condition : Test conditions: Two to three month old guppies (8 per group) were exposed to several concentrations of test material in 1.5 liter vessels for 7 days. Each vessel was filled with 1 liter of standard water (hardness 25 mg/l as CaCO3) and covered with glass. A stock solution of test material was made by dissolving it in either acetone or 2-propanol (not specified). Various volumes of stock solution were added to the test vessels to increase test concentrations geometrically (in increasing ratios of 3.2). Test solution was renewed daily. Guppies were fed 0.5 hours before each renewal with commercial fish food. Oxygen content, water temperature, and viability of fish were monitored. Oxygen content remained above 5 mg/l, and temperature was 22 +/- 1 degrees C.

LC50's were calculated according to the method of Litchfield and Wilcoxon (J Pharm Exp Ther 96:99, 1949), or by estimation from a log-probit-plot (if concentration-death relationship was too steep)

Reliability : (2) valid with restrictions. Purity of test material was not noted.
Flag : Supportive study for SIDS endpoint
02.10.2001 (29)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type :
Exposure period : 48 hours
Unit : mg/l
LC50 : no value given; no toxicity log Kow cutoff
Method : estimated using EPIWIN ECOSAR
Year : 2002
GLP : no
Test substance : 100% triethylene glycol monobutyl ether (CAS No. 143-22-6)
Remarks : Measured values used as program inputs were vapor pressure (0.0075 mm Hg), melting point (-39 degrees C), water solubility (1,000,000 mg/l), log Kow (0.51), and boiling point (283 degrees C).
Reliability : (4) unassignable. No value determined. Study is a model estimation.

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)

Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	= 2210
Method	:	other: test procedures followed those recommended by EPA and ASTM
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Toxicity of triethylene glycol monomethyl ether (CAS No. 112-35-6) and of triethylene glycol monoethyl ether (CAS No. 112-50-5) were also tested in this study. LD50 values for both chemicals were > 10000 mg/l.
Result	:	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. The LD50 value and 95% confidence limits were 2210 (1740-2800) mg/l.
Test condition	:	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 (values were not listed). 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.
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Critical study for SIDS endpoint

03.10.2001 (44)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Type	:	
Exposure period	:	96 hours
Unit	:	mg/l
EC50	:	no value given; no toxicity log Kow cutoff
Method	:	estimated using EPIWIN ECOSAR
Year	:	2002
GLP	:	no
Test substance	:	100% triethylene glycol monobutyl ether (CAS No. 143-22-6)
Remarks	:	Measured values used as program inputs were vapor pressure (0.0075 mm Hg), melting point (-39 degrees C), water solubility (1,000,000 mg/kg), log Kow (0.51), and boiling point (283 degrees C).
Reliability	:	(4) unassignable. No value estimated. Study is a model estimation.

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC50	:	> 500
EC20	:	= 270
EC90	:	> 500

Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The EC20 value at 24, 48, and 72 hours was 235.7, 235.4, and 267.1 mg/l. The EC50 value was greater than the highest concentration tested (500 mg/l). At time 0, fluorescence values ranged from 94.37 % of control for cells treated with 7.812 and 31/25 mg/l to 103.09 % of control for cells treated with 500 mg/l. The fluorescence values for cells treated with all concentrations except 125 (86.08%) and 250 mg/l (79.21%) were greater than 90% at 24 hours. At 48 hours, cells treated with 250 or 500 mg/l began to exhibit slightly lower fluorescence values than control. At 72 hours, values for cells treated with 250 or 500 mg/l were 80.3% and 75.91% of control, respectively. Most values for the 4 replicates at each concentration varied by < = 5%. However, at 48 hours, variance of values for concentrations greater than or equal to 250 mg/l ranged from 5-10%.
Test condition	:	A SAG 86.81 culture of Scenedesmus subspicatus (10,000 cells/ml) was maintained in OECD medium at 20 degrees C. Ten ml of cells in suspension was treated with 0 (control), 7.812, 15.625, 31.25, 62.5, 125, 250 or 500 mg/l test material in quadruplicate. Fluorescence of vials containing treated cells was determined 0, 24, 48 and 72 hours after treatment in a fluorimeter with a gain setting of 1. Fluorescence of 2 blank vials containing test material (at each concentration) and medium without cells was subtracted from values obtained for test vials. The values for the four tests were averaged and a standard deviation was calculated. The average fluorescence value of each concentration was presented as a percentage of control values.
Reliability	:	(2) valid with restrictions. Test material purity is unknown. Details about study conduct are lacking.
Flag	:	Critical study for SIDS endpoint

03.10.2001 (11)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	other: sewer microorganisms
Exposure period	:	16 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
IC50	:	> 5000
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Toxicity of triethylene glycol monomethyl ether (TGME, CAS No. 112-35-6) and of triethylene glycol monoethyl ether (TGEE, CAS No. 112-50-5) also were tested in this study. The LD50 values for TGME and TGEE were > 5000 mg/l and > 1000 mg/l, respectively.
Test condition	:	Selected concentrations (not listed) were incubated for 16 hours at 23 degrees C on a shaker table in the presence of nutrients, buffer, growth substrate, and sewer microorganisms. Toxicity was indicated when the resulting turbidity was at (or less than) 50% of the control (IC50). Details of the test are published in: Alsop et al., "Bacterial Growth Inhibition Tests", J. Water Pollution Control Federation, Vol 52: No. 10, October, 1980.
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.

Flag : Critical study for non-required endpoint.
25.09.2001 (44)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	40
Vehicle	:	
Value	:	= 5300 mg/kg bw
Method	:	other
Year	:	1976
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	All animals given 12.18 g/kg died within 3 hours. Eight animals given 7.73 g/kg and 6 given 5.0 g/kg died within 1 day. There were no other deaths over the course of the experiment. Signs of toxicity at 5.0 g/kg included loss of righting reflex and flaccid muscle tone; at 7.73 g/kg included comatose (6/10), flaccid muscle tone, and heavy breathing. There were no signs of toxicity in rats given 3.2 g/kg. The LD50 value (and 95% confidence limit) was 5.3 (4.1-6.8) g/kg.
Test condition	:	Rats (200-250 g) were fasted for approximately 18 hours prior to test material administration. Test material was given by intubation at 3.2, 5.0, 7.73, and 12.18 g/kg to groups of 10 animals. Food and water were freely available after treatment. Rats were observed for toxicity and death for 14 days. The LD50 value and 95% confidence limits were determined by the method of Litchfield and Wilcoxon (J Pharm Exp Ther 96:99, 1949).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint

02.10.2001 (36)

Type	:	LD50
Species	:	rat
Strain	:	other: Carworth-Wistar
Sex	:	male
Number of animals	:	
Vehicle	:	no data
Value	:	= 6.73 ml/kg bw
Method	:	other
Year	:	1962
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	It is likely that this study is the same one described in the following record (Carpenter and Striegel, 1960).
Result	:	The oral LD50 for rats averaged 6.73 ml/kg and ranged from 4.13 to 11.0 ml/kg
Test condition	:	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). Animals were observed up to 14 days after dosing for mortality. 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)
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint.

02.10.2001 (39)

Type	:	LD50

Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	15
Vehicle	:	
Value	:	= 6.73 ml/kg bw
Method	:	other
Year	:	1960
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	It is likely that this is the same study described in the previous record (Smyth et al., 1962).
Result	:	All animals receiving 16 ml/kg, 3 out of 5 dosed with 8 ml/kg, and 1 out of 5 dosed with 4 ml/kg died within 1 day of dosing. Autopsy of dead rats showed a generalized congestion of the abdominal viscera and lungs. The LD50 value was 6.73 (4.13 to 10.96) ml/kg.
Test condition	:	Male Wistar rats (5-6 weeks, 90-120 g) were intubated with test material at dose levels differing by a factor of 2.0 in a geometric series. Rats were observed each day for 14 days. Autopsies were performed on rats that died. Surviving rats were weighed at study termination. The method of moving average for calculating the LD50 was applied to the mortality data.
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint.

03.10.2001 (15)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other
Species	:	rat
Strain	:	other: albino
Sex	:	no data
Number of animals	:	6
Vehicle	:	
Exposure time	:	8 hour(s)
Method	:	other
Year	:	1962
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	It is likely that this study is the same one described in the following record (Carpenter and Striegel, 1960).
Result	:	All animals survived an 8-hr exposure period to concentrated vapor
Test substance	:	Male or 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 the 14-day observation period
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint.

02.10.2001 (39)

Type	:	other
Species	:	rat
Strain	:	Wistar
Sex	:	female
Number of animals	:	6
Vehicle	:	

Exposure time	:	8 hour(s)
Method	:	other
Year	:	1960
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	It is likely that this is the same study described in the previous record (Smyth et al., 1962).
Result	:	All animals survived the exposure.
Test substance	:	Concentrated vapor (25 degrees C) was generated by passing air at 2.5 liters/min through a fritted glass disc immersed in 50 ml of butoxy triglycol. Rats were exposed for 8 hours and observed for 14 days.
Reliability	:	(2) valid with restrictions. Purity of test material was not noted
Flag	:	Supportive study for SIDS endpoint.

02.10.2001 (15)

Type	:	LCLo
Species	:	rat
Strain	:	Wistar
Sex	:	
Number of animals	:	10
Vehicle	:	
Exposure time	:	1 hour(s)
Value	:	> 200 mg/l
Method	:	other
Year	:	1976
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Rats gained weight over the 14 day period. There were no signs of toxicity.
Test substance	:	Ten rats (200-250 g, sex not stated) were placed in a 50 liter chamber and exposed to a nominal concentration of 200 mg/liter of test material for one hour. The rats were observed daily over 14 days for signs of toxicity. Body weights were recorded prior to and 14 days after treatment.
Reliability	:	(2) valid with restrictions. Purity of test material was not noted
Flag	:	Supportive study for SIDS endpoint.

01.10.2001 (35)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	
Vehicle	:	no data
Value	:	= 3.54 ml/kg bw
Method	:	other: variation of one-day cuff method of Draize
Year	:	1962
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	It is likely that this study is the same one described in the following record (Carpenter and Striegel, 1960).
Result	:	The LD50 value averaged 3.54 ml/kg and ranged from 1.06 to 11.8 ml/kg
Test condition	:	Groups of four rabbits weighing between 2.5 to 3.5 kg were treated with 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. 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).

Reliability : (2) valid with restrictions. Purity of test material was not noted
Flag : Supportive study for SIDS endpoint.

26.09.2001 (39)

Type : LD50
Species : rabbit
Strain : New Zealand white
Sex : male
Number of animals : 16
Vehicle :
Value : = 3.54 ml/kg bw
Method : other
Year : 1960
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : It is likely that this is the same study described in the previous record (Smyth et al., 1962).
Result : Three out of four rabbits treated with 10 ml/kg died within 3 days. The remaining animal in this group lost 110 g of weight over the 14-day recovery period. Two out of four rabbits treated with 5 ml/kg or 2.5 ml/kg, and one treated with 1.25 ml/kg died by day 9. Findings upon autopsy were cherry red and hemorrhaged lungs, dark livers mottled with prominent acini, and pale and mottled kidneys. The LD50 value was 3.54 (1.06 to 11.85) ml/kg.
Test condition : Groups of 4 male rabbits (3-5 months, 2.5 kg avg) were treated with 1.25, 2.5, 5.0 or 10 ml/kg dermally (on clipped skin). A VINYLITE sheeting was used to keep the test material in contact with the skin. Rabbits were immobilized during the 24-hour skin contact period. After the dressing was removed, animals were observed for 14 days. The moving average method was used to calculate the LD50.
Reliability : (2) valid with restrictions. Purity of test material was not noted
Flag : Supportive study for SIDS endpoint.
03.10.2001 (15)

Type : LDLo
Species : rabbit
Strain : New Zealand white
Sex :
Number of animals : 10
Vehicle :
Value : > 2000 mg/kg bw
Method : other
Year : 1976
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Result : There were no deaths or signs of toxicity.
Test condition : Ten rabbits (2.3 to 3.0 kg) were clipped free of abdominal hair. Epidermal abrasions were made longitudinally every 2 to 3 cm over the clipped area of 5 rabbits. The abrasions were deep enough to penetrate the stratum corneum, but not deep enough to produce bleeding. A single dose of 2.0 g/kg was applied to the exposed area. The area was covered with gauze and the trunk wrapped with impervious material for 24 hours. The dressing was removed, rabbits were cleaned, and animals were evaluated over 14 days.
Reliability : (2) valid with restrictions. Purity of test material was not noted
Flag : Supportive study for SIDS endpoint.
03.10.2001 (34)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	
Exposure	:	open
Exposure time	:	24 hour(s)
Number of animals	:	5
PDII	:	
Result	:	moderately irritating
EC classification	:	
Method	:	other
Year	:	1962
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	An average irritation Grade of 3 was obtained with undiluted test material, indicating moderate irritation. Marked capillary injection was noted on 4 animals and moderate injection on the 5th
Test condition	:	Undiluted test solution (0.01 ml) was applied 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
Reliability	:	(2) valid with restrictions. Purity of test material was not noted
Flag	:	Supportive study for non-required endpoint.

03.10.2001 (15) (39)

Species	:	rabbit
Concentration	:	
Exposure	:	occlusive
Exposure time	:	24 hour(s)
Number of animals	:	
PDII	:	
Result	:	irritating
EC classification	:	
Method	:	other
Year	:	1960
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Listed here are dermal irritation results from an acute dermal toxicity study performed with high doses (1.25 to 10 ml/kg). Refer to Section 5.1.3 for additional details
Result	:	Marked erythema of skin was found upon removal of the dressing (doses not stated). Some small scabs and extensive desquamation were present at Day 14.
Test condition	:	Groups of 4 male rabbits (3-5 months, 2.5 kg avg) were treated with 1.25, 2.5, 5.0 or 10 ml/kg dermally (on clipped skin). A VINYLITE sheeting was used to keep the test material in contact with the skin. Rabbits were immobilized during the 24-hour skin contact period. After the dressing was removed, animals were observed for 14 days.
Reliability	:	(2) valid with restrictions. Purity of test material was not noted
Flag	:	Supportive study for non-required endpoint.

03.10.2001 (15)

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	24 hour(s)

Number of animals	:	6
PDII	:	
Result	:	not irritating
EC classification	:	
Method	:	other
Year	:	1976
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	An erythema score of 1 (barely perceptible) was observed in 1 rabbit at 24 hours (abraded skin) and another at 72 hours (intact skin). All others received erythema scores of 0. No edema was observed at 24 or 72 hours.
Test condition	:	Six rabbits were clipped over the back and sides with an electric clipper. A site (1" x 1") to the left of the spinal column was abraded. Abrasions were minor incisions through the stratum corneum that did not disturb derma or produce bleeding. Test material (0.5 ml) was applied to a surgical gauze (1" square, 2 layers thick). The patches were placed on test sites and secured with adhesive tape. The trunk was wrapped with impervious material. Patches were removed after 24 hours. Dermal reactions were evaluated at 24 and 72 hours in accordance with the Consumer Product Safety Act, Title 16 CFR 1500.41.
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint.

01.10.2001 (37)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	.1 ml
Exposure Time	:	
Comment	:	
Number of animals	:	6
Result	:	highly irritating
EC classification	:	R41: risk of severe injury to eyes
Method	:	other
Year	:	1976
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Conjunctival redness, chemosis and discharge scores of 2-3 (diffuse crimson to beefy red) were noted at all time points in all rabbits (except 1 rabbit that had a chemosis score of 1 at 72 hours). Iris scores of 1 (folds above normal, congestion, swelling, corneal injection, sluggish reaction to light) were observed in all animals at each time point. The total conjunctival score ((redness + chemosis + discharge) x 2) ranged from 10-16 out of a possible 20. The highest overall score was 21 out of a possible 110.
Test condition	:	Six New Zealand white rabbits were used in the study. Test material (0.1 ml) was instilled into the conjunctival sac of one eye of each rabbit on Day 0. Ocular reactions were graded in accordance with the Consumer Product Safety Act, Title 16 CFR 1500.42 at 1, 2, and 3 days after instillation of the test material.
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint.

02.10.2001 (38)

Species	:	rabbit
Concentration	:	
Dose	:	

Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	highly irritating
EC classification	:	
Method	:	other: Carpenter and Smyth (Am J Opthal 29:1363, 1946)
Year	:	1962
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	It is likely that this study is the same one described in the following record (Carpenter and Striegel, 1960).
Result	:	A test score of 5 was reached, indicating that the test material caused severe eye irritation.
Test condition	:	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.
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint.

02.10.2001 (39)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	irritating
EC classification	:	R41: risk of serious damage to eyes
Method	:	other
Year	:	1960
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	It is likely that this is the same study described in the previous record (Smyth et al., 1962).
Result	:	The average eye injury score was 5. Rabbit eyes were necrosed by instillation of 0.02 ml. Minor to moderate injury resulted from the instillation of 0.005 ml.
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint.

02.10.2001 (15)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	irritating
EC classification	:	R 41; risk of serious injury to eyes
Method	:	other
Year	:	1966
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The data were obtained from a report issued by the Departement Risques Chimiques et Biologiques (Section TE) in 2002. Test conditions were not provided.

Result	:	Severe redness, edema and opacity were noted after 1 hour of treatment. These conditions persisted for 8 days. After 8 days, scars were visible (eyelid vessels were considerably injected). Eye signs (redness, edema, opacity and scar) were scored from slight to very severe.
Reliability	:	(4) non-assignable. The study was not reviewed.
Flag	:	Supportive study for non-required endpoint.

02.10.2001 (2)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Species	:	rabbit
Sex	:	male/female
Strain	:	New Zealand white
Route of admin.	:	dermal
Exposure period	:	21 days
Frequency of treatment	:	6 hr/day, 5 days/week for 3 weeks
Post obs. period	:	
Doses	:	1000 mg/kg
Control group	:	other:sham
NOAEL	:	=1000 mg/kg
Method	:	other: limit test
Year	:	1986
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Toxicity of triethylene glycol monomethyl (TGME, CAS No. 112-35-6) and monoethyl ethers (TGEE, CAS No. 112-50-5) at 1000 mg/kg also was tested in this study. The skin effects noted for triethylene glycol butyl ether were more severe than those for TGME and TGEE.
Result	:	There were no deaths or signs of overt toxicity over the study period. There were no significant differences in body weights or food consumption between treated or control groups. 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. Mild to moderate desquamation and fissuring of skin was noted in most rabbits after 2 to 3 weeks of treatment with test material. This was confirmed microscopically and consisted of trace acanthosis and trace to moderate dermatitis. Testicular degeneration (scored as trace in severity) , occurred in one rabbit each from the TGEE and TGME-treated groups. This lesion was characterized by the presence of spermatid giant cells, focal tubular hypospermatogenesis, or cytoplasmic vacuolization. The pathologist stated that “random occurrence of this lesion was suggestive of its spontaneous nature and was not test article related. A high incidence of similar changes of spontaneous nature in normal New Zealand White rabbits has been reported by Morton et al. in Vet Pathol 23: 176-183, 1986 and Vet Pathol 23: 210-217, 1986.” 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. Therefore, the NOAEL is 1000 mg/kg/day.
Test condition	:	Rabbits were observed over a 51-52 day pretest period for clinical abnormalities. Prior to randomization, rabbits were fasted (19-23 hours), and blood samples were taken from the central ear artery for control

hematological and biochemical evaluations. Healthy rabbits (4- 4.5 months of age) were randomly divided into groups of 5 per sex. Prior to study initiation, hair was removed from the back of each rabbit with an electric clipper. Rabbits were shaved as necessary during the course of the study to prevent the test material from becoming matted in the hair and to facilitate accurate observations.

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

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

Body weights (weeks 1, 2, 3, and 4), clinical pathology parameters and organ weights (absolute and relative) were analyzed using Bartlett's test for homogeneity of variance and analysis of variance (one-way). The treatment groups were compared to the controls using the appropriate t-statistic (for equal or unequal variance). Dunnett's multiple comparison tables were used to judge the significance of the differences. Total bilirubin data was transformed to ranks and analyzed using a non-parametric test. All tests were two-tailed, with $p < 0.05$ and $p < 0.01$ as levels of significance.

Reliability : (2) valid with restrictions. Test was shorter than 28 days and only one dose was used.

Flag : Critical study for SIDS endpoint

03.10.2001 (28)

Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : dermal
Exposure period : 91 days
Frequency of treatment : 6 hr/day, 5 days/week
Post obs. period : none

Doses : 400, 1200, 4000 mg/kg bw
Control group : other:sham
NOAEL : = 4000 mg/kg bw (summary preparer); > 400 and < 1200 mg/kg bw (EPA)
Method : other
Year : 1990
GLP : yes
Test substance : other TS
Remark : 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).

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.

Result : 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.

Test condition : 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. 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 sacrifice), clinical chemistry (just prior to sacrifice), 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 using 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.

Test substance : The test substance was triethylene glycol monomethyl ether (TGME, CAS No. 112-35-6). Purity (as determined by gas chromatography) was 99.23 % at the onset of the study and 99.24% at completion of the in-life phase.

Conclusion : 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."

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint. A related test material was utilized.
03.10.2001 (17) (24)

Species : rat
Sex : male
Strain : no data
Route of admin. : drinking water
Exposure period : 30 days
Frequency of treatment :
Post obs. period :
Doses : 180, 750, 3300, 13290 mg/kg/day
Control group : yes
NOAEL : = 750 mg/kg bw
Method : other
Year : 1985
GLP : no data
Test substance : other TS
Result : Rats receiving the highest dose consumed only 25% of the amount of water as controls. All of them died within 6 to 24 days of exposure (average 13). Necropsy of these animals revealed congestion and cloudy swelling of the liver and cloudy swelling and degeneration of epithelium of the convoluted tubules of the kidneys. None of the other rats died. Rats exposed to 3300 mg/kg/d exhibited decreased weight gain, high blood urea concentrations (4/10), kidney damage (1/10), liver abnormalities (6/10). Animals exposed to 750 or 180 mg/kg/day appeared normal.
Test condition : Groups of 10 rats (90-120 g) were given doses of test material in the drinking water at concentrations of 0 (control), 0.12, 0.5, 2 and 8% for 30 days. The actual doses received were 0, 180, 750, 3300 and 13290 mg/kg/d. Water consumption and deaths were monitored daily.
Test substance : Test material was triethylene glycol monoethyl ether (CAS No. 112-50-5).
Reliability : (2) valid with restrictions. Purity of test material was not noted.
Flag : Supportive study for SIDS endpoint. A related test material was utilized.
03.10.2001 (40)

Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : drinking water
Exposure period : 91 days
Frequency of treatment : daily
Post obs. period : none
Doses : 400, 1200, 4000 mg/kg/day
Control group : yes, concurrent no treatment
NOAEL : = 400 mg/kg bw
LOAEL : = 1200 mg/kg bw
Method : other

Year : 1990
GLP : yes
Test substance : other TS
Remark : 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).

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

Result : 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 TGME 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 $\pm$ 0.3984) and 1200 mg/kg/day (3.951 $\pm$ 0.4191) versus control (3.214 $\pm$ 0.1519). Absolute liver weights of males treated with 4000 mg/kg/day were significantly greater than controls (25.926 $\pm$ 3.1591 versus 18.978 $\pm$ 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 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 those at 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.

Test condition : 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. 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 sacrificed 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).

Test substance : Test material was triethylene glycol monomethyl ether (CAS No. 112-35-6). The purity of the material was at least 98.7%.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint. A related test material was utilized.

03.10.2001 (23) (24)

Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 28 days
Frequency of treatment : daily
Post obs. period :
Doses : 25, 150, 1000 mg/kg/day
Control group : yes
NOAEL : = 150 mg/kg bw (NOEL)
Method : other
Year : 1993
GLP : yes
Test substance : other TS
Result : Food intake of males dosed with 1000 mg/kg/day was slightly reduced for first 2 weeks of treatment. Livers of all 5 males and some females dosed with 1000 mg/kg/day showed slight centrilobular hypertrophy (which was considered by the investigators to be adaptive). None of the controls exhibited this effect. There was no significant effect of treatment on liver weight. No effects on other organs (including ovaries and testes) were noted. A NOEL of 150 mg/kg/day was assigned by the investigator.

Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.

Reliability : (1) valid without restriction

Flag : Supportive study for SIDS endpoint. A related test material was utilized.

04.10.2001 (42)

5.5 GENETIC TOXICITY 'IN VITRO'

System of testing : Salmonella typhimurium; TA1535, TA1537, TA 98, TA100
Concentration : 20-5000 micrograms/plate
Cytotoxic conc. : > 5000 micrograms/plate
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 471 "Genetic Toxicology: Salmonella typhimurium Reverse Mutation Assay"
Year : 1983
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : The tests were valid, as positive controls induced at least a two-fold increase in frequency of mutations.

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

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

Test condition : Standard test: Test tubes containing 2 ml of soft agar, bacteria (0.1 ml of > = 10E8 S. typhimurium TA98, TA100, TA1535, or TA1537), test chemical (0.1 ml of test solution, positive control, or aqua dest. solvent) and either buffer or S-9 mix from Aroclor 1254-induced, male, Sprague Dawley rats (0.5 ml) were prepared. After mixing, the samples were poured onto minimal glucose agar plates within 30 seconds.

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

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

The Salmonella stains were periodically checked for deep rough character

(rfa), UV sensitivity (uvrB), and ampicillin resistance (R factor plasmid). Histidine auxotrophy was automatically checked in each experiment via the spontaneous mutation rate.

Test substance : Test material purity was 87.2%.
Reliability : (2) valid with restrictions. OECD guideline study, but only 4 strains were tested. Purity of test material is not high.
Flag : Critical study for SIDS endpoint.
03.10.2001 (4)

Type : Ames test
System of testing : S. typhimurium strains TA98, TA100, TA1535, TA1537, TA1538
Concentration : up to 5000 micrograms per plate
Cytotoxic conc. : > 5000 micrograms per plate
Metabolic activation : with and without
Result : negative
Method : other
Year : 1992
GLP : yes
Test substance : other TS
Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.
Reliability : (1) valid without restriction
Flag : Supportive study for SIDS endpoint. A related test material was utilized.
28.09.2001 (13)

Type : HGPRT assay
System of testing : Chinese hamster ovary cell
Concentration : 2000 to 5000 micrograms/plate
Cytotoxic conc. : >5000 micrograms
Metabolic activation : with and without
Result : negative
Method : other:Test Standard 40 CFR 798.5300
Year : 1990
GLP : yes
Test substance : other TS
Remark : 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).
Result : 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.
Test condition : 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, 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 10 6 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.

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6). Purity was 99.23%.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint. A related test material was utilized.
01.10.2001 (31)

Type : Chromosomal aberration test
System of testing : Chinese Hamster Ovary Cell
Concentration : up to 5000 micrograms/ml
Cytotoxic conc. : > 5000 micrograms/ml
Metabolic activation : with and without
Result : negative
Method : other
Year : 1992
GLP : yes
Test substance : other TS

Remark : The small random increases in the number of chromatid gaps and/or isogaps in one experiment with S-9, which were not dose-dependent and not different from the untreated controls were not considered to be compound-related effects by study personnel.

Result : Cells exposed to test material at concentrations up to 5000 micrograms/ml showed no increase in chromosome damage or no linear trend compared to negative controls in either experiment. The positive control induced significantly more cells with aberrations compared to the negative controls (for untreated control and for solvent control). In the first experiment with S-9 (up to 1875 micrograms/ml test material), there was no effect of treatment on the incidence of type of aberration observed. However, there was a significant difference in the number of cells with chromatid gaps and/or isogaps between the untreated control (7/200) and solvent control cultures (1/200). In the second experiment with S-9 (cells were treated with 1500, 3000 or 5000 micrograms/ml test material), there was a significant difference in the number of cells with aberrations including gaps (11/200) and cells with chromatid gaps and/or isogaps (8/200) at the 1500 micrograms/ml compared to the solvent control (2/199 and 0/199, respectively). There also was a significant increase in the number of cells with chromatid gaps and/or isogaps at the high concentration (5/200) compared to control, and between both controls (untreated control had 7/200). No linear trend was observed either by including or excluding the solvent control from the analysis. The positive control caused increases in aberrations with and without gaps compared to the solvent control in both studies.

Test condition : Cells (2 x 10E5) were incubated with medium containing the test compound or relevant controls [untreated control, solvent control and positive controls methyl methanesulphonate (20 micrograms/ml without S-9) and benzo(a)pyrene (25 micrograms/ml with S-9)] for either 3 hours in the presence of S9 mix (from Aroclor 1254-induced rat liver) or 24 hours in the absence of S9 mix. The concentrations of test material used (from 10 to 5000 micrograms/ml without S-9 and 100 to 5000 micrograms/ml with S-9) were chosen based on the results of preliminary miscibility and mitotic index studies. Duplicate cultures were prepared for each test condition. Two separate experiments were conducted using different concentrations. Metaphase cells were prepared on glass microscope slides for the analysis of chromosome aberrations 24 hours following exposure for the cultures with or without S9 mix. All slides were coded. Where possible, 200 metaphases were scored for each dose group. Only those cells showing the modal chromosome number (20) +/- 2 were analyzed for chromosome damage. Chromosome aberrations were classified according to the scheme described by Savage (J Med Genetics 12:103-122, 1976). The mitotic index of each group was assessed by counting the number of metaphases in a total of 1000 cells. Data were assessed for heterogeneity using the Fisher's exact test. The number of aberrations excluding gaps, aberrations including gaps, isogaps and/or chromatid gaps and polyploidy and/or endoreduplication of treated cells was compared to controls using the Fisher's exact test. A Cochran-Armitage trend test was carried out on the dose/response. The test was performed twice, once excluding control data and the other including the solvent control.

Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.

Conclusion : Study personnel concluded that under the test conditions, the test material did not induce chromosomal aberrations either in the presence or absence of S9 mix.

Reliability	:	(1) valid without restriction
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.
04.10.2001		(14)

Type	:	Bacterial reverse mutation assay
System of testing	:	E. coli WP2uvrA pKM101
Concentration	:	up to 5000 micrograms per plate
Cytotoxic conc.	:	> 5000 micrograms
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1992
GLP	:	yes
Test substance	:	other TS
Test substance	:	Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.
Reliability	:	(1) valid without restriction
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.
04.10.2001		(13)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	micronucleus assay
Species	:	mouse
Sex	:	male/female
Strain	:	other:CD-1(ICR)BR
Route of admin.	:	gavage
Exposure period	:	up to 72 hours
Doses	:	500, 1667, 5000 mg/kg bw
Result	:	negative
Method	:	other: Test Standard 40 CFR 798.5395
Year	:	1990
GLP	:	yes
Test substance	:	other TS
Remark	:	The test was valid as positive controls had significantly more MN-PCE than controls (62.2 in males and 34.6 in females).
Result	:	One female dose with 1667 mg/kg test material died prior to scheduled sacrifice. 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).
Test condition	:	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/sacrifice time) were sacrificed by cervical dislocation 24, 48 and 72 hours after treatment. Mice (5/sex) treated with 120 mg/kg cyclophosphamide and sacrificed after 24 hours of treatment served as positive controls.

Bone marrow samples were obtained from both femurs at sacrifice. 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.

Test substance : Test material was triethylene glycol monomethyl ether (CAS No. 112-35-6). Purity was 99.23%.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint. A related test material was utilized.

03.10.2001 (32)

5.7 CARCINOGENITY

5.8 TOXICITY TO REPRODUCTION

Type	:	other:91 day oral toxicity study
Species	:	rat
Sex	:	male
Strain	:	Sprague-Dawley
Route of admin.	:	drinking water
Exposure period	:	91 days
Frequency of treatment	:	daily
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
Doses	:	400, 1200, 4000 mg/kg/day
Control group	:	yes
NOAEL Parental	:	> 400 and < 1200 mg/kg bw
Method	:	other
Year	:	1990
GLP	:	yes
Test substance	:	other TS
Remark	:	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 2-ME 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 NOAEL listed is for reproductive organ toxicity. Additional details of the study are shown in section 5.4. 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).

Result : 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.

Test condition : Rats were treated with triethylene glycol monomethyl ether (TGME) for 90 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 (including testes) were recorded at necropsy. Microscopic analyses of testes and other organs were performed.

Test substance : Test material was triethylene glycol monomethyl ether (CAS No. 112-35-6). The purity of the material was at least 98.7%.

Reliability : (2) valid with restrictions. Effect on mating was not characterized.

Flag : Critical study for SIDS endpoint. A related test material was utilized.

03.10.2001 (23) (24)

Type : other:91 day dermal toxicity study
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : dermal
Exposure period : 91 days
Frequency of treatment : 6 hr/day, 5 days/week
Premating exposure period
Male :
Female :
Duration of test : 91 days
Doses : 400, 1200, 4000 mg/kg bw
Control group : other:sham
NOAEL Parental : = 4000 mg/kg bw (summary preparer); > 400 and < 1200 mg/kg bw (EPA)

Method	:	other
Year	:	1990
GLP	:	yes
Test substance	:	other TS
Remark	:	Additional details for this study can be found in Section 5.4. 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 semiferous 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 %).
Result	:	There were no indications of systemic toxicity at any dose. Mean body weight and food consumption were comparable to controls throughout the study. 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.
Test condition	:	Triethylene glycol monomethyl ether (TGME) was administered dermally to 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. Parameters evaluated throughout the study included clinical and ophthalmic observations, dermal irritation, body weight, food consumption, clinical pathology, and estrous cyclicity (daily vaginal smears during study weeks 12 and 13). 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.
Test substance	:	Test material was triethylene glycol monomethyl ether (TGME, CAS No. 112-35-6). Purity of TGME (as determined by gas chromatography) was 99.23 % at the onset of the study and 99.24% at completion of the in-life phase.
Conclusion	:	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."

Reliability : (2) valid with restrictions. Effect on mating was not characterized.
Flag : Critical study for SIDS endpoint. A related test material was utilized.
03.10.2001 (17) (24)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	other: Alpk:AP (Wistar)
Route of admin.	:	gavage
Exposure period	:	days 7-16 of gestation
Frequency of treatment	:	daily
Duration of test	:	until Day 5 of parturition
Doses	:	250 and 1000 mg/kg
Control group	:	other: both negative (water) and positive (50 and 250 mg/kg ethylene glycol monomethyl ether)
NOAEL Maternalt.	:	= 1000 mg/kg bw
NOAEL Teratogen	:	= 1000 mg/kg bw
Method	:	other: modified Chernoff-Kavlok assay (Schuler RL et al. Environ Health Persp 57:141-146. 1984)
Year	:	1986
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Triethylene glycol monomethyl ether and triethylene glycol monoethyl ether also were not teratogenic at 1000 mg/kg in this study. The EPA also 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). The NOAEL listed under teratogenicity is the NOAEL for developmental toxicity.
Result	:	Maternal Data: Dams dosed with either dose of TGBE 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.

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 TGBE. No litters were produced in either EGME group (although implantation sites were present in all animals). There were no effects on

any litter parameter measured in rats treated with either dose of TGBE.

At the dose levels tested (250 or 1000 mg/kg/day), TGBE was not embryotoxic or teratogenic (in contrast to EGME).

Test condition : 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 monobutyl ether (TGBE), 1000 mg/kg TGBE, 50 mg/kg ethylene glycol monomethyl ether (EGME), or 250 mg/kg EGME. Dose levels of TGBE 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 that 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 that 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

Test substance : Purity of triethylene glycol monobutyl ether (TGBE) was 96.91% according to manufacturer (Olin Corporation).

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint.

03.10.2001 (30) (46)

5.10 OTHER RELEVANT INFORMATION

Type : absorption

Test substance : as prescribed by 1.1 – 1.4

Remark : Absorption of ethylene glycol monomethyl ether (EGME), triethylene glycol monomethyl ether (TGME), and triethylene glycol monoethyl ether (TGEE) also were tested in this study. The rate of absorption of EGME was220 micrograms/cm2/hr. The rate of absorption of TGME was 34.0 micrograms/cm2/hr and the mean damage ratio was 3.36 (small increase in permeability). The rate of absorption of TGEE was 24.1 micrograms/ cm2/hr and the mean damage ratio was 1.37 (no increase in permeability).

Result : The mean steady state of absorption for triethylene glycol monobutyl ether was 22.2 micrograms/cm2/hr (SD +/- 8.59), which was 100-fold less than that of ethylene glycol monomethyl ether. Test material did not increase permeability of the membrane (damage ratio of 1.26).

Test condition : 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 monobutyl ether 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.

Test substance : Purity of test material (POLYSOLV-TB, triethylene glycol monobutyl ether) was 96.91%.

Reliability : (1) valid without restriction
Flag : Critical study for non-required endpoint
26.09.2001 (45)

Type : metabolism
Remark : The test material was [U-14C-ethylene]diethylene glycol butyl ether acetate (U-14C-DGBA). The specific activity was 0.951 microcuries/ micromole). The purity of the test material was 95%. Impurities detected included 2-(2-ethoxyethoxy)ethyl acetate, diethyl phthalate and DGBA containing a methyl substituent. 14C-DGBA accounted for 97.1% of the radioactivity of the preparation. Each dose solution was analyzed by GC with radiochemical detection to confirm the presence of DGBA, and by liquid scintillation spectrometry (LSS) to determine the concentration of radioactivity in the dose (and subsequently the radioactivity administered to each rat).

Male Sprague-Dawley rats were given a single oral dose of 200 or 2000 mg/kg (U-14C-DGBA). Animals were allowed free access to food and water (except that food was withdrawn for a 4 hours period immediately after dosing). Urine and feces were collected at intervals for up to 72 hours. Expired air was collected continuously. The rats were killed at this time and major tissues and organs were taken for analysis of 14C. Urine samples were analyzed by HPLC equipped with a radioactivity monitor. The presence of conjugated metabolites of DGBA in urine was investigated by selective enzymic hydrolysis and by acid hydrolysis. Fecal and tissue samples were homogenized and the radioactivity in the supernatant and combusted pellet was counted by LSS. Samples of femoral bone were digested in perchloric acid and the digest was assayed by LSS. Carcasses were homogenized in acetone, and filtered. Radioactivity in combusted residue and the filtrate was analyzed by LSS. Volatile organics in expired air were trapped on silica gel, extracted with methanol and assayed for radioactivity by LSS.

Approximately 80% of each dose was eliminated in the urine within 24 hours. Approximately 5% of the radioactivity was recovered as 14CO2 in the expired air. Minor amounts of radioactivity were recovered in feces (2-3%). Approximately 4% remained in the tissues and animal at termination (72 hours).

The major urinary metabolite was identified as 2-(2-butoxyethoxy)-acetic acid (more than 50% of the radioactivity for both doses). Diethylene glycol and an unknown metabolite with a molecular weight of 178 (tentatively identified as C8H18O4) together accounted for 21-31% of the radioactivity in urine. No unchanged DGBA or diethylene glycol monobutyl ether was detected in the urine of the rats at either dose level.

Reliability : (1) valid without restriction
31.01.2002 (18)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

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(4) BASF AG. 1989. Department of Toxicology, Project No. 40M0573/884365, Dated February 24, 1989.

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(6) BASF AG, Labor Oekologie; unveroeffentlichte Untersuchung (Unpublished study)

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(24) 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.

(25) HUELS AG. 1993. unveroeffentlichte Untersuchung (Unpublished study) Mitteilung vom (Communication from) 23.03.1993.

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Tetraethylene Glycol Methyl Ether
CAS No. 23783-42-8

SIDS Dossier (including robust summaries)

Existing Chemical : ID: 23783-42-8
CAS No. : 23783-42-8
EINECS Name : 3,6,9,12-tetraoxotridecanol
EINECS No. : 245-883-5
TSCA Name : 2,5,8,11-Tetraoxatridecan-13-ol
Molecular Formula : C9H20O5

Producer related Part
Company : American Chemistry Council's Ethylene Glycol Ether Panel
CEFIC's Oxygenated Solvents Producers Association
Kyowa Hakko Kogyo Co., Ltd.
Mitsubishi Chemical Corporation
NIPPON NYUKAZAI CO.LTD
Creation date : 29.07.2001

Substance related Part
Company : American Chemistry Council's Ethylene Glycol Ether Panel
CEFIC's Oxygenated Solvents Producers Association
Kyowa Hakko Kogyo Co., Ltd.
Mitsubishi Chemical Corporation
NIPPON NYUKAZAI CO.LTD
Creation date : 29.07.2001

Printing date : 02.12.2002
Revision date : 02.12.2002
Date of last Update : 02.12.2002

Number of Pages : 70

Chapter (profile) : Chapter: 1, 2, 3, 4, 5

1.0.1 OECD AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

Substance type : organic
Physical status : liquid
Remark : TetraGME is available only as a component of the mixture described below
18.11.02

Composition of High Boiling Point Methyl Glycol Stream

Chemical	CAS #	**Range (Weight %)**
Triethylene glycol methyl ether	112-35-6	10 - 75%
Tetraethylene glycol methyl ether	23783-42-8	4 - 80%
Pentaethylene glycol methyl ether	23778-52-1	8 - 40%
Hexaethylene glycol methyl ether	23601-40-3	1 - 5%
Ethylene glycol	107-21-1	<1%
Diethylene glycol	111-46-6	0 - 5%
Triethylene glycol	112-27-6	0 - 5%

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

2,5,8,11-Tetraoxatridecan-13-ol

2,5,8,11-Tetraoxatridecan-13-ol (7CI, 8CI, 9CI)

3,6,9,12-Tetraoxatridecan-1-ol

3,6,9,12-Tetraoxatridecanol

Methoxytetraethylene glycol

Methyltetraglycol

Methyltetraglykol

Tetraethylene glycol methyl ether

Tetraethylene glycol monomethyl ether

Tetraethyleneglycol (mono)methyl ether

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

Type	:	industrial
Category	:	Basic industry: basic chemicals
Remark	:	The principal global use is as a component in hydraulic brake fluids.
Reliability	:	(2) valid with restrictions. Original reference was not available. Information came from IUCLID data set produced by European Chemicals Bureau, creation date 11-FEB-2000.

15.07.2001

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.9 SOURCE OF EXPOSURE

Remark	:	Spillage during car maintenance and car repair activities; road accidents.
Source	:	Shell Nederland Chemie B.V. Rotterdam EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

Classified by	:	other: Hoechst AG
Labelled by	:	other: Hoechst AG
Class of danger	:	0 (generally not water polluting)
Remark	:	Einstufung bezieht sich auf das Homologengemisch mit 68 % MTeG (siehe 1.1) [Classification based on a homologous mixture with 68% methylated tetraethylene glycol, see 1.1].

(26) (28)

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

Classified by	:	other: Hoechst AG
Labelled by	:	other: Hoechst AG
Number	:	3.1.7 (organic substances)
Class of danger	:	III

(25) (28)

1.15 ADDITIONAL REMARKS

Remark	:	DISPOSAL OPTIONS Dispose to licensed disposal contractor. Recover or recycle if possible; otherwise incinerate in licensed waste incineration plant.
Source	:	Shell Nederland Chemie B.V. Rotterdam EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	= -39 ° C
Sublimation	:	
Method	:	other: DIN 51583
Year	:	1993
GLP	:	no data
Test substance	:	as prescribed by 1.1- 1.4
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Critical study for SIDS endpoint

(28)

2.2 BOILING POINT

Value	:	280 - 350 ° C
Decomposition	:	
Method	:	other: DIN 53171
Year	:	1993
GLP	:	no data
Test substance	:	as prescribed by 1.1- 1.4
Remark	:	unversetzt destillierbar [Can be distilled without decomposition]
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Critical study for SIDS endpoint

(28)

2.3 DENSITY

Type	:	density
Value	:	= 1.06 g/cm3 at 20° C
Method	:	other: DIN 51757
Year	:	1993
GLP	:	no data
Test substance	:	as prescribed by 1.1- 1.4
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Critical study for non-required endpoint

(28)

Type	:	density
Value	:	= 1.091 g/cm3 at 20° C
Method	:	other
Year	:	2000

GLP : no data
Test substance : Test material (CARBOWAX MPEG-350; CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability : (2) valid with restrictions. Original data from which MSDS was written were not available.
Flag : Supportive study for non-required endpoint. A related material was tested.
16.10.2001 (11)

Type : density
Value : = 1.06 g/cm3 at 60° F
Method : other
Year : 2000
GLP : no data
Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.
Reliability : (2) valid with restrictions. Original data from which MSDS was written were not available.
Flag : Supportive study for non-required endpoint. A related material was tested.
16.10.2001 (40)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : < .1 hPa at 20° C
Method : other
Year : 1993
GLP : no data
Test substance : as prescribed by 1.1- 1.4

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag : Critical study for SIDS endpoint
(28)

Value : .0000684 hPa at 25° C
Method : other (calculated)
Year : 2002
GLP : no
Test substance : as prescribed by 1.1- 1.4
Remark : Vapor pressure is estimated using the EPIWIN/MPBPWIN model (v1.40). This model uses algorithmic equations (methods of Antoine, Grain and Mackay) to calculate vapor pressure with inputs of melting and boiling

points. An average vapor pressure is obtained from the three methods.
Reliability : (2) valid with restrictions. Data were obtained by modeling.
Flag : Supportive study for SIDS endpoint
14.10.2001

Value : < 0.01 mm Hg at 20° C
Method : other
Year : 2000
GLP : no data
Test substance : Test material (CARBOWAX MPEG-350; CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability : (2)valid with restrictions. Original data from which MSDS was written were not available.
Flag : Supportive study for SIDS endpoint. A related material was tested.
16.10.2001 (11)

Value : < 0.01 mm Hg
Method : other
Year : 2000
GLP : no data
Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.
Reliability : (2)valid with restrictions. Original data from which MSDS was written were not available.
Flag : Supportive study for SIDS endpoint. A related material was tested.
16.10.2001 (40)

2.5 PARTITION COEFFICIENT

Log pow : = -1.73 at ° C
Method other (calculated)
Year : 2002
GLP : no
Test substance : as prescribed by 1.1- 1.4
Remark : The partition coefficient was estimated using the EPIWIN/KOWWIN Program (v1.66). This program sums up contributions to log Kow from each molecular fragment or functional group in the molecular structure. Individual fragment contributions have been established that have been demonstrated to correlate well with measured data.
Reliability : (2) valid with restrictions. Data were obtained by modeling.
Flag : Critical study for SIDS endpoint
14.10.2001

Log pow : = -.6 at ° C
Method other (calculated): Medchem Software CLOGP3, Release 3.42, Pomona College, Clermont CA

Year : 1986
GLP : not applicable
Test substance : as prescribed by 1.1- 1.4

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag : Supportive study for SIDS endpoint

(27)

2.6.1 WATER SOLUBILITY

Value : ca. 999999 mg/l at 25 ° C
Qualitative :
Pka : at 25 ° C
PH : ca. 7 at and ° C
Method : other: calculated
Year : 2002
GLP : no
Test substance : as prescribed by 1.1- 1.4
Remark : Water solubility is estimated using the EPIWIN/WSKOW Program (v1.40). This program calculates water solubility using an algorithm with Log Kow and molecular weight as inputs. The algorithm used has been demonstrated to give values that correlate reasonably well with measured data
Reliability : (2) valid with restrictions. Data were obtained by modeling.
Flag : Critical study for SIDS endpoint
14.10.2001

Value : at 20 ° C
Qualitative : miscible
Method other
Year : 1993
GLP : no data
Test substance : as prescribed by 1.1- 1.4
Pka : at 25 ° C
PH : at and ° C
Remark : pH-Wert: neutral

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag : Supportive study for SIDS endpoint

(28)

Value : 100% at 20° C
Method : other
Year : 2000
GLP : no data
Test substance : Test material (CARBOWAX MPEG-350; CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol

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

Reliability : (2) valid with restrictions. Original data from which MSDS was written were not available.

Flag : Supportive study for SIDS endpoint. A related material was tested.

16.10.2001 (11)

Qualitative : soluble
Method : other
Year : 2000
GLP : no data
Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.

Reliability : (2) valid with restrictions. Original data from which MSDS was written were not available.

Flag : Supportive study for SIDS endpoint. A related material was tested.

16.10.2001 (40)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : = 161 ° C
Type : closed cup
Method : other: DIN 51758
Year : 1993
GLP : no data
Test substance : as prescribed by 1.1- 1.4

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.

Flag : Critical study for non-required endpoint

(28)

2.8 AUTO FLAMMABILITY

Value : = 325 ° C at
Method : other: DIN 51794
Year : 1993
GLP : no data
Test substance : as prescribed by 1.1- 1.4
Remark : Zuendtemperatur [Autoignition temperature]

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.

Flag : Critical study for non-required endpoint

(28)

2.9 FLAMMABILITY

Year	:	2000
Remark	:	Material will not burn unless preheated
Test substance	:	Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.
Reliability	:	(4) not assignable. Original data from which MSDS was written were not available.
Flag	:	Critical study for non-required endpoint. A related material was tested.

16.10.2001 (40)

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	other
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Direct photolysis		
Halflife t1/2	:	= 2.4 hour(s)
Degradation	:	% after
Quantum yield	:	
Deg. Product	:	
Method	:	other (calculated)
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1- 1.4
Result	:	The hydroxyl radical rate constant was calculated to be 54.0 E-12 cm3/molecule-sec.
Source	:	The photodegradation half life and hydroxyl radical rate constant were calculated using the EPIWIN AOP (v1.90) program, based on the molecular structure. The program assumes that the hydroxyl radical will abstract a hydrogen atom from a carbon-hydrogen linkage, and considers the contributions of each carbon-hydrogen bond in the molecule as well as the relative probability that a hydrogen atom will be abstracted from each given carbon-hydrogen bond, in arriving at an overall rate constant. This program is based on the work of Atkinson, et al, who has demonstrated that this approach calculates rate constants for relatively simple, common organic compounds that correlate well with measured values. The photodegradation half-life assumes pseudo first order kinetics with a constant specified concentration of hydroxyl radical.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint

04.10.2001

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	500000 molecule/cm3
Rate constant	:	= .000000000051 cm3/(molecule*sec)
Degradation	:	= 50 % after 7.7 hour(s)
Deg. Product	:	
Method	:	other (calculated): Atkinson
Year	:	1988
GLP	:	not applicable
Test Substance	:	as prescribed by 1.1- 1.4
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Supportive study for SIDS endpoint

(25)

Type	:	air
Light source	:	

Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	1500000 molecule/cm3
Rate constant	:	= .000000507494 cm3/(molecule*sec)
Degradation	:	ca. 50 % after 2.5 hour(s)
Deg. Product	:	
Method	:	other (calculated): ATMOSPHERIC OXIDATION PROGRAM, Version 1.51 vom 13.03.94, Syracuse Research Corporation, according to Atkinson (1987 and 1988)
Year	:	1994
GLP	:	not applicable
Test substance	:	as prescribed by 1.1- 1.4
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Supportive study for SIDS endpoint

(29)

3.1.2 STABILITY IN WATER

Deg. Product	:	
Method	:	other
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1- 1.4
Remark	:	An attempt was made to estimate stability to hydrolysis using EPIWIN/ HYDROWIN (vl.67). This program can not estimate a hydrolysis rate constant for the tetraethylene glycol methyl ether molecular structure entered. It is generally recognized that organic ether bonds are resistant to hydrolysis at neutral pH in the absence of catalysts and under ambient conditions.
Source	:	PCA Services, Inc.
Reliability	:	(3) invalid

04.10.2001

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	volatility
Media	:	water - air
Air (level III)	:	2.45 E-9
Water (level III)	:	45.3
Soil (level III)	:	54.6
Biota (level II / III)	:	
Soil (level II / III)	:	
Method	:	other
Year	:	2002

Test substance	:	as prescribed by 1.1- 1.4
Remarks	:	Measured values used as program inputs were vapor pressure (0.075 mm Hg), melting point (-39 degrees C), and boiling point (315 degrees C).
Result	:	A mass amount of 0.0755% is estimated for sediment using the McKay Level III Fugacity model as performed by EPIWIN. The half-lives in hours are air (4.75), water (360), soil (360) and sediment (1440). The EPIWIN HENRY (v3.10) program was used to calculate a Henry's Law Constant of 1.57E-013 atm-m3/mole (Bond Estimate) and 7.56E-017 atm-m3/mole (Group Estimate). The EPIWIN PCKOC (v1.66) program was used to estimate a Koc (soil-sediment partition constant) of 10. The EPIWIN BCF (v2.14) program estimates a BCF (bioconcentration factor) of 3.162 and a log BCF of 0.500.
Source	:	The EPIWIN program was used to perform the McKay Level III Fugacity modeling for this compound.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint

04.10.2001 (33)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	
Contact time	:	
Degradation	:	= 71% after 20 day
Result	:	other: biodegradable
Deg. Product	:	no
Method	:	other: Biochemical oxygen demand method published in "Standard Methods for the Examination of Water and Wastewater", 16th Edition, Am. Public Health Association, 1985
Year	:	1987
GLP	:	no data
Test substance	:	other TS
Remark	:	Biological oxygen demand (BOD) of triethylene glycol monoethyl ether (TGEE, CAS No. 112-50-5) and triethylene glycol monobutyl ether (TGBE, CAS No. 143-22-6) were also tested in this study. The BOD of TGME was similar to that of TGEE, and greater than that of TGBE. The concentrations of test material and bacteria used in the test were not listed in the report.
Result	:	The calculated theoretical oxygen demand was 1.75 mg/mg. After 5, 10 and 20 days of incubation, the percent biooxidation was 29, 33, and 71%.
Test condition	:	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 2BOD 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.
Test substance	:	Test material was triethylene glycol monomethyl ether (TGME, CAS No.

112-35-6)
Reliability : (2) valid with restrictions. Purity of test material was not noted.
Flag : Supportive study for SIDS endpoint. A related test material was utilized.
02.10.2001 (46)

Type : aerobic
Inoculum : other: Belebtschlamm, industriell (Werksklaeranlage Gendorf)
Concentration : 572mg/l related to Test substance
related to
Contact time :
Degradation : = 99 % after 8 day
Result :
Kinetic of test substance : 3 hour(s) = 10 **%**

1 day = 19 **%**
3 day = 29 **%**
5 day = 52 **%**
7 day = 91%
Deg. Product :
Method : OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year : 1989
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Test condition : CSB = Eliminierung (Zeitreihenwerte gegen Wert der Ausgangskonzentration); Eliminierung durch nichtbiologische Vorgaenge ca. 10 %
Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag : Critical study for SIDS endpoint
02.10.2001 (24)

Type : aerobic
Inoculum : unknown
Concentration : 30 mg/l related to Test Substance
Degradation : = 24-85 % degradation after 28 days
Result :
Method : OECD 302 C MITI II test
Year : 1992
GLP : no data
Test substance : Polyethylene Glycol monomethyl ether (n= 4-5)
Remark : Inoculum concentration: 100 mg/l
Degradation curve was on the upward trend at the end of the test.
Reliability : (4) not assignable. The original reference was not available.
02.10.2001 (9)

3.6 BOD5, COD OR BOD5/COD RATIO

Year : 2001
GLP : no data
Test substance : Tetraethylene glycol monobutyl ether
Remark : ThOD= 2.05 g O2/g substance.

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a

reliability rating of 4 for this submission since it was not reviewed.

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	> 10000
Method	:	other: Standard Methods for the Examination of Water and Wastewater, 13th Ed., 1971
Year	:	1974
GLP	:	no data
Test substance	:	other TS
Remark	:	Toxicity of triethylene glycol monoethyl ether (TGEE, CAS No. 112-50-5) and of triethylene glycol monobutyl ether (TGBE, CAS No. 143-22-6) were also tested in this study. The LC50 values for TGEE and TGBE were >10000 and 2400 mg/l, respectively.
Result	:	The temperature of the water ranged from 71 to 76 degrees, 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. The LC50 value was higher than the highest concentration used (10000 mg/l).
Test condition	:	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.
Test substance	:	Test material was triethylene glycol monomethyl ether (TGME).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

02.10.2001 (45)

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	> 10000
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1988
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Critical study for SIDS endpoint

02.10.2001 (23)

Type	:	
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no

LC50	:	> 10000
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1988
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Critical study for SIDS endpoint

02.10.2001 (23)

Type	:	
Exposure period	:	14 days
Unit	:	mg/l
LC50	:	496,000
Method	:	estimated using EPIWIN ECOSAR
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remarks	:	Values used as program inputs were Log Kow (-1.73),
Reliability	:	(2) Valid with restrictions. Study is a model estimation.

Type	:	
Species	:	Fathead minnow
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no data
LC50	:	> 10000
Method	:	unknown
Year	:	unknown
GLP	:	no data
Test substance	:	Test material (CARBOWAX MPEG-350; CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(2) valid with restrictions. Original data from which MSDS was written were not available.
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

04.10.2001 (11)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	> 10000
Method	:	other: test practices followed those recommended by EPA and ASTM
Year	:	1987
GLP	:	no data
Test substance	:	other TS

Remark	:	Toxicity of triethylene glycol monoethyl ether (TGEE, CAS No. 112-50-5) and of triethylene glycol monobutyl ether (TGBE, CAS No. 143-22-6) were also tested in this study. The LC50 values for TGEE and TGBE were >10000 and 2210 mg/l, respectively.
Result	:	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 (respectively). The LC50 value was higher than the highest concentration used (10000 mg/l).
Test condition	:	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 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. Mortalities were recorded at 24 and 48 hours.
Test substance	:	Test substance was triethylene glycol monomethyl ether (CAS # 112-35-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Critical study for SIDS endpoint. A related test material was utilized.

02.10.2001 (46)

Type	:	
Exposure period	:	48 hours
Unit	:	mg/l
LC50	:	no value given; no toxicity log Kow cutoff
Method	:	estimated using EPIWIN ECOSAR
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remarks	:	Values used as program inputs were LogKow (-1.73)
Reliability	:	(4) not assignable. No value determined. Study is a model estimation.

Type	:	unknown
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	> 10000
Method	:	unknown
Year	:	unknown
GLP	:	no data
Test substance	:	Test material (CARBOWAX MPEG-350; CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(2) valid with restrictions. Original data from which MSDS was written were not available.
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

16.10.2001 (11)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC50	:	> 500
EC20	:	= 270
EC90	:	> 500
Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	Test substance was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Result	:	The EC20 value at 24, 48, and 72 hours was 235.7, 235.4, and 267.1 mg/l. The EC50 value was greater than the highest concentration tested (500 mg/l). At time 0, fluorescence values ranged from 94.37 % of control for cells treated with 7.812 and 31/25 mg/l to 103.09 % of control for cells treated with 500 mg/l. The fluorescence values for cells treated with all concentrations except 125 (86.08%) and 250 mg/l (79.21%) were greater than 90% at 24 hours. At 48 hours, cells treated with 250 or 500 mg/l began to exhibit slightly lower fluorescence values than control. At 72 hours, values for cells treated with 250 or 500 mg/l were 80.3% and 75.91% of control, respectively. Most values for the 4 replicates at each concentration varied by < = 5%. However, at 48 hours, variance of values for concentrations greater than or equal to 250 mg/l ranged from 5-10%.
Test condition	:	A SAG 86.81 culture of Scenedesmus subspicatus (10,000 cells/ml) was maintained in OECD medium at 20 degrees C. Ten ml of cells in suspension was treated with 0 (control), 7.812, 15.625, 31.25, 62.5, 125, 250 or 500 mg/l test material in quadruplicate. Fluorescence of vials containing treated cells was determined 0, 24, 48 and 72 hours after treatment in a fluorimeter with a gain setting of 1. Fluorescence of 2 blank vials containing test material (at each concentration) and medium without cells was subtracted from values obtained for test vials. The values for the four tests were averaged and a standard deviation was calculated. The average fluorescence value of each concentration was presented as a percentage of control values.
Reliability	:	(2) valid with restrictions. Test material purity is unknown. Details about study conduct are lacking.
Flag	:	Critical study for SIDS endpoint. A related test material was used

03.10.2001 (1)

Type	:	
Exposure period	:	96 hours
Unit	:	mg/l
EC50	:	no value given; no toxicity log Kow cutoff
Method	:	estimated using EPIWIN ECOSAR
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 – 1.4
Remarks	:	Values used as program inputs were LogKow (-1.73)

Reliability	:	(4) not assignable. No value estimated. Study is a model estimation.

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC50	:	> 500
EC20	:	> 500
EC90	:	> 500
Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	Test substance was triethylene glycol monomethyl ether (CAS No. 112-35-6).
Remark	:	It is assumed that the test conditions were very similar to those described above for triethylene glycol monobutyl ether (CAS No. 143-22-6) since the test was conducted by the same laboratory at approximately the same time.
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced by the European Chemicals Bureau. According to the OECD Secretariat, this study should be assigned a reliability rating of 4 (not assignable) for this submission (since it was not reviewed).
Flag	:	Supportive study for SIDS endpoint. A related test material was used.

03.10.2001 (2)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	other bacteria: sewer microorganisms
Exposure period	:	16 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
IC50	:	> 5000
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	other TS Toxicity of triethylene glycol monoethyl ether (TGEE, CAS No. 112-50-5) and of triethylene glycol monobutyl ether (TGBE, CAS No. 143-22-6) also were tested in this study. The LD50 values for TGEE and TGBE were >10000 and >5000 mg/l, respectively.
Test condition	:	Selected concentrations (not listed) were incubated for 16 hours at 23 degrees C on a shaker table in the presence of nutrients, buffer, growth substrate, and sewer-microorganisms. Toxicity was indicated when the resulting turbidity was at (or less than) 50% of the control (IC50). Details of the test are published in: Alsop et al., "Bacterial Growth Inhibition Tests", J. Water Pollution Control Federation, Vol 52: No. 10, October, 1980.
Test substance	:	Test substance was triethylene glycol monomethyl ether (CAS No. 112-35-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint. A related test material was utilized.

02.10.2001 (46)

Type	:	aquatic
Species	:	activated sludge

Exposure period	:	3 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC0	:	> 12500
Method	:	OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year	:	1989
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Critical study for non-required endpoint

02.10.2001 (24)

Type	:	aquatic
Species	:	anaerobic bact. from a domestic water treatment plant
Exposure period	:	24 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
SG	:	ca. 3000
Method	:	ETAD Fermentation tube method "Determination of damage to effluent bacteria by the Fermentation Tube Method"
Year	:	1985
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Critical study for non-required endpoint

02.10.2001 (24)

Type	:	unknown
Species	:	unknown
Exposure period	:	18 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
IC50	:	> 5000
Method	:	unknown
Year	:	unknown
GLP	:	no data
Test substance	:	Test material (CARBOWAX MPEG-350; CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(2) valid with restrictions. Original data from which MSDS was written were not available.
Flag	:	Supportive study for non-required endpoint. A related test material was utilized.

02.10.2001 (11)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	other:Carworth Farms-Nelson
Sex	:	male
Number of animals	:	15
Vehicle	:	
Value	:	= 11300 mg/kg bw
Method	:	other
Year	:	1958
GLP	:	no data
Test substance	:	other TS
Result	:	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. The LD50 value was 11.3 ml/kg.
Test condition	:	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.
Test substance	:	Test material was triethylene glycol monomethyl ether (CAS No. 112-35-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized

01.10.2001 (8)

Type	:	LD50
Species	:	rat
Strain	:	other:Carworth-Wistar
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 11800 mg/kg bw
Method	:	other
Year	:	1962
GLP	:	no data
Test substance	:	other TS
Result	:	The LD50 was 11.3 ml/kg (11.8 g/kg)
Test condition	:	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).
Test substance	:	Test material was triethylene glycol monomethyl ether (CAS No. 112-35-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized

01.10.2001 (41)

Type	:	LD50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	22
Vehicle	:	
Value	:	> 16 ml/kg bw
Method	:	other
Year	:	1988

GLP	:	no data
Test substance	:	other TS
Result	:	None of the animals treated with any dose of test material died. Animals gained weight over the course of the study and had normal pathology.
Test condition	:	Rats (5/sex/dose) received 8.0 or 16.0 ml/kg test material by stomach intubation. Two male rats were also dosed with 4.0 ml/kg. Doses were varied by adjusting the volume of test material or its dilution. Rats were fasted overnight before dosing. Male and female rats weighed approximately 250 and 200 g at study initiation (respectively). Animals were weighed before dosing and at days 7 and 14 after dosing. At death or sacrifice, each animal was subjected to gross pathologic evaluation.
Test substance	:	Test material (CARBOWAX MPEG-350; CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(1) valid without restriction. Study was conducted in a robust manner.
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized

02.10.2001 (38)

Type	:	LD50
Species	:	rat
Strain	:	other:albino
Sex	:	male
Number of animals	:	12
Vehicle	:	
Value	:	= 22 ml/kg bw
Method	:	other
Year	:	1947
GLP	:	no data
Test substance	:	other TS
Result	:	All animals dosed with 50 ml/kg died within 1 day. None of the rats dosed with 10 ml/kg died. Animals dosed with 10 ml/kg gained from 23 to 68 grams over 14 days. The LD50 was estimated to be 22 ml/kg (method of extrapolation not given).
Test condition	:	Groups of 6 rats (91-106 g) were dosed with 10 ml/kg (approximately 1 ml) or 50 ml/kg (approximately 4.7-5.3 ml) undiluted test material by stomach tube. Body weight gain and deaths were observed over a period of 14 days.
Test substance	:	methoxy polyethylene glycol of approximately 350 molecular weight
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized

02.10.2001 (7)

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	> 15000 mg/kg bw
Method	:	other: Interne Richtlinie der Hoechst AG [Internal Hoechst protocol].
Year	:	1977
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Critical study for SIDS endpoint
02.10.2001		(19)

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	> 2000 mg/kg bw
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1988
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Critical study for SIDS endpoint
02.10.2001		(21)

Type	:	LD50
Species	:	rat
Strain	:	Fischer 344
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Value	:	> 5000 mg/kg bw
Method	:	other
Year	:	1992
GLP	:	yes
Test substance	:	other TS
Test substance	:	Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives
Reliability	:	(1) valid without restriction
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.
04.10.2001		(12)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other
Species	:	rat
Strain	:	other: Carworth-Wistar
Sex	:	female
Number of animals	:	6
Vehicle	:	
Exposure time	:	8 hour(s)
Method	:	other

Year	:	1958
GLP	:	no data
Test substance	:	other TS
Result	:	All animals survived an 8-hr exposure period to concentrated vapor and had normal weight gains.
Test condition	:	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 the 14-day observation period.
Test substance	:	The test substance was triethylene glycol monomethyl ether (CAS 112-35-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

28.09.2001 (8) (41)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	
Vehicle	:	
Value	:	= 7400 mg/kg bw
Method	:	other
Year	:	1958
GLP	:	no data
Test substance	:	other TS
Result	:	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. The LD50 value was 7.13 ml/kg (7.4 g/kg).
Test condition	:	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).
Test substance	:	The test substance was triethylene glycol monomethyl ether (CAS 112-35-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Critical study for SIDS endpoint. A related test material was utilized.

02.10.2001 (8) (41)

Type	:	LD50
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	10

Vehicle	:	
Value	:	> 16 ml/kg bw
Method	:	other
Year	:	1988
GLP	:	no data
Test substance	:	other TS
Result	:	No animals died during the course of the study. No signs of systemic toxicity or irritation were noted.
Test condition	:	Five rabbits of each sex (weighing between 2 and 3 kg) were subjected to 24 hours of contact with the test material (16 ml/kg) , which was retained under impervious sheeting on the clipped, intact skin of the trunk. If necessary, gauze was wrapped around the trunk over the sample to prevent leakage. Bandaging tape was wrapped over the impervious sheeting. Excess fluid was removed after the contact period to diminish ingestion. Body weights were determined before and 7 and 14 days following test material application. Deaths were monitored for 14 days.
Test substance	:	The test material (CARBOWAX MPEG-350, CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), and 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(1) valid without restriction. Study was conducted in a robust manner.
Flag	:	Critical study for SIDS endpoint. A related test material was utilized.

02.10.2001 (38)

Type	:	LD50
Species	:	rat
Strain	:	Fischer 344
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Value	:	> 2000 mg/kg bw
Method	:	other
Year	:	1992
GLP	:	yes
Test substance	:	other TS
Test substance	:	Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives
Reliability	:	(1) valid without restriction
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

04.10.2001 (12)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	other: toxic dose
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male
Number of animals	:	6

Vehicle	:	
Route of admin.	:	i.v.
Exposure time	:	
Value	:	= 2200 mg/kg bw
Method	:	other
Year	:	1997
GLP	:	yes
Test substance	:	other TS
Result	:	There were no overt signs of toxicity (either clinical or gross upon necropsy) in rats (191 to 222 g) injected with 0.5g/kg/day or 1.1 g/kg/day for 5 days. Both animals injected with 2.2 g/kg/day for 5 days had labored breathing, ataxia and hypoactivity following each daily dose. No animals died.
Test condition	:	Two rats/group were injected daily with 0.5, 1.1 and 2.2 g/kg/day for 5 days. Necropsies were performed on Day 6.
Test substance	:	Test material was CARBOWAX Sentry MPEG 350 (CAS No. 9004-74-4), NF grade. This a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), and 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(1) valid without restriction
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

02.10.2001 (37)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	open
Exposure time	:	24 hour(s)
Number of animals	:	5
PDII	:	
Result	:	slightly irritating
EC classification	:	
Method	:	other
Year	:	1962
GLP	:	no data
Test substance	:	other TS
Result	:	An irritation Grade of 2 was obtained with undiluted test material, indicating minimal irritation.
Test condition	:	Undiluted test solution (0.01 ml) was applied 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.
Test substance	:	Test material was triethylene glycol monomethyl ether (CAS No. 112-35-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint. A related test material was utilized.

02.10.2001 (8) (41)

Species	:	human
Concentration	:	
Exposure	:	
Exposure time	:	72 hour(s)
Number of animals	:	
PDII	:	

Result	:	slightly irritating
EC classification	:	
Method	:	other
Year	:	1969
GLP	:	no data
Test substance	:	other TS
Result	:	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.
Test condition	:	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).
Test substance	:	Test material was triethylene glycol monomethyl ether (CAS No. 112-35-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint. A related test material was utilized.

01.10.2001 (36)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	occlusive
Exposure time	:	4 hour(s)
Number of animals	:	6
PDII	:	
Result	:	not irritating
EC classification	:	
Method	:	Draize Test
Year	:	1988
GLP	:	no data
Test substance	:	other TS
Result	:	Scores of 0 were obtained for both erythema (and eschar formation) and edema. The material was therefore non-irritating.
Test condition	:	Test material (0.5 ml) was applied to the clipped, intact skin of six rabbits (3 of each sex). The material was loosely covered with a gauze patch an impervious sheeting. Rabbits were restrained for a 4-hour contact period. Excess material was removed after contact. The skin reaction was scored by the method of Draize at one hour, and 1, 2, 3, and 7 days following dosing.
Test substance	:	Test material (CARBOWAX MPEG-350, CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol

monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).

Reliability : (1) valid without restriction. Study was conducted in a robust manner.
Flag : Supportive study for non-required endpoint. A related test material was utilized.

02.10.2001 (38)

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
PDII :
Result :
EC classification : not irritating
Method : OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year : 1988
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Remark : Einwirkzeit: 4 h; nicht kennzeichnungspflichtig [Dose duration 4 hours]

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag : Critical study for non-required endpoint
02.10.2001 (20)

Species : rabbit
Concentration : undiluted
Exposure : semiocclusive
Exposure time : 4 hour(s)
Number of animals : 6
PDII :
Result : not irritating
EC classification :
Method : other
Year : 1992
GLP : yes
Test substance : other TS
Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.
Reliability : (1) valid without restriction
Flag : Supportive study for non-required endpoint. A related test material was utilized.

04.10.2001 (12)

5.2.2 EYE IRRITATION

Species : rabbit
Concentration : undiluted
Dose : .5 ml
Exposure Time :
Comment :

Number of animals	:	
Result	:	slightly irritating
EC classification	:	
Method	:	other
Year	:	1962
GLP	:	no data
Test substance	:	other TS
Result	:	Five rabbit eyes were not injured by 0.5 ml undiluted test material (grade 1).
Test condition	:	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.
Test substance	:	Test material was triethylene glycol monomethyl ether (CAS No. 112-35-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint. A related test material was utilized.

02.10.2001 (8) (41)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	6
Result	:	slightly irritating
EC classification	:	
Method	:	other
Year	:	1988
GLP	:	no data
Test substance	:	other TS
Result	:	Instillation of test material resulted in no corneal injury or iritis. Minor conjunctival irritation developed in all 6 rabbits. Moderate discharge was seen in several of the eyes. These effects resolved by 24 hours.
Test condition	:	Six male New Zealand white rabbits were dosed with 0.1 ml of test material. The test material was instilled into the lower conjunctival sac or placed directly on one eye per animal. The eyes were scored at 1 and 4 hours, and 1, 2, 3, and 7 days after dosing. Florescein (2%) was added to the eyes before dosing and after 1 day of exposure to assess corneal injury.
Test substance	:	Test material (CARBOWAX MPEG-350, CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(1) valid without restriction. Study was conducted in a robust manner.
Flag	:	Supportive study for non-required endpoint. A related test material was utilized.

02.10.2001 (38)

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure Time	:	

Comment	:	
Number of animals	:	
Result	:	
EC classification	:	not irritating
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1988
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Einwirkzeit: 4 h; nicht kennzeichnungspflichtig [Effect after 4 hours: none of recognizable significance].
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Critical study for non-required endpoint; however study was not available for review

02.10.2001 (22)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure Time	:	72 hour(s)
Comment	:	
Number of animals	:	6
Result	:	slightly irritating
EC classification	:	
Method	:	
Year	:	1992
GLP	:	yes
Test substance	:	other TS
Test substance	:	Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives
Reliability	:	(1) valid without restriction
Flag	:	Supportive study for non-required endpoint. A related test material was utilized.

04.10.2001 (12)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	drinking water
Exposure period	:	91 days
Frequency of treatment	:	daily
Post obs. period	:	none
Doses	:	ca. 400, 1200, 4000 mg/kg/day
Control group	:	yes, concurrent no treatment

NOAEL : = 400 mg/kg bw
LOAEL : = 1200 mg/kg bw
Method : other
Year : 1990
GLP : yes
Test substance : other TS
Remark : 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).

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

Result : 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 $\pm$ 0.3984) and 1200 mg/kg/day (3.951 $\pm$ 0.4191) versus control (3.214 $\pm$ 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.

Test condition : 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. 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 sacrificed 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).

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6). The purity of the material was at least 98.7%.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint. A related test material was utilized.

02.10.2001 (13) (14)

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	dermal
Exposure period	:	91 days
Frequency of treatment	:	6 hr/day, 5 days/week
Post obs. period	:	none
Doses	:	400, 1200, 4000 mg/kg bw
Control group	:	other:sham
NOAEL	:	= 4000 mg/kg bw (summary preparer); > 400 and < 1200 mg/kg bw (EPA)
Method	:	other
Year	:	1990
GLP	:	yes
Test substance	:	other TS

Remark : 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).

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.

Result : 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.

Test condition : 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. 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 sacrifice), clinical chemistry (just prior to sacrifice), 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.

Conclusion : 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."

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6). Purity (as determined by gas chromatography) was 99.23 % at the onset of the study and 99.24% at completion of the in-life phase.

Reliability : (1) valid without restriction.

Flag : Critical study for SIDS endpoint. A related test material was utilized.

28.09.2001 (10) (14)

Species : rabbit
Sex : male
Strain : New Zealand white
Route of admin. : dermal
Exposure period : 90 days
Frequency of treatment : 6 hr/day, 5 days/week
Post obs. period :
Doses : 1 ml of 50% and 100% material (approximately 169 and 338 mg/kg/day)
Control group : yes, concurrent vehicle
NOAEL : = 338 mg/kg bw
Method : other
Year : 1985
GLP : yes
Test substance : other TS
Remark : A preliminary range-finding study in 15 rabbits dosed 6 hr/day for 9 days (Carpenter, Range finding tests on methoxy polyethylene glycols of approximate molecular weights 350, 550 and 750. Melon Institute of Industrial Research, University of Pittsburgh. Report dated 5-13-47.
1947) showed that daily administration of 1 ml of 50% or 100% test material only caused mild skin irritation. Therefore, these doses were chosen for the 90-day study.

The NOAELs for local or systemic effects were not listed by the

investigators. Based on the data, these values are 50% and 100%, respectively. Based on weights of animals determined at weekly intervals and the reported density of test material (1.09 g/ml) doses can be calculated on average mg/kg/day basis. These doses are 169 mg/kg/day (for 50%) and 338 mg/kg/day (for 100%).

Result : Mild acanthosis (epidermal thickening) was found in 3 females dosed with 100% material. Transient, dose-related erythema (Grade 1) and desquamation of skin occurred. No systemic effects were observed in rabbits treated with either 50% or 100% test material.

Test condition : Dosing: New Zealand white rabbits (10/sex/dose) were treated dermally on clipped dorsal skin with 1.0 ml of vehicle (0.1% (w/v) methyl cellulose in distilled water), 50% CARBOWAX MPEG-350 (w/v dilution in 0.1% methyl cellulose in water) or 100% CARBOWAX MPEG-350, for six hours/day, five days per week for 90 days. Body weights of males and females ranged from 2.5 to 3.2 kg and 2.5 to 3.1 kg at study initiation. Rabbits were fitted with Elizabethan collars after dosing to prevent ingestion of test material. After each 6-hour exposure the application site was wiped with a paper towel dampened with water and then dried using a towel. Rabbits were then uncollared until the next treatment.

Observations: All rabbits were observed daily (weekdays) for death, clinical signs and dermal irritation. Any irritation was scored immediately prior to dosing using the Draize system. Body weights were recorded on the morning of the first day of dosing, weekly thereafter and prior to sacrifice. Food consumption was measured weekly. Urine was collected from 5 animals/sex/group during the last two weeks of dosing and subjected to standard analyses. Standard hematology and clinical chemistry parameters were evaluated for all animals just prior to sacrifice.

Necropsy: All animals were sacrificed and necropsied after 13 weeks of treatment. Weights were recorded for liver, kidneys, brain and adrenals of all animals and testes of males. Histopathologic examinations were performed on tissues from high-dose and control animals.

Statistical Analyses: Body weight, food consumption, organ weight and clinical pathology data from the three groups were compared using Levene's test for homogeneity of variance. An analysis of variance was performed on the groups when data were homogeneous. If significant differences were found, group differences were delineated by grouped variance Student t-tests. When data were heterogeneous, Welch and Brown-Forsyth analyses were performed and significant differences among groups were determined using separate variance Student t-tests. Draize skin irritation scores were analyzed using the Kruskal-Wallis test, and significant differences in groups were determined using the Wilcoxon rank sum test (as modified by Mann-Whitney). Frequency data (i.e. histological) were compared using Fisher's exact tests. The p value of 0.05 (two-tailed) was used as the critical level of significance for all analyses.

Test substance : The test material (CARBOWAX MPEG 350, CAS No. 9004-74-4) was reported to be chemically inert (stable for > 6 months at room temperature) and 99.8% pure. This material is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).

Reliability : (1) valid without restriction.

Flag : Critical study for SIDS endpoint. A related test material was utilized.

02.10.2001 (6) (7) (16)

Species	:	rat
Sex	:	male
Strain	:	Sprague-Dawley
Route of admin.	:	dermal
Exposure period	:	4 weeks
Frequency of treatment	:	5 days/week
Post obs. period	:	
Doses	:	1250, 2500, 5000 mg/kg/day
Control group	:	other:sham
NOAEL	:	= 1250 mg/kg
Method	:	other
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Remark	:	One, 3, and 2 animals in the low-, mid- and high-dose groups slipped their collars and therefore may have ingested the material during grooming. Results in these animals were not significantly different from those animals that did not slip their collars. Therefore, possible ingestion of material in these animals did not appear to affect the results of the study. The investigators did not identify a NOAEL for the study. However, they stated "that there were no indications of systemic toxicity secondary to repeated cutaneous exposure to MPEG-350 in this study." Based on the information given, the summary preparer assigned a NOAEL of 1250 mg/kg/day. This value is based on significant effects on body weight or weight gain at higher doses (although the authors stated that these effects may have been due to use of Elizabethan collars). Although the absolute weights of the thymus and testes of rats treated with 1.25 g/kg/day were significantly less than control, relative weights of these organs were not different from control, there were no histological changes in these organs, and these effects were not noted at higher doses. Therefore, they were considered by the summary preparer to be unrelated to treatment.
Result	:	Minor, transient irritation was noted at the application site of all treated animals. Body weights of animals given 5.0 g/kg/day and body weight gains of animals given 2.5 g/kg/day were depressed. Absolute weights of the thymus and testes of rats treated with 1.25 g/kg/day were 83% and 93%, respectively of control weights (significantly different). Relative weights of these organs were not significantly different from control. There were no pathological abnormalities in either of these organs.
Test condition	:	Male rats (52 days old) were divided into 4 groups of 15 animals (control, low-, mid-, and high-dose groups and were acclimated to Elizabethan collars for 7 days before treatment. One mid-dose and 3 high-dose animals were dropped before treatment because they appeared dehydrated. Each group was treated with 0 (sham control), 1.25, 2.5 or 5 g/kg/day test material on shaved backs. Rats were sacrificed 3 days after the last treatment.
Test substance	:	Test material was Carbowax MPEG-350 (CAS No. 9004-74-4) from Union Carbide. This material is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3). Test material also contained 1 ppm of 2-methoxyethanol.
Reliability	:	(1) valid without restriction
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

02.10.2001 (15) (16)

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	28 days
Frequency of treatment	:	daily
Post obs. period	:	
Doses	:	25, 150, 1000 mg/kg/day
Control group	:	yes
NOAEL	:	= 150 mg/kg bw (NOEL)
Method	:	other
Year	:	1993
GLP	:	yes
Test substance	:	other TS
Result	:	Food intake of males dosed with 1000 mg/kg/day was slightly reduced for first 2 weeks of treatment. Livers of all 5 males and some females dosed with 1000 mg/kg/day showed slight centrilobular hypertrophy (which was considered by the investigators to be adaptive). None of the controls exhibited this effect. There was no significant effect of treatment on liver weight. No effects on other organs (including ovaries and testes) were noted. A NOEL of 150 mg/kg/day was assigned by the investigator.
Test substance	:	Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.
Reliability	:	(1) valid without restriction
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

04.10.2001 (42)

Species	:	rabbit
Sex	:	male/female
Strain	:	New Zealand white
Route of admin.	:	dermal
Exposure period	:	3 weeks
Frequency of treatment	:	6 hr/day, 5 days/week
Post obs. period	:	
Doses	:	1000 mg/kg
Control group	:	other:sham
NOAEL	:	= 1000 mg/kg bw
Method	:	other
Year	:	1986
GLP	:	yes
Test substance	:	other TS
Result	:	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.

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

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

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

Body weights (weeks 1, 2, 3, and 4), clinical pathology parameters and organ weights (absolute and relative) were analyzed using Bartlett's test for homogeneity of variance and analysis of variance (one-way). The treatment groups were compared to the controls using the appropriate t-statistic (for equal or unequal variance). Dunnett's multiple comparison tables were used to judge the significance of the differences. Total bilirubin data was transformed to ranks and analyzed using a non-parametric test. All tests were two-tailed, with $p < 0.05$ and $p < 0.01$ as levels of significance.

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6).

Reliability : (2) valid with restrictions. Test material purity was not stated.

Flag : Supportive study for SIDS endpoint. A related test material was utilized.

06.09.2001 (30)

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	dermal
Exposure period	:	12 days
Frequency of treatment	:	daily
Post obs. period	:	
Doses	:	1000, 2500, 4000 mg/kg/day
Control group	:	yes
NOAEL	:	= 4000 mg/kg bw
Method	:	other
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Result	:	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.
Test condition	:	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.
Test substance	:	The test substance was triethylene glycol monomethyl ether (CAS 112-35-6). Purity is unknown.
Reliability	:	(2) valid with restrictions.
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

10.09.2001 (49)

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley

Route of admin.	:	i.v.
Exposure period	:	14 days
Frequency of treatment	:	daily
Post obs. period	:	
Doses	:	1000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL	:	= 1000 mg/kg
Method	:	other
Year	:	1997
GLP	:	yes
Test substance	:	other TS
Remark	:	An increase in aspartate aminotransferase activity, rather than a decrease is indicative of liver toxicity.
Result	:	There was no effect of treatment on body or organ weights or hematological values. Tissues (including testes) from treated animals were histologically similar to those of controls. There was a significant difference in aspartate aminotransferase activity in control (95 +/- 13 IU/L) and treated males (81 +/- 6 IU/L) that was not considered by the investigators to be related to treatment since the values for both groups were within the normal expected range.
Test condition	:	Groups of six rats/sex (6-8 weeks of age, 114 g to 189 g) were dosed intravenously for 14 consecutive days with either vehicle (0.9% sodium chloride, USP), or 1 g/kg/day test material. Animals were observed daily for general health. Body weights were recorded on days 1, 8 and 15 of treatment. All animals were euthanized on day 15. Blood was collected from the posterior vena cava and standard hematological and clinical chemistries were performed. The heart, liver, spleen, kidneys, adrenal glands and gonads were weighed, fixed, and processed for microscopic evaluation. The data were analyzed using a standard BMDP Statistical Software Package.
Test substance	:	Test material was CARBOWAX Sentry MPEG-350 (CAS No. 9004-74-4), NF grade. This material is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(1) valid without restriction
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

02.10.2001 (35)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium strains TA98, TA100, TA1535, TA1537
Concentration	:	up to 5000 micrograms/plate
Cytotoxic conc.	:	> 5000 micrograms/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	other:Test Standard 40 CFR 798.5265
Year	:	1990
GLP	:	yes
Test substance	:	other TS
Remark	:	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.
Result	:	Concentrations up to 5000 micrograms/plate did not cause toxicity or cause an increase in mutagenicity above that of negative controls.

Test condition : 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 induces 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.

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6). Purity was 99.23%.

Reliability : (2) valid with restrictions. Only 4 strains of bacteria were used in the test.

Flag : Critical study for SIDS endpoint. A related test material was utilized.

01.10.2001 (39)

Type : Ames test
System of testing : S. typhimurium strains TA 98, TA100, TA1535, TA1537, TA1538
Concentration : 1, 3, 10, 30, 110 mg/plate
Cytotoxic conc. : > 110 mg/plate
Metabolic activation : with and without
Result : negative
Method : other
Year : 1984
GLP : yes
Test substance : other TS
Remark : The test was valid, as positive controls caused at least a 9-fold increase in the number of mutant colonies and negative controls exhibited spontaneous reversion rates that were within the historical range.
Result : Mutagenic activity was not observed with any concentration in any of the strains (with or without bacterial activation).
Test condition : Test material was dissolved in water to a concentration of 300 mg/ml for doses of 30 mg/plate and below. All subsequent dilutions were made in the same solvent. Dilutions of test substance were made fresh each day and were gravimetrically analyzed. The volume of test material used in each test was 100 microliters. If necessary, phosphate buffered saline was added to adjust the volume.

A preliminary toxicity test was performed in strain TA100 to determine concentrations to use on other strains (TA98, TA1535, TA1537, TA1538). None of the doses used (up to 100 mg/plate) were toxic. Test material was tested in the Ames assay in triplicate at five doses (1, 3, 10, 30 and 110

mg/plate). Testing was performed with and without metabolic activation (0.5 ml of S9 mix containing 50 microliters of S9 liver homogenate from Aroclor 1254-induced, Sprague-Dawley male rats). Concurrent water and positive controls (4-nitro-o-phenylenediamine for TA98 and TA 1538, sodium azide for TA100 and TA1535 and 9-aminoacridine for TA1537 in the absence of S9 and 2-aminoanthracene for all stains in the presence of S9) were run with each test. The test material was considered to be positive if it induced at least a 2-fold and dose-related increase in mutant colonies with respect to the control.

Test substance : The test material (CARBOWAX MPEG-350; CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).

Purity of test material was 99.8%. Impurities included 0.1% water, 0.05% ethylene glycol, 0.05% diethylene glycol, and 50-150 ppm BHT.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint. A related test material was utilized.
28.09.2001 (44)

Type : Ames test
System of testing : S. typhimurium strains TA98, TA100, TA1535, TA1537, TA1538
Concentration : up to 5000 micrograms per plate
Cytotoxic conc. : > 5000 micrograms per plate
Metabolic activation : with and without
Result : negative
Method : other
Year : 1992
GLP : yes
Test substance : other TS
Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.
Reliability : (1) valid without restriction
Flag : Supportive study for SIDS endpoint. A related test material was utilized.
28.09.2001 (4)

Type : HGPRT assay
System of testing : Chinese hamster ovary cell
Concentration : 2000 to 5000 micrograms/plate
Cytotoxic conc. : >5000 micrograms
Metabolic activation : with and without
Result : negative
Method : other:Test Standard 40 CFR 798.5300
Year : 1990
GLP : yes
Test substance : other TS
Remark : 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).

Result : 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.

Test condition : 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, 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 10 6 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.

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-

6). Purity was 99.23%.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint. A related test material was utilized.
01.10.2001 (32)

Type : Chromosomal aberration test
System of testing : Chinese Hamster Ovary Cell
Concentration : up to 5000 micrograms/ml
Cytotoxic conc. : > 5000 micrograms/ml
Metabolic activation : with and without
Result : negative
Method : other
Year : 1992
GLP : yes
Test substance : other TS
Remark : The small random increases in the number of chromatid gaps and/or isogaps in one experiment with S-9, which were not dose-dependent and not different from the untreated controls were not considered to be compound-related effects by study personnel.
Result : Cells exposed to test material at concentrations up to 5000 micrograms/ml showed no increase in chromosome damage or no linear trend compared to negative controls in either experiment. The positive control induced significantly more cells with aberrations compared to the negative controls (for untreated control and for solvent control). In the first experiment with S-9 (up to 1875 micrograms/ml test material), there was no effect of treatment on the incidence of type of aberration observed. However, there was a significant difference in the number of cells with chromatid gaps and/or isogaps between the untreated control (7/200) and solvent control cultures (1/200). In the second experiment with S-9 (cells were treated with 1500, 3000 or 5000 micrograms/ml test material), there was a significant difference in the number of cells with aberrations including gaps (11/200) and cells with chromatid gaps and/or isogaps (8/200) at the 1500 micrograms/ml compared to the solvent control (2/199 and 0/199, respectively). There also was a significant increase in the number of cells with chromatid gaps and/or isogaps at the high concentration (5/200) compared to control, and between both controls (untreated control had 7/200). No linear trend was observed either by including or excluding the solvent control from the analysis. The positive control caused increases in aberrations with and without gaps compared to the solvent control in both studies.
Test condition : Cells (2 x 10E5) were incubated with medium containing the test compound or relevant controls [untreated control, solvent control and positive controls methyl methanesulphonate (20 micrograms/ml without S-9) and benzo(a)pyrene (25 micrograms/ml with S-9)] for either 3 hours in the presence of S9 mix (from Aroclor 1254-induced rat liver) or 24 hours in the absence of S9 mix. The concentrations of test material used (from 10 to 5000 micrograms/ml without S-9 and 100 to 5000 micrograms/ml with S-9) were chosen based on the results of preliminary miscibility and mitotic index studies. Duplicate cultures were prepared for each test condition. Two separate experiments were conducted using different concentrations. Metaphase cells were prepared on glass microscope slides for the analysis of chromosome aberrations 24 hours following exposure for the cultures with or without S9 mix. All slides were coded. Where possible, 200 metaphases were scored for each dose group. Only those cells showing the modal chromosome number (20) +/- 2 were analyzed for chromosome damage. Chromosome aberrations were classified according to the scheme described by Savage (J Med Genetics 12:103-122, 1976). The mitotic index of each group was assessed by counting the number of metaphases in a total of 1000 cells. Data were assessed for heterogeneity using the Fisher's exact test. The number of aberrations excluding gaps,

aberrations including gaps, isogaps and/or chromatid gaps and polyploidy and/or endoreduplication of treated cells was compared to controls using the Fisher's exact test. A Cochran-Armitage trend test was carried out on the dose/response. The test was performed twice, once excluding control data and the other including the solvent control.

Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.

Conclusion : Study personnel concluded that under the test conditions, the test material did not induce chromosomal aberrations either in the presence or absence of S9 mix.

Reliability : (1) valid without restriction

Flag : Supportive study for SIDS endpoint. A related test material was utilized.

04.10.2001 (5)

Type : Bacterial reverse mutation assay
System of testing : E. coli WP2uvrA pKM101
Concentration : up to 5000 micrograms per plate
Cytotoxic conc. : > 5000 micrograms
Metabolic activation : with and without
Result : negative
Method : other
Year : 1992
GLP : yes
Test substance : other TS

Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.

Reliability : (1) valid without restriction

Flag : Supportive study for SIDS endpoint. A related test material was utilized.

04.10.2001 (4)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : micronucleus assay
Species : mouse
Sex : male/female
Strain : other:CD-1(ICR) BR
Route of admin. : gavage
Exposure period : up to 72 hours
Doses : 500, 1667, 5000 mg/kg bw
Result : negative
Method : other:Test Standard 40 CFR 798.5395
Year : 1990
GLP : yes
Test substance : other TS
Remark : The test was valid as positive controls had significantly more MN-PCE than controls (62.2 in males and 34.6 in females).
Result : One female dose with 1667 mg/kg test material died prior to scheduled sacrifice. 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).

Test condition : 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/sacrifice time) were sacrificed by cervical dislocation 24, 48 and 72 hours after treatment. Mice (5/sex) treated with 120 mg/kg cyclophosphamide and sacrificed after 24 hours of treatment served as positive controls.

Bone marrow samples were obtained from both femurs at sacrifice. 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.

Test substance : Test material was triethylene glycol monomethyl ether (CAS No. 112-35-6). Purity was 99.23%.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint. A related test material was utilized.

01.10.2001 (34)

5.7 CARCINOGENITY

5.8 TOXICITY TO REPRODUCTION

Type : other:91 day oral toxicity study
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : drinking water
Exposure period : 91 days
Frequency of treatment : daily
Premating exposure period
Male :
Female :
Duration of test : 91 days

Doses	:	ca. 400, 1200, 4000 mg/kg/day
Control group	:	yes
NOAEL Parental	:	= 1200 mg/kg bw (summary preparer); > 400 and < 1200 mg/kg bw (EPA)
Method	:	other
Year	:	1990
GLP	:	yes
Test substance	:	other TS
Remark	:	The authors state that "a possible contributing factor in the development of testicular lesions at the high dose was low-level contamination of the test substance with the known testicular toxicant 2-methoxyethanol (EGME). EGME was present in the test substance at a concentration of 0.02 – 0.04 %, resulting in a EGME dose up to 1.7 mg/kg/day for animals in the high dose group. Given the length of the study, it is possible that EGME contributed to the testicular lesions. A comparison between the doses of EGME and TGME required to produce testicular toxicity indicated that TGME is 350 times less potent than EGME in producing testicular lesions in the rat." The dose of TGME that caused testicular toxicity (4000 mg/kg/day) is 4 times greater than the 1000 mg/kg/day limit dose generally recommended for subchronic studies. The NOAEL listed is for reproductive organ toxicity. Other results are shown in section 5.4. 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).
Result	:	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.
Test condition	:	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.
Test substance	:	Test substance was triethylene glycol monomethyl ether (CAS No. 112-35-6). The purity was at least 98.7%.
Reliability	:	(2) valid with restrictions. Effect on mating was not characterized
Flag	:	Critical study for SIDS endpoint. A related test material was utilized.

02.10.2001 (13)(14)

Type	:	other: 91 day dermal toxicity study
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	dermal
Exposure period	:	91 days
Frequency of treatment	:	6 hr/day, 5 days/week
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	91 days
Doses	:	400, 1200, 4000 mg/kg bw
Control group	:	other:sham
NOAEL Parental	:	= 4000 mg/kg bw (summary preparer); > 400 and < 1200 mg/kg bw (EPA)
Method	:	other
Year	:	1990
GLP	:	yes
Test substance	:	other TS
Remark	:	Additional details for this study can be found in Section 5.4. 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 semiferous 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 %).
Result	:	There were no indications of systemic toxicity at any dose. Mean body weight and food consumption were comparable to controls throughout the study. 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.
Test condition	:	Triethylene glycol monomethyl ether (TGME) was administered dermally to 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.

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6). Purity (as determined by gas chromatography) was 99.23 % at the onset of the study and 99.24% at completion of the in-life phase.

Conclusion : 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 unattected in this TGME study. Taking all factors into considereation, the testicular lesions observed in this dermal study could not be directly attributed to TGME exposure."

Reliability : (2) valid with restrictions. Effect on mating was not characterized

Flag : Critical study for SIDS endpoint. A related test material was utilized.

28.09.2001 (10) (14)

Type : other:90 day repeated dose toxicity study
Species : rabbit
Sex : male/female
Strain : New Zealand white
Route of admin. : dermal
Exposure period : 90 days
Frequency of treatment : 6 hr/day, 5 days/week
Premating exposure period
Male :
Female :
Duration of test : 90 days
Doses : 1 ml of 50% and 100% material (approximately 169 and 338 mg/kg/day)
Control group : yes, concurrent vehicle
NOAEL Parental : = 338 mg/kg bw
Method : other
Year : 1985
GLP : yes
Test substance : other TS

Remark : A preliminary range-finding study in 15 rabbits dosed 6 hr/day for 9 days showed that daily administration of 1 ml of 50% or 100% test material only caused mild skin irritation. Therefore, these doses were chosen for the 90-day study.

Based on weights of animals determined at weekly intervals and the reported density of test material (1.09 g/ml) doses can be calculated on average mg/kg/day basis. These doses are 169 mg/kg/day (for 50%) and 338 mg/kg/day (for 100%).

The NOAEL listed is for reproductive organ toxicity. Further details of this study can be found in Section 5.4. The NOAEL for systemic effects was not listed by the investigators. Based on the data, this value is 100% (338 mg/kg/day).

Result : No effects on any sex organ were observed

Test condition : Dosing: New Zealand white rabbits (10/sex/dose) were treated dermally on clipped dorsal skin with 1.0 ml of vehicle (0.1% (w/v) methyl cellulose in distilled water), 50% CARBOWAX MPEG-350 (w/v dilution in 0.1% methyl cellulose in water) or 100% CARBOWAX MPEG-350, for six hours/day, five days per week for 90 days. Body weights of males and females ranged from 2.5 to 3.2 kg and 2.5 to 3.1 kg at study initiation. Rabbits were fitted with Elizabethan collars after dosing to prevent ingestion of test material. After each 6-hour exposure the application site was wiped with a paper towel dampened with water and then dried using a towel. Rabbits were then uncollared until the next treatment.

Observations: All rabbits were observed daily (weekdays) for death, clinical signs and dermal irritation. Body weights were recorded on the morning of the first day of dosing, weekly thereafter and prior to sacrifice. Food consumption was measured weekly. Urine was collected from 5 animals/sex/group during the last two weeks of dosing and subjected to standard analyses. Standard hematology and clinical chemistry parameters were evaluated for all animals just prior to sacrifice.

Necropsy: All animals were sacrificed and necropsied after 13 weeks of treatment. Weights were recorded for liver, kidneys, brain and adrenals of all animals and testes of males. Histopathologic examinations were performed on tissues (including testes, epididymes, prostate, accessory sex glands, uterus, ovaries and mammary gland) from high-dose and control animals.

Test substance : The test material (CARBOWAX MPEG 350, CAS No. 9004-74-4) was reported to be chemically inert (stable for > 6 months at room temperature) and 99.8% pure. This material is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).

Reliability : (2) valid with restrictions. Effect on mating was not characterized

Flag : Critical study for SIDS endpoint. A related test material was utilized.

02.10.2001 (6) (16)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat

Sex : female

Strain : other:Alpk:AP (Wistar)

Route of admin.	:	gavage
Exposure period	:	days 7-16 of gestation
Frequency of treatment	:	daily
Duration of test	:	until Day 5 following parturition
Doses	:	250 and 1000 mg/kg
Control group	:	other: both negative (water) and positive (50 and 250 mg/kg ethylene glycol monomethyl ether)
NOAEL Maternalt.	:	= 1000 mg/kg bw
NOAEL Teratogen	:	= 1000 mg/kg bw
Method	:	other: modified Chernoff-Kavlok assay (Schuler et al., Environ Health Persp 57:141-146, 1984)
Year	:	1986
GLP	:	yes
Test substance	:	other TS
Remark	:	Triethylene glycol monoethyl ether and triethylene glycol monobutyl ether also were not teratogenic at 1000 mg/kg. The EPA also 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). The NOAEL listed under teratogenicity is the NOAEL for developmental toxicity.
Result	:	Maternal Data: 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. 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). 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. At the doses tested (250 or 1000 mg/kg/day), TGME was not embryotoxic or teratogenic (in contrast to EGME).
Test condition	:	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.

Test substance : The test material was triethylene glycol monomethyl ether (TGME, CAS 112-35-6). Purity was listed as 99.98% by the supplier (Olin Corporation).

Conclusion : 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.

Reliability : (1) valid without restriction

Flag : Supportive study for SIDS endpoint. A related test material was utilized.

28.09.2001 (31) (48)

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : days 6 to 15 of gestation
Frequency of treatment : daily
Duration of test : 15 Days
Doses : 625, 1250, 2500, 5000 mg/kg/day
Control group : yes, concurrent vehicle
NOAEL Maternalt. : = 1250 mg/kg bw
NOAEL Teratogen : = 625 mg/kg bw
Method : other
Year : 1990
GLP : yes
Test substance : other TS
Remark : 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. The NOAEL listed under teratogenicity is the NOAEL for developmental toxicity.

Result : Maternal: 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.

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.

Fetal: 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.

Test condition : 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 sacrificed 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 sacrifice.

Maternal and fetal incidence data were analyzed suing 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.

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6).

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint. A related test material was utilized.

02.10.2001 (18)

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	day 6 of gestation through postnatal day 21
Frequency of treatment	:	daily
Duration of test	:	38 Days
Doses	:	300, 1650, 3000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	= 1650 mg/kg bw (summary preparer, EPA)
NOAEL Teratogen	:	= 300 mg/kg NOEL (study personnel); 300 mg/kg day NOAEL (EPA)
Method	:	other
Year	:	1992
GLP	:	yes
Test substance	:	other TS
Remark	:	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). 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). The NOAEL listed under teratogenicity is the NO(A)EL for developmental toxicity.
Result	:	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 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. 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.” Necropsy of maternal animals in the high- dose group revealed significantly heavier kidneys than controls. Kidney weights increased in a dose-dependent manner. 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 shown to be significantly advanced in the pups from the mid- and high-dose groups.

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.

Necropsy of maternal animals revealed that kidneys from the maternal animals exposed to 3000 mg/kg/day of TGME were significantly heavier than controls. 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.

Test condition : 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 sacrifice

were removed and separated into the telencephalon, diencephalon, medulla oblongata/pons, and the cerebellum. These sections were all weighed separately.

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

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6).The analyzed chemical purity was 99.2%.

Conclusion : "In conclusion, TGME administered by gavage to pregnant and lactating CD" (Sprague- Dawley) rats resulted in no overt signs of maternal toxicity. In addition, no discernible effects were noted in the offspring on motor activity, active avoidance, or neuropathology at exposures up to 3000 mg/kg/day. Exposure to TGME at 3000 mg/kg/day resulted in increases in auditory startle amplitude and decreases in latency to maximum startle, but no changes in the habituation process evaluated in the auditory startle test. The significance of these auditory startle observations with regard to the condition of the test animals is not clear. Exposure to TGME at levels of 1650 and 3000 mg/kg/day produced developmental toxicity evidenced by decreased *postnatal* weight gains. Therefore, the no observable effect level" (NOEL) for this study is considered to be equal to or greater than 300 mg/kg/day."

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint. A related test material was utilized.

01.08.2002 (3)

Species : rabbit
Sex : female
Strain : New Zealand white
Route of admin. : gavage
Exposure period : days 6 to 18 of gestation
Frequency of treatment : daily
Duration of test : 24 days
Doses : 250, 500, 1000, 1500 mg/kg/day
Control group : yes, concurrent vehicle
NOAEL Maternalt. : = 500 mg/kg bw
NOAEL Teratogen : = 1000 mg/kg bw
Method : other
Year : 1990
GLP : yes
Test substance : other TS

Remark : 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). The NOAEL listed under teratogenicity is the NOAEL for developmental toxicity.

Result : Maternal: 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. 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.

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.

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.

Fetal: 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.

Test condition : 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 sacrificed 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.

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6).

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint. A related test material was utilized.

28.09.2001 (17)

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : days 7-17 of gestation
Frequency of treatment :
Duration of test :

Doses : 25, 150, 1000 mg/kg/day
Control group : yes
NOAEL Maternalt. : = 1000 mg/kg bw
NOAEL Teratogen : = 1000 mg/kg bw
Method : Chernoff-Kavlok teratogenicity screening test
Year : 1993
GLP : yes
Test substance : other TS

Remark : It is not known whether the decreased mean litter weights or birth index at 25 mg/kg/day or the increased mean litter weights at 1000 mg/kg/day are significantly different from control, since statistical analyses were not performed. However, these findings do not appear to be related to treatment since they are not dose-dependent. Since the investigators concluded that 1000 mg/kg/day Brake Fluid DOT4 did not cause fetal growth retardation or embryo or fetal lethality, the NOAEL for these effects is 1000 mg/kg/day. The NOAEL listed under teratogenicity is the NOAEL for developmental toxicity.

Result : There was no effect of Brake Fluid DOT4 on maternal body weight of food intake. Mean litter weights of low dose animals were slightly lower than negative controls at birth (79 +/- 24 g vs. 90 +/- 23 g in sham control) and on day 5 of lactation (109 +/- 29 g vs. 133 +/- 34 g in sham control). In contrast, mean litter weights of high dose animals were higher than negative controls at birth (97 +/- 10 g) and on day 5 of lactation (150 +/- 24 g). The authors stated that the reduction at 25 mg/kg/day could be related to slightly smaller litter sizes (the birth index was 85 +/- 15 vs. 95 +/- 7 in the sham control). Two rats in this group had a lower number of implant sites (8 and 6) than the others (ranged from 15-19), which led to a decrease in the number of pups delivered(5 in each of the animals vs. 13-18 in the others). Another low dose animal that had 16 implant sites only delivered 9 pups. The birth index of animals treated with 150 (94 +/- 6) or 1000 mg/kg/day test material (95 +/- 6) was similar to the sham control (95 +/- 7). There was no effect of treatment on the number of dead pups (4 in control vs. 1 in each treated group). There were no treatment-related necropsy findings. There was no effect of treatment with Brake Fluid DOT 4 of the duration of gestation, the number of females littering, the mean number of implant sites, or the live birth index or viability index. Based on these data, the authors concluded that 1000 mg/kg/day Brake Fluid DOT4 did not cause fetal growth retardation or embryolethality.

By contrast, the positive control animals lost weight from days 7 to 21 of gestation. All nine pregnant animals treated with ethylene glycol diethyl ether (EGDE) resorbed their litters. Most animals treated with EGDE had enlarged livers and/or spleens.

Test condition : Groups of 10 female rats were dosed by oral gavage with 25, 150 or 1000 mg/kg/day test material on days 7-17 of gestation. Additional groups of females were sham dosed (negative control) or dosed with 1000 mg/kg/day ethylene glycol diethyl ether (positive control). Animals were allowed to litter naturally, and any that did not deliver by day 25 of gestation were killed. Dams and surviving pups were killed on day 5 of lactation. Body weights were recorded on days 1, 7 and 21 of gestation and on day 5 of lactation (or at termination for animals that did not reproduce). Food intake was recorded over days 1 to 7 and 7 to 17 of gestation, day 17 of gestation to day 1 of lactation and days 1-5 of lactation. The birth index [total number of pups born (live and dead) x 100/ number of implantation sites], live birth index (number of pups alive at day 1 of lactation/ total number of pups born x 100) and viability index (number of pups alive on day 5 of lactation/ number of pups alive on day 1 of lactation x 100) were calculated for each litter and group. Litter weights were recorded on days 1 and 5 of lactation and the uteri of all dams were examined for implantation sites. Statistical analyses were not performed. Pups were not necropsied.

Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.

Reliability : ((2) valid with restrictions. Pups were not examined for malformations.

Statistical analyses were not performed.

Flag : Critical study for SIDS endpoint. A related test material was utilized.
04.10.2001 (43)

5.10 OTHER RELEVANT INFORMATION

Type : absorption
Remark : Absorption of ethylene glycol monomethyl ether (EGME), triethylene glycol monoethyl ether (TGEE), and triethylene glycol monobutyl ether (TGBE) also were tested in this study. The rate of absorption of EGME was220 micrograms/cm2/hr. The rate of absorption of TGEE was 24.1 micrograms/cm2/hr and the mean damage ratio was 1.37 (no increase in permeability). The rate of absorption of TGBE was 22.2 micrograms/cm2/hr and the mean damage ratio was 1.26 (no increase in permeability).
Result : 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).
Test condition : 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 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.
Test substance : Purity of test material (POLYSOLV-TM, triethylene glycol monomethyl ether (TGME)) was 99.98%.
Reliability : (1) valid without restriction
02.10.2001 (47)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

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TETRA ETHYLENE GLYCOL BUTYL ETHER
CAS No. 1559-34-8

SIDS Dossier (including robust summaries)

Existing Chemical	**:**	ID: 1559-34-8
CAS No.	**:**	1559-34-8
EINECS Name	**:**	3,6,9,12-tetraoxahexadecan-1-ol
EINECS No.	**:**	216-322-1
Molecular Weight	**:**	250
Molecular Formula	**:**	C12H26O5

Producer Related Part

Company	:	American Chemistry Council's Ethylene Glycol Ether Panel CEFIC's Oxygenated Solvents Producers Association Kyowa Hakko Kogyo Co., Ltd. Mitsubishi Chemical Corporation NIPPON NYUKAZAI CO.LTD
Creation date	:	03.10.2001

Substance Related Part

Company	:	American Chemistry Council's Ethylene Glycol Ether Panel CEFIC's Oxygenated Solvents Producers Association Kyowa Hakko Kogyo Co., Ltd. Mitsubishi Chemical Corporation NIPPON NYUKAZAI CO.LTD
Creation date	:	03.10.2001

Memo	**:**	
Printing date	**:**	02.12.2002
Revision date	**:**	02.12.2002
Date of last Update	**:**	02.12.2002
Number of Pages	**:**	80
Chapter (profile)	**:**	Chapter: 1, 2, 3, 4, 5

1.0.1 OECD AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

Substance type : organic
Physical status : liquid
Remark : TetraGBE is available only as a component of the mixture described below.

11.02.2000

Composition of High Boiling Point Butyl Glycol Stream

Chemical	CAS #	**Range (Weight%)**
Diethylene glycol butyl ether	112-34-5	1 – 20%
Triethylene glycol butyl ether	143-22-6	25 - 75%
Tetraethylene glycol butyl ether	1559-34-8	20 - 60%
Pentaethylene glycol butyl ether	1786-94-3	8 - 20%
Hexaethylene glycol butyl ether	4403-55-8	2 - 10%
Other high molecular weight chains	N/A	<4%
Triethylene glycol	112-27-6	0 - 5%
Tetraethylene glycol	112-60-7	0 – 5%

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

Butyl tetraglycol
15.05.1995

butyltetraglycol
30.04.1996

butyltetraglycol ether
30.04.1996

Tetraethyleneglycol (mono)butylether
30.05.1995

tetraethyleneglycol monobutyl ether
14.10.1997

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

Type	:	industrial
Category	:	basic industry: basic chemicals
Remark	:	The principal global end use is in the formulation of hydraulic brake fluids.
Reliability	:	(1) valid without restriction

14.10.2001 (12)

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.9 SOURCE OF EXPOSURE

1.10.1 RECOMMENDATIONS/PRECAUTIONARY MEASURES

1.10.2 EMERGENCY MEASURES

1.11 PACKAGING

1.12 POSSIB. OF RENDERING SUBST. HARMLESS

1.13 STATEMENTS CONCERNING WASTE

1.14.1 WATER POLLUTION

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	ca. -33 ° C
Sublimation	:	no
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	Polyethylene glycol monobutyl ether (CAS No. 9004-77-7), purity 98-99%
Remark	:	Polyethylene glycol monobutyl ether (CAS No. 9004-77-7) is a mixture of ethylene glycol butyl ethers of varying chain lengths or number of ethylene glycol units linked together. The chain lengths range from 2 (diethylene glycol butyl ether) to 12 (dodecaethylene glycol butyl ether) or higher, with the distribution of chain lengths following a rough bell shaped curve about the mean chain length. Polyethylene glycol monobutyl ether includes tetraethylene glycol butyl ether as one significant component. The melting points of triethylene glycol methyl ether (-48 degrees C), triethylene glycol ethyl ether (-18.7 degrees C), triethylene glycol butyl ether (-48 degrees C), and polyethylene glycol methyl ether (MPEG350)(-39 degrees C) as well as polyethylene glycol monobutyl ether offer ample documentation that these higher molecular weight ethers all have melting points well below 0 degrees C. These melting points were obtained from IUCLID databases for these materials.
Reliability	:	(2) valid with restrictions. Details on how value was obtained are unknown.

Value	:	ca. 91.1 ° C
Sublimation	:	No
Method	:	Other: estimated
Year	:	
GLP	:	no
Test substance	:	As Prescribed by 1.1-1.4
Remark	:	The value of 91.1° C, which is obtained by EPIWIN/MPBPWIN ((v1.40) has not been used, because it is known to be incorrect. The commercial substance remains a liquid well below zero degrees C.
Reliability	:	(4) invalid. See remark.

2.2 BOILING POINT

Value	:	ca. 332 ° C at 1013 hPa
Decomposition	:	no
Method	:	other
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 – 1.4
Remark	:	The boiling point is estimated using the EPIWIN/MPBPWIN model (v1.40). This model uses the method of Stein and Brown using inputs of molecular structure and functionality.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint.
14.10.2001		

Value	:	ca. 311 ° C at 760 mmHg
Sublimation	:	no
Method	:	other
Year	:	
GLP	:	no data

Test substance : Polyethylene glycol monobutyl ether (CAS No. 9004-77-7), purity 98-99%
Remark : Polyethylene glycol monobutyl ether (CAS No. 9004-77-7) is a mixture of ethylene glycol butyl ethers of varying chain lengths or number of ethylene glycol units linked together. The chain lengths range from 2 (diethylene glycol butyl ether) to 12 (dodecaethylene glycol butyl ether) or higher, with the distribution of chain lengths following a rough bell shaped curve about the mean chain length. Polyethylene glycol monobutyl ether includes tetraethylene glycol butyl ether as one significant component.
Reliability : (2) valid with restrictions. Details on how value was obtained are unknown.
Flag : Critical study for SIDS endpoint. A related material was tested.
14.10.2001 (14)

2.3 DENSITY

Value : 1.004 at 20° C
Sublimation : no
Method : other
Year :
GLP : no data
Test substance : Polyethylene glycol monobutyl ether (CAS No. 9004-77-7), purity 98-99%
Remark : Polyethylene glycol monobutyl ether (CAS No. 9004-77-7) is a mixture of ethylene glycol butyl ethers of varying chain lengths or number of ethylene glycol units linked together. The chain lengths range from 2 (diethylene glycol butyl ether) to 12 (dodecaethylene glycol butyl ether) or higher, with the distribution of chain lengths following a rough bell shaped curve about the mean chain length. Polyethylene glycol monobutyl ether includes tetraethylene glycol butyl ether as one significant component.
Reliability : (2) valid with restrictions. Details on how value was obtained are unknown.
Flag : Critical study for SIDS endpoint. A related material was tested.
14.10.2001 (14)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : < .0001 hPa at 25° C
Decomposition : no
Method : other (calculated)
Year : 2002
GLP : No
Test substance : as prescribed by 1.1 – 1.4
Decomposition : No
Remark : Vapor pressure is estimated using the EPIWIN/MPBPWIN model (v1.40). This model uses algorithmic equations (methods of Antoine, Grain and Mackay) to calculate vapor pressure with inputs of melting and boiling points. An average vapor pressure is obtained from the three methods.
Reliability : (2) valid with restrictions. Data were obtained by modeling.
Flag : Critical study for SIDS endpoint.
14.10.2001

Value : < 0.01 mmHg at 20° C
Sublimation : no
Method : other
Year :

GLP : no data
Test substance : Polyethylene glycol monobutyl ether (CAS No. 9004-77-7), purity 98-99%
Remark : Polyethylene glycol monobutyl ether (CAS No. 9004-77-7) is a mixture of ethylene glycol butyl ethers of varying chain lengths or number of ethylene glycol units linked together. The chain lengths range from 2 (diethylene glycol butyl ether) to 12 (dodecaethylene glycol butyl ether) or higher, with the distribution of chain lengths following a rough bell shaped curve about the mean chain length. Polyethylene glycol monobutyl ether includes tetraethylene glycol butyl ether as one significant component.
Reliability : (2) valid with restrictions. Details on how value was obtained are unknown.
Flag : Critical study for SIDS endpoint. A related material was tested.
14.10.2001 (14)

2.5 PARTITION COEFFICIENT

Log pow : ca. -.26 at ° C
Method : other (calculated)
Year : 2002
GLP : No
Test substance : as prescribed by 1.1 – 1.4
Remark : The partition coefficient was estimated using the EPIWIN/KOWWIN Program (v1.66). This program sums up contributions to log Kow from each molecular fragment or functional group in the molecular structure. Individual fragment contributions have been established that have been demonstrated to correlate well with measured data.
Reliability : (2) valid with restrictions. Data were obtained by modeling.
Flag : Critical study for SIDS endpoint.
14.10.2001

2.6.1 WATER SOLUBILITY

Value : ca. 945800 mg/l at 25 ° C
Qualitative :
Pka : at 25 ° C
PH : = 7 at and ° C
Method : Other: calculated
Year : 2002
GLP : No
Test substance : as prescribed by 1.1 – 1.4
Remark : Water solubility is estimated using the EPIWIN/WSKOW Program (v1.40). This program calculates water solubility using an algorithm with Log Kow and molecular weight as inputs. The algorithm used has been demonstrated to give values that correlate reasonably well with measured data.
Reliability : (2) valid with restrictions. Data were obtained by modeling.
Flag : Supportive study for SIDS endpoint.
14.10.2001

Value : at ° C
Qualitative : miscible
Pka : at 25 ° C
PH : At and ° C
Method : Other
Year : 2001
GLP : No
Test substance : as prescribed by 1.1 – 1.4
Reliability : (2) valid with restrictions. Original reference was not available. Information

(including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.

Flag : Critical study for SIDS endpoint.
14.10.2001

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : > 100 ° C
Type : closed cup
Method : Other
Year : 2001
GLP : No
Test substance : as prescribed by 1.1 – 1.4

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag : Critical study for non-required endpoint.
15.05.1995

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Method : Other
Year : 2001
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Result : not explosive

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag : Critical study for non-required endpoint.

2.11 OXIDIZING PROPERTIES

Method : other
Year : 2001
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Result : no oxidizing properties

Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a

reliability rating of 4 for this submission since it was not reviewed.

Flag : Critical study for non-required endpoint.

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	1000000 molecule/cm3
Rate constant	:	.000000000063 cm3/(molecule*sec)
Degradation	:	50 % after 3.1 hour(s)
Deg. Product	:	
Method	:	OECD Guide-line draft "Photochemical Oxidative Degradation in the Atmosphere"
Year	:	1991
GLP	:	not applicable
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Alcohols and ethers do not absorb UV light in the environmentally significant range (>290 nm) and are commonly used as solvents for obtaining UV spectra. Calculated with the Atkinson Method
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint.

30.05.1995 (50)

Type	:	air
Light source	:	other
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Direct photolysis		
Halflife t1/2	:	= 2 hour(s)
Degradation	:	% after
Quantum yield	:	
Deg. Product	:	
Method	:	other (calculated)
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The hydroxyl radical rate constant was calculated to be 65.56 E-12 cm3/molecule-sec.
Source	:	The photodegradation half-life and hydroxyl radical rate constant were calculated using the EPIWIN AOP (v1.90) program, based on the molecular structure. This program assumes that the hydroxyl radical will abstract a hydrogen atom from a carbon-hydrogen linkage, and considers the contributions of each carbon-hydrogen bond in the molecule as well as the relative probability that a hydrogen atom will be abstracted from each given carbon-hydrogen bond, in arriving at an overall rate constant. This program is based on the work of Atkinson et al, who has demonstrated that this approach provides rate constants for relatively simple, common organic compounds that correlate well with measured values. The photodegradation half-life assumes pseudo first order kinetics with a constant specified concentration of hydroxyl radical.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint.

14.10.2001

3.1.2 STABILITY IN WATER

Degradation	:	50 % after 33 month at pH and degree C
Deg. Product	:	
Method	:	other
Year	:	1995
GLP	:	not applicable
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Based on QSAR calculation hydrolysis is not likely to be an important transformation mechanism for this chemical. Alcohols and ethers are generally resistant to hydrolysis.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint.

30.05.1995 (34) (58)

Type	:	abiotic
t1/2 pH4	:	at degree C
t1/2 pH7	:	at degree C
t1/2 pH9	:	at degree C
Deg. Product	:	
Method	:	other
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 – 1.4
Result	:	This substance, which contains primarily ether linkages, is not expected to hydrolyze readily in water at neutral pHs. It is generally recognized that ether linkages are highly resistant to hydrolysis.
Source	:	EPIWIN HYDROWIN (v1.67) program.
Reliability	:	(3) invalid. Hydrolysis rate cannot be estimated for ethers by the EPIWIN HYDROWIN program.

14.10.2001

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	volatility
Media	:	water - air
Air (level III)	:	6.59E-009
Water (level III)	:	45.1
Soil (level III)	:	54.8
Biota (level II / III)	:	
Soil (level II / III)	:	
Method	:	other
Year	:	2001
GLP	:	not applicable
Test substance	:	as prescribed by 1.1 - 1.4
Remarks	:	One measured value was used as a program input: melting point (-33 degrees C).[Rod, since this MP is not for 100% test material (it is for the poly material, don't you think we shouldn't input it ?]

Result	:	A mass amount of 0.0755% is estimated for sediment using the EPIWIN Level III Fugacity model. The half-lives in hours are air (3.91), water (360), soil (360) and sediment (1.44E+3). The EPIWIN HENRY (v3.10) program was used to calculate a Henry's Law Constant of 2.03E-016 atm-m3/mole (Group Estimate) and 3.67E-013 atm-m3/mole (Bond Estimate). The EPIWIN PCKOC (1.66) program estimates a Koc (soil-sediment partition constant) of 10. The EPIWIN BCF (v2.14) program estimates a BCF (bioconcentration factor) of 3.162 or a log BCF of 0.500.
Source	:	Level III Fugacity modeling was performed by the EPIWIN program, based on the McKay model.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint.
27.07.2001		

Type	:	adsorption
Media	:	water - soil
Air (level I)	:	
Water (level I)	:	
Soil (level I)	:	
Biota (level II / III)	:	
Soil (level II / III)	:	
Method	:	other
Year	:	1995
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Based on a calculated Koc (0.23 l/kg) the substance is expected to be highly mobile in soil.
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Supportive study for SIDS endpoint.
20.03.1995		(55)

Type	:	volatility
Media	:	water - air
Air (level I)	:	
Water (level I)	:	
Soil (level I)	:	
Biota (level II / III)	:	
Soil (level II / III)	:	
Method	:	other
Year	:	1982
GLP	:	not applicable
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Based on the calculated Henry's Law (4.327E-5 Pa.m3/mole) constant the volatization of the substance can be considered unimportant as inter-media transfer mechanism.
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Supportive study for SIDS endpoint.
30.05.1995		(34)

3.3.2 DISTRIBUTION

Media	:	air - biota - sediment(s) - soil - water
Method	:	calculation according Mackay, Level I
Year	:	1991
GLP	:	not applicable
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	According to the MacKay Level I calculation the environmental distribution will be: air 0% water 100% soil/sediment 0%
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for non-required endpoint.

28.03.1995 (35)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	other:non-acclimated sewage microorganisms
Contact time	:	
Degradation	:	= 47 % after 20 day
Result	:	
Deg. Product	:	not measured
Method	:	other: as described in "Standard Methods for the Examination of Water and Wastewater, 16th Ed., USPHA, Washington, D. C., 1985)
Year	:	1987
GLP	:	no data
Test substance	:	other TS
Remark		Biological oxygen demand (BOD) of triethylene glycol monomethyl ether (TGME; CAS No. 112-35-6) and triethylene glycol monoethyl ether (CAS No. 112-50-5) were also tested in this study. The 20 day BOD of both of these chemicals (71%) was greater than that of triethylene glycol monobutyl ether. The concentration of test material and bacteria were not listed in the report.
Result	:	The calculated theoretical oxygen demand of TGBE was 2.10 mg/mg. After 10 and 20 days of incubation, the percent biooxidation was 5, and 47%.
Test condition	:	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.
Test substance	:	Test material was triethylene glycol monobutyl ether (TGBE, CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

(61)

Type	:	aerobic
Inoculum	:	other: industrial activated sludge (Gendorf, Germany sewage treatment plant)
Concentration	:	572mg/l related to Test substance
Degradation	:	= 99 % after 8 day
Result	:	
Kinetic of test substance	:	3 hour(s) 10 **%** 1 day 19 **%** 3 day 29 **%** 5 day 52 **%** 7 day 91 **%**
Deg. Product	:	
Method	:	OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year	:	1989
GLP	:	no data
Test substance	:	other TS
Test condition	:	CSB = elimination (time sequence values versus initial concentration value): Elimination through non-biological processes = ca.10%
Test substance	:	Test material was tetraethylene glycol monomethyl ether (CAS No. 23783-42-8).
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

04.10.2001 (29)

3.6 BOD5, COD OR BOD5/COD RATIO

Year	:	2001
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	ThOD= 2.05 g O2/g substance.
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Non-required endpoint.

3.7 BIOACCUMULATION

Year	:	2001
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Based on the QSAR calculation (BCF = 1) and on the calculated log Pow (-0.26) the substance will not bioaccumulate significantly.
Reliability	:	(2) valid with restrictions. Data were extrapolated from models.
Flag	:	Critical study for non-required endpoint

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	= 2400
Method	:	other: as described in "Standard Methods for the Examination of Water and Wastewater, 13th Ed., 1971.
Year	:	1974
GLP	:	no data
Test substance	:	other TS
Remark	:	Toxicity of triethylene glycol monomethyl ether (CAS No. 112-35-6) and of triethylene glycol monoethyl ether (CAS No. 112-50-5) were also tested in this study. LC50 values for both chemicals were > 10000 mg/l.
Result	:	The 24-hr, 48-hr and 96-hr LC50 values were 2400 mg/l.
Test condition	:	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.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Critical study for SIDS endpoint. A related material was tested.

(60)

Type	:	
Exposure period	:	14 days
Unit	:	mg/l
LC50	:	31,259
Method	:	estimated using EPIWIN ECOSAR
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 – 1.4
Remarks	:	One value was used as a program input: Log Kow (-0.26).
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.

Type	:	semistatic
Species	:	Poecilia reticulata (Fish, fresh water)
Exposure period	:	7 day
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	= 197
Method	:	other
Year	:	1981
GLP	:	no data
Test substance	:	other TS
Remark	:	The molecular weight of the test material (206 g/mole) was used to convert the log LC50 (in micromoles/liter) to the LC50 (in mg/l).
Result	:	The log of the LC50 was calculated to be 2.98 micromoles/l.
Test condition	:	Two to three month old guppies (8 per group) were exposed to several concentrations of test material in 1.5 liter vessels for 7 days. Each vessel was filled with 1 liter of standard water (hardness 25 mg/l as CaCO3) and covered with glass. A stock solution of test material was made by

dissolving it in either acetone or 2-propanol (not specified). Various volumes of stock solution were added to the test vessels to increase test concentrations geometrically (in increasing ratios of 3.2). Test solution was renewed daily. Guppies were fed 0.5 hours before each renewal with commercial fish food. Oxygen content, water temperature, and viability of fish were monitored. Oxygen content remained above 5 mg/l, and temperature was 22 +/- 1 degrees C.

LC50's were calculated according to the method of Litchfield and Wilcoxon (J Pharm Exp Ther 96:99, 1949), or by estimation from a log-probit-plot (if concentration-death relationship was too steep).

Test substance : Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability : (2) valid with restrictions. Purity of test material was not noted.
Flag : Supportive study for SIDS endpoint. A related material was tested.
04.10.2001 (31)

Type : static
Species : Brachydanio rerio (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : no
LC50 : > 10000
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 1988
GLP : yes
Test substance : other TS

Test substance : Test material was tetraethylene glycol monomethyl ether (CAS No. 23783-42-8).
Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag : Supportive study for SIDS endpoint. A related material was tested
04.10.2001 (25)

Type :
Species : Brachydanio rerio (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : no
LC50 : > 10000
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 1988
GLP : yes
Test substance : other TS

Test substance : Test material was tetraethylene glycol monomethyl ether (CAS No. 23783-42-8).
Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag : Supportive study for SIDS endpoint. A related material was tested.
04.10.2001 (25)

Type :
Species : Fathead minnow
Exposure period : 96 hour(s)
Unit : mg/l

Analytical monitoring	:	no data
LC50	:	> 10000
Method	:	unknown
Year	:	unknown
GLP	:	no data
Test substance	:	Test material (CARBOWAX MPEG-350; CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(2) valid with restrictions. Original data from which MSDS was written were not available.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

04.10.2001 (15)

Type	:	static
Species	:	Leuciscus Idus (Golden Orfe)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	> 2150 and < 4640
Method	:	DIN 38 412
Year	:	1989
GLP	:	no data
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6). Purity was 87.2%
Result	:	The 24-hr, 48-hr and 96-hr LD50 values were > 2150 and < 4640 mg/l. All fish exposed to 4640 mg/l died within 4 hours. No deaths were observed at 2150 mg/l. Apathy and tumbling were noted at 2150 mg/l. No symptoms of toxicity were observed at 1000 mg/l.
Test condition	:	Ten fish/group were exposed to 0, 1000, 2150, 4640 or 10000 mg/l test material in glass aquariums (30 cm x 22 cm x 24 cm) containing 10 liters of water (2.8 g fish/liter water) after a 3 day acclimation period. Food was withdrawn 1 day before and during exposure. The average length and weight of fish were 6.7 cm and 2.8 g, respectively. The water had a total hardness, acid capacity, ratio Ca/Mg, ratio Na/K, pH and temperature of 2.5 mmol/l, 0.8 mmol/l, 4:1, 10:1, 8.0, and 20 degrees C. Water was continuously aerated with oil-free air.
Reliability	:	(2) valid with restrictions. Purity of test material was not high.
Flag	:	Supportive study for SIDS endpoint. A related material was tested

30.11.2001 (4)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	= 2210
Method	:	other: test practices followed those recommended by EPA and ASTM
Year	:	1987
GLP	:	no data
Test substance	:	other TS

Remark	:	Toxicity of triethylene glycol monomethyl ether (CAS No. 112-35-6) and of triethylene glycol monoethyl ether (CAS No. 112-50-5) also were tested in this study. LC50 values for both chemicals were > 10000 mg/l.
Result	:	The LC50 value and 95% confidence limits were 2210 (1740-2800) mg/l.
Test condition	:	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.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Critical study for SIDS endpoint. A related material was tested.

(61)

Type	:	
Exposure period	:	48 hours
Unit	:	mg/l
LC50	:	no value given; no toxicity log Kow cutoff
Method	:	estimated using EPIWIN ECOSAR
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 – 1.4
Remarks	:	One value was used as a program input: Log Kow (-0.26).
Reliability	:	(4) not assignable. No value determined. Study is a model estimation.

Type	:	unknown
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	> 10000
Method	:	unknown
Year	:	unknown
GLP	:	no data
Test substance	:	Test material (CARBOWAX MPEG-350; CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(2) valid with restrictions. Original data from which MSDS was written were not available.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

16.10.2001 (15)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC50	:	> 500
EC20	:	= 270
EC90	:	> 500
Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	Test substance was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Result	:	The EC20 value at 24, 48, and 72 hours was 235.7, 235.4, and 267.1 mg/l. The EC50 value was greater than the highest concentration tested (500 mg/l). At time 0, fluorescence values ranged from 94.37 % of control for cells treated with 7.812 and 31/25 mg/l to 103.09 % of control for cells treated with 500 mg/l. The fluorescence values for cells treated with all concentrations except 125 (86.08%) and 250 mg/l (79.21%) were greater than 90% at 24 hours. At 48 hours, cells treated with 250 or 500 mg/l began to exhibit slightly lower fluorescence values than control. At 72 hours, values for cells treated with 250 or 500 mg/l were 80.3% and 75.91% of control, respectively. Most values for the 4 replicates at each concentration varied by < = 5%. However, at 48 hours, variance of values for concentrations greater than or equal to 250 mg/l ranged from 5-10%.
Test condition	:	A SAG 86.81 culture of Scenedesmus subspicatus (10,000 cells/ml) was maintained in OECD medium at 20 degrees C. Ten ml of cells in suspension was treated with 0 (control), 7.812, 15.625, 31.25, 62.5, 125, 250 or 500 mg/l test material in quadruplicate. Fluorescence of vials containing treated cells was determined 0, 24, 48 and 72 hours after treatment in a fluorimeter with a gain setting of 1. Fluorescence of 2 blank vials containing test material (at each concentration) and medium without cells was subtracted from values obtained for test vials. The values for the four tests were averaged and a standard deviation was calculated. The average fluorescence value of each concentration was presented as a percentage of control values.
Reliability	:	(2) valid with restrictions. Test material purity is unknown. Details about study conduct are lacking.
Flag	:	Critical study for SIDS endpoint. A related test material was used.

03.10.2001 (1)

Type	:	
Exposure period	:	96 hours
Unit	:	mg/l
EC50	:	no value given; no toxicity log Kow cutoff
Method	:	estimated using EPIWIN ECOSAR
Year	:	2002
GLP	:	no
Test substance	:	as prescribed by 1.1 –1.4
Remarks	:	One value was used as a program input: Log Kow (-0.26).
Reliability	:	(4) not assignable. No value estimated. Study is a model estimation.

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC50	:	> 500
EC20	:	> 500
EC90	:	> 500
Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	Test substance was triethylene glycol monomethyl ether (CAS No. 112-35-6).
Remark	:	It is assumed that the test conditions were very similar to those described above for triethylene glycol monobutyl ether (CAS No. 143-22-6) since the test was conducted by the same laboratory at approximately the same time.
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Supportive study for SIDS endpoint. A related test material was used.

03.10.2001 (2)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	Sewer microorganisms
Exposure period	:	16 hour(s)
Unit	:	
Analytical monitoring	:	no
IC50	:	> 5000
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	other TS
Remark	:	Toxicity of triethylene glycol monomethyl ether (TGME, CAS No. 112-35-6) and of triethylene glycol monoethyl ether (TGEE, CAS No. 112-50-5) were also tested in this study. The LD50 values for TGME and TGEE were > 5000 mg/l and > 10000 mg/l, respectively.
Test condition	:	Selected concentrations (not listed) were incubated for 16 hours at 23 degrees C on a shaker table in the presence of nutrients, buffer, growth substrate, and sewer-microorganisms. Toxicity was indicated when the resulting turbidity was at (or less than) 50% of the control (IC50). Details of the test are published in: Alsop et al., "Bacterial Growth Inhibition Tests", J. Water Pollution Control Federation, Vol 52: No. 10, October, 1980.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint. A related material was tested.

04.10.2001 (61)

Type	:	aquatic
Species	:	activated sludge
Exposure period	:	3 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC0	:	> 12500
Method	:	OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year	:	1989

GLP	:	no data
Test substance	:	other TS
Test substance	:	Test material was tetraethylene glycol monomethyl ether (CAS No. 23783-42-8).
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Supportive study for non-required endpoint. A related material was tested.

04.10.2001 (26)

Type	:	aquatic
Species	:	anaerobic bact. from a domestic water treatment plant
Exposure period	:	24 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
SG:	:	ca. 3000
Method	:	ETAD Fermentation tube method "Determination of damage to effluent bacteria by the Fermentation Tube Method"
Year	:	1985
GLP	:	no data
Test substance	:	other TS
Source	:	Hoechst AG Frankfurt/Main
Test substance	:	Test material was tetraethylene glycol monomethyl ether (CAS No. 23783-42-8).
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Supportive study for non-required endpoint. A related material was tested.

04.10.2001 (26)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	40
Vehicle	:	
Value	:	= 5300 mg/kg bw
Method	:	other
Year	:	1976
GLP	:	no data
Test substance	:	other TS
Result	:	All animals given 12.18 g/kg died within 3 hours. Eight animals given 7.73 g/kg and 6 given 5.0 g/kg died within 1 day. There were no other deaths over the course of the experiment. Signs of toxicity at 5.0 g/kg included loss of righting reflex and flaccid muscle tone; at 7.73 g/kg included comatose (6/10), flaccid muscle tone, and heavy breathing. There were no signs of toxicity in rats given 3.2 g/kg. The LD50 value (and 95% confidence limit) was 5.3 (4.1-6.8) g/kg.
Test condition	:	Rats (200-250 g) were fasted for approximately 18 hours prior to test material administration. Test material was given by intubation at 3.2, 5.0, 7.73, and 12.18 g/kg to groups of 10 animals. Food and water were freely available after treatment. Rats were observed for toxicity and death for 14 days. The LD50 value and 95% confidence limits were determined by the method of Litchfield and Wilcoxon (J Pharm Exp Ther 96:99, 1949).
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

(38)

Type	:	LD50
Species	:	rat
Strain	:	other: Carworth-Wistar
Sex	:	male
Number of animals	:	
Vehicle	:	no data
Value	:	= 6.73 ml/kg bw
Method	:	other
Year	:	1962
GLP	:	no data
Test substance	:	other TS
Remark	:	It is likely that this study is the same one described in the following record (Carpenter and Striegel, 1960).
Result	:	The oral LD50 for rats averaged 6.73 ml/kg and ranged from 4.13 to 11.0 ml/kg.
Test condition	:	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). Animals were observed up to 14 days after dosing for mortality. The LD50 value and its fiducial range (plus or minus 1.96 standard deviations) were estimated by the method of Thompson (Bacteriol Rev 11: 115, 1947) using the Tables of Weil (Biometrics 8: 249, 1952).
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

(54)

Type	:	LD50
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	15
Vehicle	:	
Value	:	= 6.73 ml/kg bw
Method	:	other
Year	:	1960
GLP	:	no data
Test substance	:	other TS
Remark	:	It is likely that this is the same study described in the previous record (Smyth et al., 1962).
Result	:	All animals receiving 16 ml/kg died, 3 out of 5 dosed with 8 ml/kg, and 1 out of 5 dosed with 4 ml/kg died within 1 day of dosing. Autopsy of dead rats showed a generalized congestion of the abdominal viscera and lungs. The LD50 value was 6.73 (4.13 to 10.96) ml/kg.
Test condition	:	Male Wistar rats (5-6 weeks, 90-120 g) were intubated with test material at dose levels differing by a factor of 2.0 in a geometric series. Rats were observed each day for 14 days. Autopsies were performed on rats that died. Surviving rats were weighed at study termination. The method of moving average for calculating the LD50 was applied to the mortality data.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

(11)

Type	:	LD50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	22
Vehicle	:	
Value	:	> 16 ml/kg bw
Method	:	other
Year	:	1988
GLP	:	no data
Test substance	:	other TS
Result	:	None of the animals treated with any dose of test material died. Animals gained weight over the course of the study and had normal pathology.
Test condition	:	Rats (5/sex/dose) received 8.0 or 16.0 ml/kg test material by stomach intubation. Two male rats were also dosed with 4.0 ml/kg. Doses were varied by adjusting the volume of test material or its dilution. Rats were fasted overnight before dosing. Male and female rats weighed approximately 250 and 200 g at study initiation. Animals were weighed before dosing and at days 7 and 14 after dosing. At death or sacrifice, each animal was subjected to gross pathologic evaluation.
Test substance	:	Test material (CARBOWAX MPEG-350; CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(1) valid without restriction. Study was conducted in a robust manner.

Flag	:	Supportive study for SIDS endpoint. A related material was tested.
04.10.2001		(48)
Type	:	LD50
Species	:	rat
Strain	:	other: albino
Sex	:	male
Number of animals	:	12
Vehicle	:	
Value	:	= 22 ml/kg bw
Method	:	other
Year	:	1947
GLP	:	no data
Test substance	:	other TS
Result	:	All animals dosed with 50 ml/kg died within 1 day. None of the rats dosed with 10 ml/kg died. Animals dosed with 10 ml/kg gained from 23 to 68 grams over 14 days. The LD50 was estimated to be 22 ml/kg (method of extrapolation not given).
Test condition	:	Groups of 6 rats (91-106 g) were dosed with 10 ml/kg (approximately 1 ml) or 50 ml/kg (approximately 4.7-5.3 ml) undiluted test material by stomach tube. Body weight gain and deaths were observed over a period of 14 days.
Test substance	:	methoxy polyethylene glycol of approximately 350 molecular weight
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.
04.10.2001		(9)
Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	> 15000 mg/kg bw
Method	:	other: Interne Richtlinie der Hoechst AG
Year	:	1977
GLP	:	no data
Test substance	:	other TS
Test substance	:	Test material was tetraethylene glycol monomethyl ether (CAS No. 23783-42-8).
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.
04.10.2001		(23)
Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	> 2000 mg/kg bw
Method	:	OECD Guide-line 401 "Acute Oral Toxicity"
Year	:	1988
GLP	:	yes
Test substance	:	other TS

Test substance	:	Test material was tetraethylene glycol monomethyl ether (CAS No. 23783-42-8).
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

04.10.2001 (24)

Type	:	LD50
Species	:	rat
Strain	:	Fischer 344
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Value	:	> 5000 mg/kg bw
Method	:	other
Year	:	1992
GLP	:	yes
Test substance	:	other TS
Test substance	:	Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives
Reliability	:	(1) valid without restriction
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

04.10.2001 (16)

Type	:	LD50
Species	:	rat
Strain	:	other: Carworth Farms-Nelson
Sex	:	male
Number of animals	:	15
Vehicle	:	
Value	:	= 11300 mg/kg bw
Method	:	other
Year	:	1958
GLP	:	no data
Test substance	:	other TS
Result	:	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. The LD50 value was 11.3 ml/kg.
Test condition	:	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.
Test substance	:	Test material was triethylene glycol monomethyl ether (CAS No. 112-35-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

01.10.2001 (10)

Type	:	LD50

Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	40
Vehicle	:	
Value	:	= 8500 mg/kg bw
Method	:	other
Year	:	1977
GLP	:	no data
Test substance	:	other TS
Result	:	One rat given 7.12 g/kg died on day 10. Nine out of 10 rats given 10.14 g/kg died by day 3, and all rats given 14.43 g/kg died within 24 hours. Signs of toxicity were lethargy, ataxia, blood in the urogenital area and piloerection.
Test condition	:	Rats (200-300 g) were fasted for approximately 18 hours prior to test material administration. Test material was given by intubation at 5.0, 7.12, 10.14, and 14.43 g/kg to groups of 10 animals. Food and water were freely available after treatment. Rats were observed for toxicity and death for 14 days. The LD50 value and 95% confidence limits were determined by the method of Horn (Biometrics 12:311, 1956).
Test substance	:	Test material was triethylene glycol monoethyl ether (CAS No. 112-50-5).
Reliability	:	(2) not assignable. Purity of test material is not stated
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

01.10.2001 (43)

Type	:	LD50
Species	:	rat
Strain	:	other: albino
Sex	:	male
Number of animals	:	40
Vehicle	:	other: 1% Tergitol
Value	:	= 10610 mg/kg bw
Method	:	other
Year	:	1945
GLP	:	no
Test substance	:	other TS
Result	:	All rats given 7.95 g/kg lived to day 14. The incidence of mortality in the other groups was 1/10 for the 8.9 g/kg group, 6/10 for the 10.0 g/kg group, and 10.10 for the 12.6 g/kg group. All deaths occurred within 5 days. Survivors gained weight and appeared normal histologically. The LD50 value was calculated as 10.61 g/kg, with a range of 9.98 to 11.28 g/kg.
Test condition	:	Groups of 10 male rats (87-124 g) were given test material by gavage as a dispersion in 1% Tergitol 7 at doses of 7.95, 8.9, 10.0, and 12.6 g/kg (1.4 to 3.0 ml of dispersion containing 0.5 g/ml). Mortality was recorded over 14 days. Body weights were determined at study termination (for survivors).
Test substance	:	Test material was triethylene glycol monoethyl ether (CAS No. 112-50-5).
Reliability	:	(2) valid with restrictions. Purity of test material is not known.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

01.10.2001 (51)(52)(53)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LCLo
Species	:	rat
Strain	:	Wistar
Sex	:	
Number of animals	:	10
Vehicle	:	

Exposure time	:	1 hour(s)
Value	:	> 200 mg/l
Method	:	other
Year	:	1976
GLP	:	no data
Test substance	:	other TS
Result	:	Rats gained weight over the 14 day period. There were no signs of toxicity. All animals survived the exposure.
Test condition	:	Ten rats (200-250 g, sex not stated) were placed in a 50 liter chamber and exposed to a nominal concentration of 200 mg/liter of test material for one hour. The rats were observed daily over 14 days for signs of toxicity. Body weights were recorded prior to and 14 days after treatment.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

(39)

Type	:	other
Species	:	rat
Strain	:	other: albino
Sex	:	no data
Number of animals	:	6
Vehicle	:	
Exposure time	:	8 hour(s)
Method	:	other
Year	:	1962
GLP	:	no data
Test substance	:	other TS
Remark	:	It is likely that this study is the same one described in the following record (Carpenter and Striegel, 1960).
Result	:	All animals survived an 8-hr exposure period to concentrated vapor.
Test condition	:	Male or 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 the 14-day observation period.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

(54)

Type	:	other
Species	:	rat
Strain	:	Wistar
Sex	:	female
Number of animals	:	6
Vehicle	:	
Exposure time	:	8 hour(s)
Method	:	other
Year	:	1960
GLP	:	no data
Test substance	:	other TS
Remark	:	It is likely that this is the same study described in the previous record (Smyth et al., 1962).
Result	:	All animals survived the exposure.
Test condition	:	Concentrated vapor (25 degrees C) was generated by passing air at 2.5

liters/min through a fritted glass disc immersed in 50 ml of butoxy triglycol. Rats were exposed for 8 hours and observed for 14 days.

Test substance : Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability : (2) valid with restrictions. Purity of test material was not noted.
Flag : Supportive study for SIDS endpoint. A related material was tested.

(11)

Type : LCLo
Species : rat
Strain : Wistar
Sex :
Number of animals : 10
Vehicle :
Exposure time : 1 hour
Value : > 200 mg/l
Method : other
Year : 1977
GLP : no data
Test substance : other TS
Result : Rats gained weight over the 14 day period. There were no signs of toxicity. All animals survived the exposure.
Test condition : Ten rats (200-250 g, sex not stated) were placed in a 50 liter chamber and exposed to a nominal concentration of 200 mg/liter of test material for one hour. The rats were observed daily over 14 days for signs of toxicity. Body weights were recorded prior to and 14 days after treatment.
Test substance : Test material was triethylene glycol monoethyl ether (CAS No. 112-50-5).
Reliability : (2) valid with restrictions. Purity of test material was not noted.
Flag : Supportive study for SIDS endpoint. A related material was tested.

(44)

Type : other
Species : rat
Strain : other: Carworth-Wistar
Sex : female
Number of animals : 6
Vehicle :
Exposure time : 8 hour(s)
Method : other
Year : 1958
GLP : no data
Test substance : other TS
Result : All animals survived an 8-hr exposure period to concentrated vapor and had normal weight gains.
Test condition : 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 the 14-day observation period.
Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6).
Reliability : (2) valid with restrictions. Purity of test material was not noted.
Flag : Supportive study for SIDS endpoint. A related test material was utilized.
28.09.2001 (10) (54)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	
Vehicle	:	no data
Value	:	= 3.54 ml/kg bw
Method	:	other: variation of one-day cuff method of Draize
Year	:	1962
GLP	:	no data
Test substance	:	other TS
Remark	:	It is likely that this study is the same one described in the following record (Carpenter and Striegel, 1960).
Result	:	The LD50 value averaged 3.54 ml/kg and ranged from 1.06 to 11.8 ml/kg.
Test condition	:	Groups of four rabbits weighing between 2.5 to 3.5 kg were treated with 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. 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).
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

(54)

Type	:	LD50
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	16
Vehicle	:	
Value	:	= 3.54 ml/kg bw
Method	:	other
Year	:	1960
GLP	:	no data
Test substance	:	other TS
Remark	:	It is likely that this is the same study described in the previous record (Smyth et al., 1962).
Result	:	Three out of four rabbits treated with 10 ml/kg died within 3 days. The remaining animal in this group lost 110 g of weight over the 14-day recovery period. Two out of four rabbits treated with 5 ml/kg or 2.5 ml/kg, and 1 treated with 1.25 ml/kg died by day 9. Findings upon autopsy were cherry red and hemorrhaged lungs, dark livers mottled with prominent acini, and pale and mottled kidneys. The LD50 value was 3.54 (1.06 to 11.85) ml/kg.
Test condition	:	Groups of 4 male rabbits (3-5 months, 2.5 kg avg) were treated with 1.25, 2.5, 5.0 or 10 ml/kg dermally (on clipped skin). A VINYLITE sheeting was used to keep the test material in contact with the skin. Rabbits were immobilized during the 24-hour skin contact period. After the dressing was removed, animals were observed for 14 days. The moving average method was used to calculate the LD50.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

(11)

Type	:	LDLo
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	
Number of animals	:	10
Vehicle	:	
Value	:	> 2000 mg/kg bw
Method	:	other
Year	:	1976
GLP	:	no data
Test substance	:	other TS
Result	:	There were no deaths or signs of toxicity.
Test condition	:	Ten rabbits (2.3 to 3.0 kg) were clipped free of abdominal hair. Epidermal abrasions were made longitudinally every 2 to 3 cm over the clipped area of 5 rabbits. The abrasions were deep enough to penetrate the stratum corneum, but not deep enough to produce bleeding. A single dose of 2.0 g/kg was applied to the exposed area. The area was covered with gauze and the trunk wrapped with impervious material for 24 hours. The dressing was removed, rabbits were cleaned, and animals were evaluated over 14 days.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

(37)

Type	:	LD50
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Value	:	> 16 ml/kg bw
Method	:	other
Year	:	1988
GLP	:	no data
Test substance	:	other TS
Result	:	No animals died during the course of the study. No signs of systemic toxicity or irritation were noted.
Test condition	:	Five rabbits of each sex (weighing between 2 and 3 kg) were subjected to 24 hours of contact with the test material (16 ml/kg) , which was retained under impervious sheeting on the clipped, intact skin of the trunk. If necessary, gauze was wrapped around the trunk over the sample to prevent leakage. Bandaging tape was wrapped over the impervious sheeting. Excess fluid was removed after the contact period to diminish ingestion. Body weights were determined before and 7 and 14 days following test material application. Deaths were monitored for 14 days.
Test substance	:	Test material (CARBOWAX MPEG-350) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(1) valid without restriction
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

04.10.2001 (48)

Type	:	LD50
Species	:	rat
Strain	:	Fischer 344
Sex	:	male/female
Number of animals	:	10
Value	:	> 2000 mg/kg bw
Method	:	other
Year	:	1992
GLP	:	yes
Test substance	:	other TS
Test substance	:	Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives
Reliability	:	(1) valid without restriction.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

04.10.2001 (16)

Type	:	LD50
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	
Vehicle	:	
Value	:	= 7400 mg/kg bw
Method	:	other
Year	:	1958
GLP	:	no data
Test substance	:	other TS
Result	:	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. The LD50 value was 7.13 ml/kg (7.4 g/kg).
Test condition	:	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).
Test substance	:	The test substance was triethylene glycol monomethyl ether (CAS 112-35-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

02.10.2001 (10) (54)

Type	:	LD50
Species	:	rabbit
Strain	:	
Sex	:	

Number of animals	:	
Vehicle	:	
Value	:	= 8200 mg/kg bw
Method	:	other
Year	:	1951
GLP	:	no
Test substance	:	other TS
Result	:	LD50 value was 8 ml/kg (8.2 mg/kg)
Test substance	:	The test substance was triethylene glycol monoethyl ether (CAS 112-50-5).
Reliability	:	(4) not assignable. Details on how value was obtained were not given.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

02.10.2001 (53)

Type	:	LDLo
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	
Number of animals	:	10
Vehicle	:	
Value	:	> 2000 mg/kg bw
Method	:	other
Year	:	1977
GLP	:	no data
Test substance	:	other TS
Result	:	There were no deaths or signs of systemic toxicity.
Test condition	:	Ten rabbits (1.9 to 3.2 kg) were clipped free of abdominal hair. Epidermal abrasions were made longitudinally every 2 to 3 cm over the clipped area of 5 rabbits. The abrasions were deep enough to penetrate the stratum corneum, but not deep enough to produce bleeding. A single dose of 2.0 g/kg was applied to the exposed area. The area was covered with gauze and the trunk wrapped with impervious material for 24 hours. The dressing was removed, rabbits were cleaned, and animals were evaluated over 14 days.
Test substance	:	Test material was triethylene glycol monoethyl ether (CAS No. 112-50-5).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related material was tested.

(42)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	
Exposure	:	open
Exposure time	:	24 hour(s)
Number of animals	:	5
PDII	:	
Result	:	moderately irritating
EC classification	:	
Method	:	other
Year	:	1962
GLP	:	no data
Test substance	:	other TS
Result	:	An average irritation Grade of 3 was obtained with undiluted test material, indicating mild irritation. Marked capillary injection was noted on 4 animals

and moderate injection on the 5th.

Test condition	:	Undiluted test solution (0.01 ml) was applied 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.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Critical study for non-required endpoint. A related material was tested. (11) (54)

Species	:	rabbit
Concentration	:	
Exposure	:	occlusive
Exposure time	:	24 hour(s)
Number of animals	:	
PDII	:	
Result	:	
EC classification	:	
Method	:	other
Year	:	1960
GLP	:	no data
Test substance	:	other TS
Remark	:	Listed here are dermal irritation results from an acute dermal toxicity study performed with high doses (1.25 to 10 ml/kg). Refer to Section 5.1.3 for additional details
Result	:	Marked erythema of skin was found upon removal of the dressing (doses not stated). Some small scabs and extensive desquamation were present at Day 14.
Test condition	:	Groups of 4 male rabbits (3-5 months, 2.5 kg avg) were treated with 1.25, 2.5, 5.0 or 10 ml/kg dermally (on clipped skin). A VINYLITE sheeting was used to keep the test material in contact with the skin. Rabbits were immobilized during the 24-hour skin contact period. After the dressing was removed, animals were observed for 14 days.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint. A related material was tested. (11)

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	24 hour(s)
Number of animals	:	6
PDII	:	
Result	:	not irritating
EC classification	:	
Method	:	other
Year	:	1976
GLP	:	no data
Test substance	:	other TS
Result	:	An erythema score of 1 (barely perceptible) was observed in 1 rabbit at 24 hours (abraded skin) and another at 72 hours (intact skin). All others received erythema scores of 0. No edema was observed at 24 or 72 hours.
Test condition	:	Six rabbits were clipped over the back and sides with an electric clipper. A site (1" x 1") to the left of the spinal column was abraded. Abrasions were minor incisions through the stratum corneum that did not disturb the derma or produce bleeding. Test material (0.5 ml) was applied to a surgical gauze (1" square, 2 layers thick). The patches were placed on test sites and secured with adhesive tape. The trunk was wrapped with impervious material. Patches were removed after 24 hours. Dermal reactions were

evaluated at 24 and 72 hours in accordance with the Consumer Product Safety Act, Title 16 CFR 1500.41.

Test substance : Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability : (2) valid with restrictions. Purity of test material was not noted.
Flag : Supportive study for non-required endpoint. A related material was tested.
(40)

Species : rabbit
Concentration : undiluted
Exposure : occlusive
Exposure time : 4 hour(s)
Number of animals : 6
PDII :
Result : not irritating
EC classification :
Method : Draize Test
Year : 1988
GLP : no data
Test substance : other TS
Result : Scores of 0 were obtained for both erythema (and eschar formation) and edema. The material was therefore non-irritating.
Test condition : Test material (0.5 ml) was applied to the clipped, intact skin of six rabbits (3 of each sex). The material was loosely covered with a gauze patch an impervious sheeting. Rabbits were restrained for a 4-hour contact period. Excess material was removed after contact. The skin reaction was scored by the method of Draize at one hour, and 1, 2, 3, and 7 days following dosing.
Test substance : Test material (CARBOWAX MPEG-350, CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability : (1) valid without restriction. Study was conducted in a robust manner.
Flag : Supportive study for non-required endpoint. A related material was tested.
(48)

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
PDII :
Result :
EC classification : not irritating
Method : OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year : 1988
GLP : yes
Test substance : other TS
Remark : Einwirkzeit: 4 h; nicht kennzeichnungspflichtig [Effect after 4 hours: none of recognizable significance.]

Test substance : Test material was tetraethylene glycol monomethyl ether (CAS No. 23783-42-8).
Reliability : (2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.

Flag	:	Supportive study for non-required endpoint. A related material was tested.
04.10.2001		(27)
Species	:	rabbit
Concentration	:	undiluted
Exposure	:	semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	6
PDII	:	
Result	:	not irritating
EC classification	:	
Method	:	other
Year	:	1992
GLP	:	yes
Test substance	:	other TS
Test substance	:	Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.
Reliability	:	(1) valid without restriction. Study was conducted in a robust manner.
Flag	:	Supportive study for non-required endpoint. A related material was tested.
04.10.2001		(16)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	open
Exposure time	:	24 hour(s)
Number of animals	:	5
PDII	:	
Result	:	slightly irritating
EC classification	:	
Method	:	other
Year	:	1962
GLP	:	no data
Test substance	:	other TS
Result	:	An irritation Grade of 2 was obtained with undiluted test material, indicating minimal irritation.
Test condition	:	Undiluted test solution (0.01 ml) was applied 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.
Test substance	:	Test material was triethylene glycol monomethyl ether (CAS No. 112-35-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint. A related material was tested.
02.10.2001		(10) (54)

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	24 hour(s)
Number of animals	:	6
PDII	:	
Result	:	not irritating
EC classification	:	
Method	:	other

Year	:	1977
GLP	:	no data
Test substance	:	other TS
Result	:	An erythema score of 1 (barely perceptible) was observed in 2 rabbits at 24 hours (intact and abraded skin). All others received erythema scores of 0. The mean erythema score was 0.33. No edema was observed at 24 or 72 hours. The mean primary irritation score was 0.17.
Test condition	:	Six rabbits were clipped over the back and sides with an electric clipper. A site to the left of the spinal column was abraded. Abrasions were minor incisions through the stratum corneum that did not disturb the derma or produce bleeding. Test material (0.5 ml) was applied to a surgical gauze (1" square, 2 layers thick). The patches were placed on test sites and secured with adhesive tape. The trunk was wrapped with impervious material. Patches were removed after 24 hours. Dermal reactions were evaluated at 24 and 72 hours in accordance with the Consumer Product Safety Act, Title 16 CFR 1500.41.
Test substance	:	Test material was triethylene glycol monoethyl ether (CAS No. 112-50-5).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint. A related material was tested.

(45)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	.1 ml
Exposure Time	:	
Comment	:	
Number of animals	:	6
Result	:	irritating
EC classification	:	R41: risk of severe injury to eyes
Method	:	other
Year	:	1976
GLP	:	no data
Test substance	:	other TS
Result	:	Conjunctival redness, chemosis and discharge scores of 2-3 (diffuse crimson to beefy red) were noted at all time points in all rabbits (except 1 rabbit that had a chemosis score of 1 at 72 hours). Iris scores of 1 (folds above normal, congestion, swelling, corneal injection, sluggish reaction to light) were observed in all animals at each time point. The total conjunctival score ((redness + chemosis + discharge) x 2) ranged from 10-16 out of a possible 20. The highest overall score was 21 out of a possible 110.
Test condition	:	Six New Zealand white rabbits were used in the study. Test material (0.1 ml) was instilled into the conjunctival sac of one eye of each rabbit on Day 0. Ocular reactions were graded in accordance with the Consumer Product Safety Act, Title 16 CFR 1500.42 at 1, 2, and 3 days after instillation of the test material.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint. A related material was tested.

(41)

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	6

Result	:	highly irritating
EC classification	:	
Method	:	other: Carpenter and Smyth (Am J Opthal 29:1363, 1946)
Year	:	1962
GLP	:	no data
Test substance	:	other TS
Remark	:	It is likely that this study is the same one described in the following record (Carpenter and Striegel, 1960).
Result	:	A test score of 5 was reached, indicating that the test material caused severe eye irritation.
Test condition	:	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.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint. A related material was tested. (54)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	highly irritating
EC classification	:	R41: risk of severe injury to eyes
Method	:	other
Year	:	1960
GLP	:	no data
Test substance	:	other TS
Remark	:	It is likely that this is the same study described in the previous record (Smyth et al., 1962).
Result	:	The average eye injury score was 5. Rabbit eyes were necrosed by instillation of 0.02 ml. Minor to moderate injury resulted from the instillation of 0.005 ml.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint. A related material was tested. (11)

Species	:	rabbit
Concentration	:	
Dose	:	.1 ml
Exposure Time	:	
Comment	:	
Number of animals	:	6
Result	:	slightly irritating
EC classification	:	
Method	:	other
Year	:	1988
GLP	:	no data
Test substance	:	other TS
Result	:	Instillation of test material resulted in no corneal injury or iritis. Minor conjunctival irritation developed in all 6 rabbits. Moderate discharge was seen in several of the eyes. These effects resolved by 24 hours.
Test condition	:	Six male New Zealand white rabbits were dosed with 0.1 ml of test

material. The test material was instilled into the lower conjunctival sac or placed directly on one eye per animal. The eyes were scored at 1 and 4 hours, and 1, 2, 3, and 7 days after dosing. Florescein (2%) was added to the eyes before dosing and after 1 day of exposure to assess corneal injury.

Test substance	:	Test material (CARBOWAX MPEG-350, CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(1) valid without restriction. Study was conducted in a robust manner.
Flag	:	Supportive study for non-required endpoint. A related material was tested. (48)

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	not irritating
EC classification	:	
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1988
GLP	:	yes
Test substance	:	other TS
Remark	:	Einwirkzeit: 4 h; nicht kennzeichnungspflichtig.[Effect after 4 hours: none of recognizable significance].

Test substance	:	Test material was tetraethylene glycol monomethyl ether (CAS No. 23783-42-8).
Reliability	:	(2) valid with restrictions. Original reference was not available. Information (including the reliability code) came from a previous IUCLID data set produced for the European Chemicals Bureau. This study is assigned a reliability rating of 4 for this submission since it was not reviewed.
Flag	:	Supportive study for non-required endpoint. A related material was tested.

04.10.2001 (28)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure Time	:	72 hour(s)
Comment	:	
Number of animals	:	6
Result	:	slightly irritating
EC classification	:	
Method	:	
Year	:	1982
GLP	:	yes
Test substance	:	other TS
Test substance	:	Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, (20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives

Reliability	:	(1) valid without restriction. Study was conducted in a robust manner.
Flag	:	Supportive study for non-required endpoint. A related material was tested.
04.10.2001		(16)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.5 ml
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	slightly irritating
EC classification	:	
Method	:	other
Year	:	1962
GLP	:	no data
Test substance	:	other TS
Result	:	Five rabbit eyes were not injured by 0.5 ml undiluted test material (grade 1).
Test condition	:	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.
Test substance	:	Test material was triethylene glycol monomethyl ether (CAS No. 112-35-6).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint. A related material was tested.
02.10.2001		(10) (54)

Species	:	rabbit
Concentration	:	
Dose	:	.1 ml
Exposure Time	:	
Comment	:	
Number of animals	:	6
Result	:	irritating
EC classification	:	
Method	:	other
Year	:	1977
GLP	:	no data
Test substance	:	other TS
Result	:	Conjunctival redness, chemosis and/or discharge scores of 1 or 2 were noted at 24 hours in all rabbits. These findings completely resolved in 2 rabbits by 72 hours. Slight redness and discharge was observed in 4 and 2 rats (respectively) at 72 hours. Iris and corneal opacity scores of 0 were observed in all animals at each time point. The total conjunctival score [(redness + chemosis + discharge) x 2] at 24 hours ranged from 2-8 out of a possible 20. The highest overall score was 8 out of a possible 110.
Test condition	:	Six New Zealand white rabbits were used in the study. Test material (0.1 ml) was instilled into the conjunctival sac of one eye of each rabbit on Day 0. The contralateral eye served as a control. Ocular reactions were graded in accordance with the Consumer Product Safety Act, Title 16 CFR 1500.42 at 1, 2, and 3 days after instillation of the test material.
Test substance	:	Test material was triethylene glycol monoethyl ether (CAS No. 112-50-5).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for non-required endpoint. A related material was tested.

(46)

5.3 SENSITIZATION

5.4.1 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	dermal
Exposure period	:	91 days
Frequency of treatment	:	6 hr/day, 5 days/week
Post obs. period	:	none
Doses	:	400, 1200, 4000 mg/kg bw
Control group	:	other:sham
NOAEL	:	= 4000 mg/kg bw (summary preparer); > 400 and < 1200 mg/kg bw (EPA)
Method	:	other
Year	:	1990
GLP	:	yes
Test substance	:	other TS
Remark	:	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). 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 for Sprague-Dawley rats (0-17%).
Result	:	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.

Test condition : 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. 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 sacrifice), clinical chemistry (just prior to sacrifice), 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.

Conclusion : 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 unattected in this TGME study. Taking all factors into considereation, the testicular lesions observed in this dermal study could not be directly attributed to TGME exposure."

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6). Purity (as determined by gas chromatography) was 99.23 % at the onset of the study and 99.24% at completion of the in-life phase.

Reliability : (1) valid without restriction.

Flag : Critical study for SIDS endpoint. A related test material was utilized.

04.10.2001 (13) (18)

Species : rabbit
Sex : male
Strain : New Zealand white
Route of admin. : dermal
Exposure period : 90 days
Frequency of treatment : 6 hr/day, 5 days/week
Post obs. period :
Doses : 1 ml of 50% and 100% material (approximately 169 and 338 mg/kg/day)
Control group : yes, concurrent vehicle
NOAEL : = 338 mg/kg bw
Method : other
Year : 1985
GLP : yes
Test substance : other TS
Remark : A preliminary range-finding study in 15 rabbits dosed 6 hr/day for 9 days (Carpenter, Range finding tests on methoxy polyethylene glycols of approximate molecular weights 350, 550 and 750. Melon Institute of Industrial Research, University of Pittsburgh. Report dated 5-13-47. 1947) showed that daily administration of 1 ml of 50% or 100% test material only caused mild skin irritation. Therefore, these doses were chosen for the 90-day study.

The NOAELs for local or systemic effects were not listed by the investigators. Based on the data, these values are 50% and 100%, respectively. Based on weights of animals determined at weekly intervals and the reported density of test material (1.09 g/ml) doses can be calculated on average mg/kg/day basis. These doses are 169 mg/kg/day (for 50%) and 338 mg/kg/day (for 100%).

Result : Mild acanthosis (epidermal thickening) was found in 3 females dosed with 100% material. Transient, dose-related erythema (Grade 1) and

desquamation of skin occurred. No systemic effects were observed in rabbits treated with either 50% or 100% test material.

Test condition : Dosing: New Zealand white rabbits (10/sex/dose) were treated dermally on clipped dorsal skin with 1.0 ml of vehicle (0.1% (w/v) methyl cellulose in distilled water), 50% CARBOWAX MPEG-350 (w/v dilution in 0.1% methyl cellulose in water) or 100% CARBOWAX MPEG-350, for six hours/day, five days per week for 90 days. Body weights of males and females ranged from 2.5 to 3.2 kg and 2.5 to 3.1 kg at study initiation. Rabbits were fitted with Elizabethan collars after dosing to prevent ingestion of test material. After each 6-hour exposure the application site was wiped with a paper towel dampened with water and then dried using a towel. Rabbits were then uncollared until the next treatment.

Observations: All rabbits were observed daily (weekdays) for death, clinical signs and dermal irritation. Any irritation was scored immediately prior to dosing using the Draize system. Body weights were recorded on the morning of the first day of dosing, weekly thereafter and prior to sacrifice. Food consumption was measured weekly. Urine was collected from 5 animals/sex/group during the last two weeks of dosing and subjected to standard analyses. Standard hematology and clinical chemistry parameters were evaluated for all animals just prior to sacrifice.

Necropsy: All animals were sacrificed and necropsied after 13 weeks of treatment. Weights were recorded for liver, kidneys, brain and adrenals of all animals and testes of males. Histopathologic examinations were performed on tissues from high-dose and control animals.

Statistical Analyses: Body weight, food consumption, organ weight and clinical pathology data from the three groups were compared using Levene's test for homogeneity of variance. An analysis of variance was performed on the groups when data were homogeneous. If significant differences were found, group differences were delineated by grouped variance Student t-tests. When data were heterogeneous, Welch and Brown-Forsyth analyses were performed and significant differences among groups were determined using separate variance Student t-tests. Draize skin irritation scores were analyzed using the Kruskal-Wallis test, and significant differences in groups were determined using the Wilcoxon rank sum test (as modified by Mann-Whitney). Frequency data (i.e. histological) were compared using Fisher's exact tests. The p value of 0.05 (two-tailed) was used as the critical level of significance for all analyses.

Test substance : The test material (CARBOWAX MPEG 350, CAS No. 9004-74-4) was reported to be chemically inert (stable for > 6 months at room temperature) and 99.8% pure. This material is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).

Reliability : (1) valid without restriction.

Flag : Critical study for SIDS endpoint. A related test material was utilized.

04.10.2001 (8) (20)

Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : dermal
Exposure period : 4 weeks

Frequency of treatment	:	5 days/week
Post obs. period	:	
Doses	:	1250, 2500, 5000 mg/kg/day
Control group	:	other:sham
NOAEL	:	= 1250 mg/kg
Method	:	other
Year	:	1987
GLP	:	yes
Test substance	:	other TS
Remark	:	One, 3, and 2 animals in the low-, mid- and high-dose groups slipped their collars and therefore may have ingested the material during grooming. Results in these animals were not significantly different from those animals that did not slip their collars. Therefore, possible ingestion of material in these animals did not appear to affect the results of the study. The investigators did not identify a NOAEL for the study. However, they stated "that there were no indications of systemic toxicity secondary to repeated cutaneous exposure to MPEG-350 in this study." Based on the information given, the summary preparer assigned a NOAEL of 1250 mg/kg/day. This value is based on significant effects on body weight or weight gain at higher doses (although the authors stated that these effects may have been due to use of Elizabethan collars). Although the absolute weights of the thymus and testes of rats treated with 1.25 g/kg/day were significantly less than control, relative weights of these organs were not different from control, there were no histological changes in these organs, and these effects were not noted at higher doses. Therefore, they were considered by the summary preparer to be unrelated to treatment.
Result	:	Minor, transient irritation was noted at the application site of all treated animals. Body weights of animals given 5.0 g/kg/day and body weight gains of animals given 2.5 g/kg/day were depressed. Absolute weights of the thymus and testes of rats treated with 1.25 g/kg/day were 83% and 93%, respectively of control weights (significantly different). Relative weights of these organs were not significantly different from control. There were no pathological abnormalities in either of these organs.
Test condition	:	Male rats (52 days old) were divided into 4 groups of 15 animals (control, low-, mid-, and high-dose groups and were acclimated to Elizabethan collars for 7 days before treatment. One mid-dose and 3 high-dose animals were dropped before treatment because they appeared dehydrated. Each group was treated with 0 (sham control), 1.25, 2.5 or 5 g/kg/day test material on shaved backs. Rats were sacrificed 3 days after the last treatment.
Test substance	:	Test material was Carbowax MPEG-350 (CAS No. 9004-74-4) from Union Carbide. This material is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3). Test material also contained 1 ppm of 2-methoxyethanol.
Reliability	:	(1) valid without restriction
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

04.10.2001 (19) (20)

Species	:	rabbit
Sex	:	male/female
Strain	:	New Zealand white

Route of admin.	:	dermal
Exposure period	:	21 days
Frequency of treatment	:	6 hr/day, 5 days/week for 3 weeks
Post obs. period	:	
Doses	:	1000 mg/kg
Control group	:	other:sham
NOAEL	:	=1000 mg/kg
Method	:	other: limit test
Year	:	1986
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Toxicity of triethylene glycol monomethyl (TGME, CAS No. 112-35-6) and monoethyl ethers (TGEE, CAS No. 112-50-5) at 1000 mg/kg also was tested in this study. The skin effects noted for triethylene glycol butyl ether were more severe than those for TGME and TGEE.
Result	:	There were no deaths or signs of overt toxicity over the study period. There were no significant differences in body weights or food consumption between treated or control groups. 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. Mild to moderate desquamation and fissuring of skin was noted in most rabbits after 2 to 3 weeks of treatment with test material. This was confirmed microscopically and consisted of trace acanthosis and trace to moderate dermatitis. Testicular degeneration (scored as trace in severity) , occurred in one rabbit each from the TGEE and TGME-treated groups. This lesion was characterized by the presence of spermatid giant cells, focal tubular hypospermatogenesis, or cytoplasmic vacuolization. The pathologist stated that “random occurrence of this lesion was suggestive of its spontaneous nature and was not test article related. A high incidence of similar changes of spontaneous nature in normal New Zealand White rabbits has been reported by Morton et al. in Vet Pathol 23: 176-183, 1986 and Vet Pathol 23: 210-217, 1986.” 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. Therefore, the NOAEL is 1000 mg/kg/day.
Test condition	:	Rabbits were observed over a 51-52 day pretest period for clinical abnormalities. Prior to randomization, rabbits were fasted (19-23 hours), and blood samples were taken from the central ear artery for control hematological and biochemical evaluations. Healthy rabbits (4- 4.5 months of age) were randomly divided into groups of 5 per sex. Prior to study initiation, hair was removed from the back of each rabbit with an electric clipper. Rabbits were shaved as necessary during the course of the study to prevent the test material from becoming matted in the hair and to facilitate accurate observations. One group of rabbits was left untreated and the other was treated with 1000 mg/kg test material, five days per week for 3 weeks. Dose volumes were calculated based on the specific gravity of test material (as determined at the study site) and the body weight of animals (determined weekly). Test material was placed on the back using a 5 cc plastic syringe. A glass rod was used to evenly distribute the dose over the test site. Following dosing, test sites (of all animals, including controls) were wrapped with gauze bandaging and Dermiform tape and plastic restraint collars were attached to the rabbits. Collars were removed after 6 hours, and test sites (of all animals, including controls) were washed with tepid tap water and dried with paper towels. All animals were fasted for 19-

23 hours before study termination.

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

Body weights (weeks 1, 2, 3, and 4), clinical pathology parameters and organ weights (absolute and relative) were analyzed using Bartlett's test for homogeneity of variance and analysis of variance (one-way). The treatment groups were compared to the controls using the appropriate t-statistic (for equal or unequal variance). Dunnett's multiple comparison tables were used to judge the significance of the differences. Total bilirubin data was transformed to ranks and analyzed using a non-parametric test. All tests were two-tailed, with $p < 0.05$ and $p < 0.01$ as levels of significance.

Test substance : Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6).
Reliability : (2) valid with restrictions. Test duration was shorter than 28 days.
Flag : Supportive study for SIDS endpoint. A related test material was utilized.
04.10.2001 (30)

Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : dermal
Exposure period : 14 days
Frequency of treatment : daily
Post obs. period :
Doses : 1000, 2500, 4000 mg/kg/day
Control group : yes
NOAEL : = 4000 mg/kg bw
Method : other
Year : 1987
GLP : yes
Test substance : other TS
Result : 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.

Test condition	:	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.
Test substance	:	The test substance was triethylene glycol monomethyl ether (CAS 112-35-6). Purity is unknown.
Reliability	:	(2) valid with restrictions.
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.
10.09.2001		(64)

Species	:	rat
Sex	:	male/female
Strain	**:**	Sprague-Dawley
Route of admin.	**:**	drinking water
Exposure period	**:**	91 days
Frequency of treatment	**:**	daily
Post obs. period	**:**	none
Doses	**:**	ca. 400, 1200, 4000 mg/kg/day
Control group	**:**	yes, concurrent no treatment
NOAEL	**:**	= 400 mg/kg bw
LOAEL	**:**	= 1200 mg/kg bw
Method	**:**	other
Year	**:**	1990
GLP	**:**	yes
Test substance	**:**	other TS
Remark	**:**	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). The authors state that “a possible contributing factor in the development of testicular lesions at the high dose was low-level contamination of the test substance with the known testicular toxicant 2-methoxyethanol (EGME). EGME was present in the test substance at a concentration of 0.02 – 0.04 %, resulting in a EGME dose up to 1.7 mg/kg/day for animals in the high dose group. Given the length of the study, it is possible that EGME contributed to the testicular lesions. A comparison between the doses of

EGME and TGME required to produce testicular toxicity indicated that TGME is 350 times less potent than EGME in producing testicular lesions in the rat." The dose of TGME that caused testicular toxicity (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 has determined 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).

Result **:** 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.

Test condition : 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. 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 sacrificed 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).

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6). The purity of the material was at least 98.7%.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint. A related test material was utilized.

04.10.2001 (17) (18)

Species : rat
Sex : male
Strain : no data
Route of admin. : drinking water
Exposure period : 30 days

Frequency of treatment	:	
Post obs. period	:	
Doses	:	180, 750, 3300, 13290 mg/kg/day
Control group	:	yes
NOAEL	:	= 750 mg/kg bw
Method	:	other
Year	:	1985
GLP	:	no data
Test substance	:	other TS
Result	:	Rats receiving the highest dose consumed only 25% of the amount of water as controls. All of them died within 6 to 24 days of exposure (average 13). Necropsy of these animals revealed congestion and cloudy swelling of the liver and cloudy swelling and degeneration of epithelium of the convoluted tubules of the kidneys. None of the other rats died. Rats exposed to 3300 mg/kg/d exhibited decreased weight gain, high blood urea concentrations (4/10), kidney damage (1/10), liver abnormalities (6/10). Animals exposed to 750 or 180 mg/kg/day appeared normal.
Test condition	:	Groups of 10 rats (90-120 g) were given doses of test material in the drinking water at concentrations of 0 (control), 0.12, 0.5, 2 and 8% for 30 days. The actual doses received were 0, 180, 750, 3300 and 13290 mg/kg/d. Water consumption and deaths were monitored daily.
Test substance	:	Test material was triethylene glycol monoethyl ether (CAS No. 112-50-5).
Reliability	:	(2) valid with restrictions. Purity of test material was not noted.
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

04.10.2001 (51)

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	28 days
Frequency of treatment	:	daily
Post obs. period	:	
Doses	:	25, 150, 1000 mg/kg/day
Control group	:	yes
NOAEL	:	= 150 mg/kg bw (NOEL)
Method	:	other
Year	:	1993
GLP	:	yes
Test substance	:	other TS
Result	:	Food intake of males dosed with 1000 mg/kg/day was slightly reduced for first 2 weeks of treatment. Livers of all 5 males and some females dosed with 1000 mg/kg/day showed slight centrilobular hypertrophy (which was considered by the investigators to be adaptive). None of the controls exhibited this effect. There was no significant effect of treatment on liver weight. No effects on other organs (including ovaries and testes) were noted. A NOEL of 150 mg/kg/day was assigned by the investigator.
Test substance	:	Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.
Reliability	:	(1) valid without restriction
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

04.10.2001 (56)

Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	i.v.
Exposure period	:	14 days
Frequency of treatment	:	daily
Post obs. period	:	
Doses	:	1000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL	:	= 1000 mg/kg
Method	:	other
Year	:	1997
GLP	:	yes
Test substance	:	other TS
Remark	:	An increase in aspartate aminotransferase activity, rather than a decrease is indicative of liver toxicity.
Result	:	There was no effect of treatment on body or organ weights or hematological values. Tissues (including testes) from treated animals were histologically similar to those of controls. There was a significant difference in aspartate aminotransferase activity in control (95 +/- 13 IU/L) and treated males (81 +/- 6 IU/L) that was not considered by the investigators to be related to treatment since the values for both groups were within the normal expected range.
Test condition	:	Groups of six rats/sex (6-8 weeks of age, 114 g to 189 g) were dosed intravenously for 14 consecutive days with either vehicle (0.9% sodium chloride, USP), or 1 g/kg/day test material. Animals were observed daily for general health. Body weights were recorded on days 1, 8 and 15 of treatment. All animals were euthanized on day 15. Blood was collected from the posterior vena cava and standard hematological and clinical chemistries were performed. The heart, liver, spleen, kidneys, adrenal glands and gonads were weighed, fixed, and processed for microscopic evaluation. The data were analyzed using a standard BMDP Statistical Software Package.
Test substance	:	Test material was CARBOWAX Sentry MPEG-350 (CAS No. 9004-74-4), NF grade. This material is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).
Reliability	:	(1) valid without restriction
Flag	:	Supportive study for SIDS endpoint. A related test material was utilized.

02.10.2001 (47)

5.5 GENETIC TOXICITY 'IN VITRO'

System of testing	:	Salmonella typhimurium; TA1535, TA1537, TA 98, TA100
Concentration	:	20-5000 micrograms/plate
Cytotoxic conc.	:	> 5000 micrograms/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 471 "Genetic Toxicology: Salmonella typhimurium Reverse Mutation Assay"
Year	:	1983
GLP	:	no data
Test substance	:	other TS
Remark	:	The tests were valid, as positive controls induced at least a two-fold increase in frequency of mutations.

Result : Standard test: The average number of revertant in the controls for strains TA98, TA100, TA1535, and TA1537 in the absence of S-9 were 23, 114, 16, and 9. Addition of S-9 to strain TA98 increased the control mutation frequency to 34. S-9 had no effect on the frequency of mutations in the other strains. Positive controls induced an average of from 152 revertants in TA1535 to 1690 revertants in TA100. The number of revertants induced by test material was not increased from that of control at any concentration. The average number of revertants in cultures treated with test material (in the absence or presence of S-9) ranged from 109-140 in TA100, 12-21 in TA1535, and 8-11 in TA1537. Similar to control TA98 cultures, the average number of revertants in TA98 cultures treated with test material in the presence of S-9 (33-36) were higher than in the absence of S-9 (19-24). Preincubation test: The average number of revertant in the controls for strains TA98, TA100, TA1535, and TA1537 in the absence of S-9 were 24, 111, 17, and 8. Addition of S-9 to strains TA98 and TA1535 increased the control mutation frequency to 33 and 23, respectively. S-9 had no substantial effect on the frequency of mutations in the other strains. Positive controls induced an average of from 94 revertants in TA1537 to 1127 revertants in TA100. The number of revertants induced by test material was not increased from that of control at any concentration. The average number of revertants in cultures treated with test material (in the absence or presence of S-9) ranged from 108-135 in TA100 and 7-11 in TA1537. Similar to control TA98 cultures, the average number of revertants in TA98 and TA1535 cultures treated with test material in the presence of S-9 (35-41 and 18-26, respectively) were higher than in the absence of S-9 (19-24 and 14-18, respectively).

Test condition : Standard test: Test tubes containing 2 ml of soft agar, bacteria (0.1 ml of > = 10E8 S. typhimurium TA98, TA100, TA1535, or TA1537), test chemical (0.1 ml of test solution, positive control, or aqua dest. solvent) and either buffer or S-9 mix from Aroclor 1254-induced, male, Sprague Dawley rats (0.5 ml) were prepared. After mixing, the samples were poured onto minimal glucose agar plates within 30 seconds.

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

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

The Salmonella stains were periodically checked for deep rough character (rfa), UV sensitivity (uvrB), and ampicillin resistance (R factor plasmid).

Histidine auxotrophy was automatically checked in each experiment via the spontaneous mutation rate.

Test substance : Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6). Test material purity was 87.2%.

Reliability : (2) valid with restrictions. This was an OECD guideline study, but only 4 strains were tested. Purity of test material is not high.

Flag : Critical study for SIDS endpoint. A related test material was used.

03.10.2001 (3)

Type : Ames test
System of testing : S. typhimurium strains TA98, TA100, TA1535, TA1537
Concentration : up to 5000 micrograms/plate
Cytotoxic conc. : > 5000 micrograms/plate
Metabolic activation : with and without
Result : negative
Method : other: Test Standard 40 CFR 798.5265
Year : 1990
GLP : yes
Test substance : other TS
Remark : 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.
Result : Concentrations up to 5000 micrograms/plate did not cause toxicity or cause an increase in mutagenicity above that of negative controls.
Test condition : 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.

Test substance : Test substance was triethylene glycol monomethyl ether (CAS No. 112-35-6). Purity was 99.23%.

Reliability : (2) valid with restrictions. Only four strains of bacteria were used in the test.

Flag : Supportive study for SIDS endpoint. A related test material was utilized.

04.10.2001 (49)

Type : Ames test
System of testing : S. typhimurium TA98, TA100, TA1535, TA1537, TA1538

Concentration : 1, 3, 10, 30, 110 mg/plate
Cytotoxic conc. : > 110 mg/plate
Metabolic activation : with and without
Result : negative
Method : other
Year : 1984
GLP : yes
Test substance : other TS
Remark : The test was valid, as positive controls caused mutagenicity and negative controls exhibited spontaneous reversion rates that were within historical range.
Result : Mutagenic activity was not observed with any concentration in any of the strains (with or without bacterial activation).
Test condition : Test material was dissolved in water to a concentration of 300 mg/ml for doses of 30 mg/plate and below. All subsequent dilutions were made in the same solvent. Dilutions of test substance were made fresh each day and were gravimetrically analyzed. The volume of test material used in each test was 100 microliters. If necessary, phosphate buffered saline was added to adjust the volume.

A preliminary toxicity test was performed in strain TA100 to determine concentrations to use on other strains (TA98, TA1535, TA1537, TA1538). None of the doses used (up to 100 mg/plate) were toxic. Test material was tested in the Ames assay in triplicate at five doses (1, 3, 10, 30 and 110 mg/plate). Testing was performed with and without metabolic activation (0.5 ml of S9 mix containing 50 microliters of S9 liver homogenate from Aroclor 1254-induced, Sprague-Dawley male rats). Concurrent water and positive controls (4-nitro-o-phenylenediamine for TA98 and TA 1538, sodium azide for TA100 and TA1535 and 9-aminoacridine for TA1537 in the absence of S9 and 2-aminoanthracene for all stains in the presence of S9) were run with each test.
Test substance : The test material (CARBOWAX MPEG-350; CAS No. 9004-74-4) is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).

Purity of test material was 99.8%. Impurities included 0.1% water, 0.05% ethylene glycol, 0.05% diethylene glycol, and 50-150 ppm BHT.
Reliability : (1) valid without restriction
Flag : Supportive study for SIDS endpoint. A related test material was utilized.
04.10.2001 (59)

Type : Ames test
System of testing : S. typhimurium strains TA98, TA100, TA1535, TA1537, TA1538
Concentration : up to 5000 micrograms per plate
Cytotoxic conc. : > 5000 micrograms per plate
Metabolic activation : with and without
Result : negative
Method : other
Year : 1992
GLP : yes
Test substance : other TS
Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No.

143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.

Reliability : (1) valid without restriction
Flag : Supportive study for SIDS endpoint. A related test material was utilized.
04.10.2001 (7)

Type : Bacterial reverse mutation assay
System of testing : E. coli WP2uvrA pKM101
Concentration : up to 5000 micrograms per plate
Cytotoxic conc. : > 5000 micrograms
Metabolic activation : with and without
Result : negative
Method : other
Year : 1992
GLP : yes
Test substance : other TS
Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.
Reliability : (1) valid without restriction
Flag : Supportive study for SIDS endpoint. A related test material was utilized.
04.10.2001 (7)

Type : HGPRT assay
System of testing : Chinese hamster ovary cell
Concentration : 2000 to 5000 micrograms/plate
Cytotoxic conc. : > 5000 micrograms
Metabolic activation : with and without
Result : negative
Method : other: Test Standard 40 CFR 798.5300
Year : 1990
GLP : yes
Test substance : other TS
Remark : 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).
Result : 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.
Test condition : 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.

Test substance : The test substance was triethylene glycol monomethyl ether (CAS No. 112-35-6). Purity was 99.23%.
Flag : Supportive study for SIDS endpoint. A related test material was utilized.
Reliability : (1) valid without restriction
04.10.2001 (33)

Type : Chromosomal aberration test
System of testing : Chinese Hamster Ovary Cell
Concentration : up to 5000 micrograms/ml
Cytotoxic conc. : > 5000 micrograms/ml
Metabolic activation : with and without
Result : negative
Method : other
Year : 1992
GLP : yes
Test substance : other TS

Remark : The small random increases in the number of chromatid gaps and/or isogaps in one experiment with S-9, which were not dose-dependent and not different from the untreated controls were not considered to be compound-related effects by study personnel.

Result : Cells exposed to test material at concentrations up to 5000 micrograms/ml showed no increase in chromosome damage or no linear trend compared to negative controls in either experiment. The positive control induced significantly more cells with aberrations compared to the negative controls (for untreated control and for solvent control). In the first experiment with S-9 (up to 1875 micrograms/ml test material), there was no effect of treatment on the incidence of type of aberration observed. However, there was a significant difference in the number of cells with chromatid gaps and/or isogaps between the untreated control (7/200) and solvent control cultures (1/200). In the second experiment with S-9 (cells were treated with 1500, 3000 or 5000 micrograms/ml test material), there was a significant difference in the number of cells with aberrations including gaps (11/200) and cells with chromatid gaps and/or isogaps (8/200) at the 1500 micrograms/ml compared to the solvent control (2/199 and 0/199, respectively). There also was a significant increase in the number of cells with chromatid gaps and/or isogaps at the high concentration (5/200) compared to control, and between both controls (untreated control had 7/200). No linear trend was observed either by including or excluding the solvent control from the analysis. The positive control caused increases in aberrations with and without gaps compared to the solvent control in both studies.

Test condition : Cells (2 x 10E5) were incubated with medium containing the test compound or relevant controls [untreated control, solvent control and positive controls methyl methanesulphonate (20 micrograms/ml without S-9) and benzo(a)pyrene (25 micrograms/ml with S-9)] for either 3 hours in the presence of S9 mix (from Aroclor 1254-induced rat liver) or 24 hours in the absence of S9 mix. The concentrations of test material used (from 10 to 5000 micrograms/ml without S-9 and 100 to 5000 micrograms/ml with S-9) were chosen based on the results of preliminary miscibility and mitotic index studies. Duplicate cultures were prepared for each test condition. Two separate experiments were conducted using different concentrations. Metaphase cells were prepared on glass microscope slides for the analysis of chromosome aberrations 24 hours following exposure for the cultures with or without S9 mix. All slides were coded. Where possible, 200 metaphases were scored for each dose group. Only those cells showing the modal chromosome number (20) +/- 2 were analyzed for chromosome damage. Chromosome aberrations were classified according to the scheme described by Savage (J Med Genetics 12:103-122, 1976). The mitotic index of each group was assessed by counting the number of metaphases in a total of 1000 cells. Data were assessed for heterogeneity using the Fisher's exact test. The number of aberrations excluding gaps, aberrations including gaps, isogaps and/or chromatid gaps and polyploidy and/or endoreduplication of treated cells was compared to controls using the Fisher's exact test. A Cochran-Armitage trend test was carried out on the dose/response. The test was performed twice, once excluding control data and the other including the solvent control.

Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.

Conclusion : Study personnel concluded that under the test conditions, the test material did not induce chromosomal aberrations either in the presence or absence of S9 mix.

Reliability : (1) valid without restriction
Flag : Supportive study for SIDS endpoint. A related test material was utilized.
04.10.2001 (6)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : micronucleus assay
Species : mouse
Sex : male/female
Strain : other:CD-1 (ICR)BR
Route of admin. : gavage
Exposure period : up to 72 hours
Doses : 500, 1667, 5000 mg/kg bw
Result : negative
Method : other: Test Standard 40 CFR 798.5395
Year : 1990
GLP : yes
Test substance : other TS
Remark : The test was valid as positive controls had significantly more MN-PCE than controls (62.2 in males and 34.6 in females).
Result : One female dose with 1667 mg/kg test material died prior to scheduled sacrifice. 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).
Test condition : 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/sacrifice time) were sacrificed by cervical dislocation 24, 48 and 72 hours after treatment. Mice (5/sex) treated with 120 mg/kg cyclophosphamide and sacrificed after 24 hours of treatment served as positive controls.

Bone marrow samples were obtained from both femurs at sacrifice. 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.
Test substance : Test material was triethylene glycol monomethyl ether (CAS no. 112-35-6). Purity was 99.23%.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint. A related test material was utilized.

(36)

5.7 CARCINOGENITY

5.8 TOXICITY TO REPRODUCTION

Type	:	other: 91 day dermal toxicity study
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	dermal
Exposure period	:	91 days
Frequency of treatment	:	6 hr/day, 5 days/week
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	91 days
Doses	:	400, 1200, 4000 mg/kg bw
Control group	:	other:sham
NOAEL Parental	:	= 4000 mg/kg bw (summary preparer); > 400 and < 1200 mg/kg bw (EPA)
Method	:	other
Year	:	1990
GLP	:	yes
Test substance	:	other TS
Remark	:	Additional details for this study can be found in Section 5.4. 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 semiferous 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 %).
Result	:	There were no indications of systemic toxicity at any dose. Mean body weight and food consumption were comparable to controls throughout the study. 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.

Test condition : Triethylene glycol monomethyl ether (TGME) was administered dermally to 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.

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6). Purity (as determined by gas chromatography) was 99.23 % at the onset of the study and 99.24% at completion of the in-life phase.

Conclusion : 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."

Reliability : (2) valid with restrictions. Effect on mating was not characterized

Flag : Critical study for SIDS endpoint. A related test material was utilized.

03.10.2001 (13)(18)

Type : other:90 day repeated dose toxicity study
Species : rabbit
Sex : male/female
Strain : New Zealand white
Route of admin. : dermal
Exposure period : 90 days
Frequency of treatment : 6 hr/day, 5 days/week
Premating exposure period

Male	:	
Female	:	
Duration of test	:	90 days
Doses	:	1 ml of 50% and 100% material (approximately 169 and 338 mg/kg/day)
Control group	:	yes, concurrent vehicle
NOAEL Parental	:	= 338 mg/kg bw
Method	:	other
Year	:	1985
GLP	:	yes
Test substance	:	other TS
Remark	:	A preliminary range-finding study in 15 rabbits dosed 6 hr/day for 9 days showed that daily administration of 1 ml of 50% or 100% test material only caused mild skin irritation. Therefore, these doses were chosen for the 90-day study. Based on weights of animals determined at weekly intervals and the reported density of test material (1.09 g/ml) doses can be calculated on average mg/kg/day basis. These doses are 169 mg/kg/day (for 50%) and 338 mg/kg/day (for 100%). The NOAEL listed is for reproductive organ toxicity. Further details of this study can be found in Section 5.4. The NOAEL for systemic effects was not listed by the investigators. Based on the data, this value is 100% (338 mg/kg/day).
Result	:	No effects on any sex organ were observed
Test condition	:	Dosing: New Zealand white rabbits (10/sex/dose) were treated dermally on clipped dorsal skin with 1.0 ml of vehicle (0.1% (w/v) methyl cellulose in distilled water), 50% CARBOWAX MPEG-350 (w/v dilution in 0.1% methyl cellulose in water) or 100% CARBOWAX MPEG-350, for six hours/day, five days per week for 90 days. Body weights of males and females ranged from 2.5 to 3.2 kg and 2.5 to 3.1 kg at study initiation. Rabbits were fitted with Elizabethan collars after dosing to prevent ingestion of test material. After each 6-hour exposure the application site was wiped with a paper towel dampened with water and then dried using a towel. Rabbits were then uncollared until the next treatment. Observations: All rabbits were observed daily (weekdays) for death, clinical signs and dermal irritation. Body weights were recorded on the morning of the first day of dosing, weekly thereafter and prior to sacrifice. Food consumption was measured weekly. Urine was collected from 5 animals/sex/group during the last two weeks of dosing and subjected to standard analyses. Standard hematology and clinical chemistry parameters were evaluated for all animals just prior to sacrifice. Necropsy: All animals were sacrificed and necropsied after 13 weeks of treatment. Weights were recorded for liver, kidneys, brain and adrenals of all animals and testes of males. Histopathologic examinations were performed on tissues (including testes, epididymes, prostate, accessory sex glands, uterus, ovaries and mammary gland) from high-dose and control animals.
Test substance	:	The test material (CARBOWAX MPEG 350, CAS No. 9004-74-4) was reported to be chemically inert (stable for > 6 months at room temperature) and 99.8% pure. This material is a mixture of several methylated glycol ethers of differing molecular weight (ranging from diethylene glycol monomethyl ether (C2) to heptadecaethylene glycol monomethyl ether (C17)). The majority of the material is in the C5-C11 range (87.445%). It contains 4.347 % (by weight) tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 1.303% triethylene glycol monomethyl ether (CAS No. 112-35-6), 0.181% diethylene glycol monomethyl ether (CAS No. 111-77-3).

Reliability	:	(2) valid with restrictions. Effect on mating was not characterized
Flag	:	Critical study for SIDS endpoint. A related test material was utilized.
02.10.2001		(8) (20)

Type	:	other:91 day oral toxicity study
Species	:	rat
Sex	:	male
Strain	:	Sprague-Dawley
Route of admin.	:	drinking water
Exposure period	:	91 days
Frequency of treatment	:	daily
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	91 days
Doses	:	ca. 400, 1200, 4000 mg/kg/day
Control group	:	yes
NOAEL Parental	:	= 1200 mg/kg bw (summary preparer); > 400 and < 1200 mg/kg bw (EPA)
Method	:	other
Year	:	1990
GLP	:	yes
Test substance	:	other TS
Remark	:	The authors state that “a possible contributing factor in the development of testicular lesions at the high dose was low-level contamination of the test substance with the known testicular toxicant 2-methoxyethanol (EGME). EGME was present in the test substance at a concentration of 0.02 – 0.04 %, resulting in a EGME dose up to 1.7 mg/kg/day for animals in the high dose group. Given the length of the study, it is possible that EGME contributed to the testicular lesions. A comparison between the doses of EGME and TGME required to produce testicular toxicity indicated that TGME is 350 times less potent than EGME in producing testicular lesions in the rat.” The dose of TGME that caused testicular toxicity (4000 mg/kg/day) is 4 times greater than the 1000 mg/kg/day limit dose generally recommended for subchronic studies. The NOAEL listed is for reproductive organ toxicity. Other results are shown in section 5.4. 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).
Result	:	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.

Test condition : 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.

Test substance : Test substance was triethylene glycol monomethyl ether (CAS No. 112-35-6). The purity was at least 98.7%.

Reliability : (2) valid with restrictions. Effect on mating was not characterized

Flag : Critical study for SIDS endpoint. A related test material was utilized.

02.10.2001 (17)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : other:Alpk:AP (Wistar)
Route of admin. : gavage
Exposure period : days 7-16 of gestation
Frequency of treatment : daily
Duration of test : until Day 5 of parturition
Doses : 250 and 1000 mg/kg
Control group : other: both negative (water) and positive (50 and 250 mg/kg ethylene glycol monomethyl ether)
NOAEL Maternalt. : >= 1000 mg/kg bw
NOAEL Teratogen : >= 1000 mg/kg bw
Method : other:modified Chernoff-Kavlok assay (Schuler RL et al. Environ Health Persp 57:141-146, 1984)
Year : 1986
GLP : yes
Test substance : other TS
Remark : Triethylene glycol monomethyl ether and triethylene glycol monoethyl ether also were not teratogenic at 1000 mg/kg. The EPA also 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). The NOAEL listed under teratogenicity is the NOAEL for developmental toxicity.
Result : Maternal Data: Dams dosed with either dose of TGBE 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.

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 TGBE. No litters were produced in either EGME group (although implantation sites were present in all animals). There were no effects on any litter parameter measured in rats treated with either dose of TGBE.

At the dose levels tested (250 or 1000 mg/kg/day), TGBE was not embryotoxic or teratogenic (in contrast to EGME).

Test condition	:	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 monobutyl ether (TGBE), 1000 mg/kg TGBE, 50 mg/kg ethylene glycol monomethyl ether (EGME), or 250 mg/kg EGME. Dose levels of TGBE 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.
Test substance	:	Test material was triethylene glycol monobutyl ether (CAS No. 143-22-6). Purity was 96.91% according to manufacturer (Olin Corporation).
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint. A related test material was utilized. (32) (63)

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	Days 6 to 15 of gestation
Frequency of treatment	:	daily
Duration of test	:	15 Days
Doses	:	625, 1250, 2500, 5000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	= 1250 mg/kg bw
NOAEL Teratogen	:	= 625 mg/kg bw
Method	:	other
Year	:	1990
GLP	:	yes
Test substance	:	other TS
Remark	:	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. The NOAEL listed

under teratogenicity is the NOAEL for developmental toxicity.

Result : Maternal: 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.

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.

Fetal: 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.

Test condition : 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 sacrificed 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 sacrifice.

Maternal and fetal incidence data were analyzed suing 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.

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6).
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint. A related test material was utilized.
02.10.2001 (22)

Species : rabbit
Sex : female
Strain : New Zealand white
Route of admin. : gavage
Exposure period : days 6 to 18 of gestation
Frequency of treatment : daily
Duration of test : 24 days
Doses : 250, 500, 1000, 1500 mg/kg/day
Control group : yes, concurrent vehicle
NOAEL Maternalt. : = 500 mg/kg bw
NOAEL Teratogen : = 1000 mg/kg bw
Method : other
Year : 1990
GLP : yes
Test substance : other TS
Remark : 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). The NOAEL listed under teratogenicity is the NOAEL for developmental toxicity.
Result : Maternal: 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. 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.

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.

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.

Fetal: 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.

Test condition : 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 sacrificed 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.

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6).

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint. A related test material was utilized.

28.09.2001 (21)

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : days 7-17 of gestation
Frequency of treatment :
Duration of test :
Doses : 25, 150, 1000 mg/kg/day
Control group : yes
NOAEL Maternalt. : = 1000 mg/kg bw
NOAEL Teratogen : = 1000 mg/kg bw
Method : Chernoff-Kavlok teratogenicity screening test
Year : 1993
GLP : yes
Test substance : other TS

Remark : It is not known whether the decreased mean litter weights or birth index at 25 mg/kg/day or the increased mean litter weights at 1000 mg/kg/day are significantly different from control, since statistical analyses were not performed. However, these findings do not appear to be related to treatment since they are not dose-dependent. Since the investigators concluded that 1000 mg/kg/day Brake Fluid DOT4 did not cause fetal growth retardation or embryo or fetal lethality, the NOAEL for these effects is 1000 mg/kg/day. The NOAEL listed under teratogenicity is the NOAEL for developmental toxicity.

Result : There was no effect of Brake Fluid DOT4 on maternal body weight of food intake. Mean litter weights of low dose animals were slightly lower than negative controls at birth (79 +/- 24 g vs. 90 +/- 23 g in sham control) and on day 5 of lactation (109 +/- 29 g vs. 133 +/- 34 g in sham control). In contrast, mean litter weights of high dose animals were higher than negative controls at birth (97 +/- 10 g) and on day 5 of lactation (150 +/- 24 g). The authors stated that the reduction at 25 mg/kg/day could be related to slightly smaller litter sizes (the birth index was 85 +/- 15 vs. 95 +/- 7 in the sham control). Two rats in this group had a lower number of implant sites (8 and 6) than the others (ranged from 15-19), which led to a decrease in the number of pups delivered(5 in each of the animals vs. 13-18 in the others). Another low dose animal that had 16 implant sites only delivered 9 pups. The birth index of animals treated with 150 (94 +/- 6) or 1000 mg/kg/day test material (95 +/- 6) was similar to the sham control (95 +/- 7). There was no effect of treatment on the number of dead pups (4 in control vs. 1 in each treated group). There were no treatment-related necropsy findings. There was no effect of treatment with Brake Fluid DOT 4 of the duration of gestation, the number of females littering, the mean number of implant sites, or the live birth index or viability index. Based on these data, the authors concluded that 1000 mg/kg/day Brake Fluid DOT4 did not cause fetal growth retardation or embryolethality.

By contrast, the positive control animals lost weight from days 7 to 21 of gestation. All nine pregnant animals treated with ethylene glycol diethyl ether (EGDE) resorbed their litters. Most animals treated with EGDE had enlarged livers and/or spleens.

Test condition : Groups of 10 female rats were dosed by oral gavage with 25, 150 or 1000 mg/kg/day test material on days 7-17 of gestation. Additional groups of females were sham dosed (negative control) or dosed with 1000 mg/kg/day ethylene glycol diethyl ether (positive control). Animals were allowed to litter naturally, and any that did not deliver by day 25 of gestation were killed. Dams and surviving pups were killed on day 5 of lactation. Body weights were recorded on days 1, 7 and 21 of gestation and on day 5 of lactation (or at termination for animals that did not reproduce). Food intake was recorded over days 1 to 7 and 7 to 17 of gestation, day 17 of gestation to day 1 of lactation and days 1-5 of lactation. The birth index [total number of pups born (live and dead) x 100/ number of implantation sites], live birth index (number of pups alive at day 1 of lactation/ total number of pups born x 100) and viability index (number of pups alive on day 5 of lactation/ number of pups alive on day 1 of lactation x 100) were calculated for each litter and group. Litter weights were recorded on days 1 and 5 of lactation and the uteri of all dams were examined for implantation sites. Statistical analyses were not performed. Pups were not necropsied.

Test substance : Test material is a mixture containing 30-50% triethylene glycol monomethyl ether borate ester (CAS No. 106008-94-0), 3-30% triethylene glycol monobutyl ether borate ester, 20-30% triethylene glycol monomethyl ether (CAS No. 112-35-6), 2-10% triethylene glycol monobutyl ether (CAS No. 143-22-6), 20-30% tetraethylene glycol monomethyl ether (CAS No. 23783-42-8), 2-10% tetraethylene glycol monobutyl ether (CAS No. 1559-34-8), and < 1% minor additives.

Reliability : ((2) valid with restrictions. Pups were not examined for malformations.

Statistical analyses were not performed.

Flag : Supportive study for SIDS endpoint. A related test material was utilized.
04.10.2001 (57)

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	day 6 of gestation through postnatal Day 21
Frequency of treatment	:	daily
Duration of test	:	38 Days
Doses	:	300, 1650, 3000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	= 1650 mg/kg bw (summary preparer, EPA)
NOAEL Teratogen	:	= 300 mg/kg NOEL (study personnel); 300 mg/kg day NOAEL (EPA)
Method	:	other
Year	:	1992
GLP	:	yes
Test substance	:	other TS
Remark	:	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). 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). The NOAEL listed under teratogenicity is the NO(A)EL for developmental toxicity.
Result	:	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 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. 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.” Necropsy of maternal animals in the high- dose group revealed significantly heavier kidneys than controls. Kidney weights increased in a dose-dependent manner. 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 shown to be significantly advanced in the pups from the mid- and high-dose groups. 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.

Necropsy of maternal animals revealed that kidneys from the maternal animals exposed to 3000 mg/kg/day of TGME were significantly heavier than controls. 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.

Test condition : 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 sacrifice 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.

Test substance : The test substance was triethylene glycol monomethyl ether (CAS 112-35-6).The analyzed chemical purity was 99.2%.

Conclusion : "In conclusion, TGME administered by gavage to pregnant and lactating CD" (Sprague- Dawley) rats resulted in no overt signs of maternal toxicity. In addition, no discernible effects were noted in the offspring on motor activity, active avoidance, or neuropathology at exposures up to 3000 mg/kg/day. Exposure to TGME at 3000 mg/kg/day resulted in increases in auditory startle amplitude and decreases in latency to maximum startle, but no changes in the habituation process evaluated in the auditory startle test. The significance of these auditory startle observations with regard to the condition of the test animals is not clear. Exposure to TGME at levels of 1650 and 3000 mg/kg/day produced developmental toxicity evidenced by decreased *postnatal* weight gains. Therefore, the no observable effect level" (NOEL) for this study is considered to be equal to or greater than 300 mg/kg/day."

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint. A related test material was utilized.
01.08.2002 (5)

5.10 OTHER RELEVANT INFORMATION

Type : absorption

Remark : Absorption of ethylene glycol monomethyl ether (EGME), triethylene glycol monomethyl ether (TGME), and triethylene glycol monoethyl ether (TGEE) also were tested in this study. The rate of absorption of EGME was220 micrograms/cm2/hr. The rate of absorption of TGME was 34.0 micrograms/cm2/hr and the mean damage ratio was 3.36 (small increase in permeability). The rate of absorption of TGEE was 24.1 micrograms/cm2/hr, and the mean damage ratio was 1.37 (no increase in permeability).

Result : The mean steady state of absorption for triethylene glycol monobutyl ether was 22.2 micrograms/cm2/hr (SD +/- 8.59), which was 100-fold less than that of ethylene glycol monomethyl ether. Test material did not increase permeability of the membrane (damage ratio of 1.26).

Test condition : 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 monobutyl ether 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.

Test substance : Purity of test material (POLYSOLV-TB, triethylene glycol monobutyl ether) was 96.91%.

Reliability : (1) valid without restriction

(62)

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