FOREWORD INTRODUCTION

1,2-DIHYDROXYPROPANE

CAS:57-55-6

SIDS Initial Assessment Report for 11th SIAM

(USA, January 23-26, 2001)

Chemical Name : Propylene glycol

CAS No: 57-55-6

Sponsor Country: U.S.A

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HISTORY: At SIAM 11 the conclusion of Low Priority for Further Work was agreed. Revisions to the SIAR and preparation of Robust Summaries were requested and agreed.

COMMENTS:

Deadline for circulation:

Date of Circulation:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	57-55-6
Chemical Name	Propylene glycol (1,2-dihydroxypropane)
Structural Formula	CH_3-CHOH-CH_2OH

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Propylene glycol (PG) is not acutely toxic. The lowest oral LD50 values range between 18 and 23.9 grams (5 different species) and the reported dermal LD50 is 20.8 grams. PG is essentially non-irritating to the skin and mildly irritating to the eyes. Numerous studies support that PG is not a skin sensitizer. Repeated exposures of rats to propylene glycol in drinking water or feed did not result in adverse effects at levels up to 10% in water (estimated at about 10 g/kg bw/day) or 5% in feed (dosage reported as 2.5 g/kg bw/day) for periods up to 2 years. In cats, two studies of at least 90 days duration show that a species-specific effect of increased Heinz bodies was observed (NOAEL = 80 mg/kg bw/day; LOAEL = 443 mg/kg bw/day), with other haematological effects (decrease in number of erythrocytes and erythrocyte survival) reported at higher doses (6-12% in diet, or3.7-10.1 g/cat/day). Propylene glycol did not cause fetal or developmental toxicity in rats, mice, rabbits, or hamsters (NOAELs range from 1.2 to 1.6 g/kg bw/day in four species). No reproductive effects were found when propylene glycol was administered at up to 5% in the drinking water (reported as 10.1 g/kg bw/day) of mice. Propylene glycol was not a genetic toxicant as demonstrated by a battery of *in vivo* (micronucleus, dominant lethal, chromosome aberration) and *in vitro* (bacterial and mammalian cells and cultures) studies. No increase in tumors was found in all tissues examined when propylene glycol was administered in the diet of rats (2.5 g/kg bw/day for 2 years), or applied to the skin of female rats (100% PG; total dose not reported; 14 months) or mice (mouse dose estimated at about 2 g/kg bw/week; lifetime). These data support a lack of carcinogenicity for PG.

Environment

Propylene glycol is not volatile, but is miscible with water. Air monitoring data are not available, but concentrations of propylene glycol in the atmosphere are expected to be extremely low because of its low vapor pressure and high water solubility. It is readily biodegraded in water or soil. Four studies reported >60% biodegradation in water in 10 days. PG is not expected to bioaccumulate, with a calculated BCF <1. Measured freshwater aquatic toxicity data for fish, daphnia and algae report LC/EC_{50} values of >18,000 mg/l. Therefore, PG is not acutely toxic to aquatic organisms except at very high concentrations. Using an assessment factor of 100 and the *Ceriodaphnia* data (48-hour EC_{50} = 18,340 mg/l), the PNEC is 183 mg/l.

Exposure

PG production capacity in the US was 1312 million pounds (596 kilotonnes) in 1998. Domestic demand was 1050 million pounds (477 kilotonnes). PG is used as an ingredient in cosmetics at concentrations of <0.1% to >50%. Approximately 4000 cosmetic products contained PG in 1994. Uses

of PG, with percent of demand, are: unsaturated polyester resins, 26 percent; antifreeze and de-icing fluids, 22 percent; food, drug and cosmetics uses, 18 percent; liquid detergents, 11 percent; functional fluids (inks, specialty anti-freeze, de-icing lubricants), 4 percent; pet foods, 3 percent; paints and coatings, 5 percent; tobacco, 3 percent; miscellaneous, including plasticizer use, 8 percent.

NATURE OF FURTHER WORK RECOMMENDED

No further work is recommended.

FULL SIDS SUMMARY

CAS NO: 57-55-6		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point	--	NG	<-60°C
			NG	<-57°C
2.2	Boiling Point	--	NG	187.4-189°C
2.3	Density	--	NG	1.032-1.036 g/cm3
2.4	Vapour Pressure	--	NG	0.11 hPa at 20°C
			NG	0.08 mm Hg
2.5	Partition Coefficient (Log K_{ow})	--	NG	ca. -1.41 to –0.3
2.6 A.	Water Solubility	--	NG	Soluble at 25°C
B.	PH	--	--	
	Pka	--	--	
2.12	Oxidation:Reduction Potential	--	--	
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation	--	Est. (AopWin v 1.90)	Half Life = 10.012 hr
3.1.2	Stability in Water	--	--	--
3.2	Monitoring Data	--	--	--
3.3	Transport and Distribution	--	Fugacity model (Level III)	2.98% in air; 48.8% in water; 48.1% in soil; 0.07% in sediments.
3.5	Biodegradation	--	Other, APHA 1971	Readily biodegradable (79% after 20 days; aerobic, unacclimated sludge)
		--	NG	Degraded (100% after 12 days; aerobic, soil microorganisms
		--	NG	Readily biodegradable (aerobic, 84-99% after 24 hr; acclim. and unacclim. Sludge
		--	NG	Degraded to methane by anaerobic soil organisms in sandy loam, but not in surface sand
3.7	Bioaccumulation	--	Calc. from Kow	BCF of 1.4
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	Oncorhynchus mykiss	96-hr lethality; OECD TG 203	LC50 = 51600 mg/L (static)
		Pimephales promelas	96-hr lethality; OECD TG 203	LC50 = 46500 mg/L (static)
		Pimephales promelas	96-hr lethality; OECD TG 203	LC50 = 51400 mg/L (static)
4.2	Acute Toxicity to Aquatic Invertebrates *(Daphnia)*	Daphnia magna	48-hr toxicity; OECD TG 202	LC50 = 43500 mg/L (static)

CAS NO: 57-55-6		SPECIES	PROTOCOL	RESULTS
		Mysidopsis bahia	96-hr lethality; Other, EPA 797.1930	LC50 = 18800 mg/L (static)
		Ceriodaphnia sp.	48-hr lethality; Other	LC50 = 18340 mg/L (static) NOAEC = 13020 mg/L (static)
4.3	Toxicity to Aquatic Plants e.g. Algae	Selenastrum capricornutum	14-day growth rate; OECD TG 201	NOEC = 15000 mg/L EC50 = 19000 mg/L (96-hr) EC50 = 18100 mg/L (14-day)
		Skeletonema costatum	14-day growth rate; OECD TG 201	EC50 = 19100 mg/L (96-hr) EC50 = <5300 mg/L (14-day) NOEC = <5300 mg/L (14-day)
4.5.1	Chronic Toxicity to Fish	--	--	No data
4.5.2	Chronic Toxicity to Aquatic Invertebrates (*Daphnia*)	Ceriodaphnia sp.	Reproduction; Other, EPA	NOEC = 13020 mg/L IC25 = 13470 mg/L
4.6.1	Toxicity to Soil Dwelling Organisms	--	--	No data
4.6.2	Toxicity to Terrestrial Plants	--	--	No data
4.6.3	Toxicity to Other Non- Mammalian Terrestrial Species (Including Birds)	--	--	No data
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Acute lethality; NG	LD50 = 22000 mg/kg
		Mouse	Acute lethality; NG	LD50 = 24900 mg/kg
		Guinea pig	Acute lethality; NG	LD50 = 19700 mg/kg
5.1.2	Acute Inhalation Toxicity	--	--	No data
5.1.3	Acute Dermal Toxicity	Rabbit	Acute lethality; NG	LD50 = 20800 mg/kg
5.2.1	Skin Irritation	Rabbit	OECD TG 404	Not Irritating (undiluted, 4 hr, occluded)
		Rabbit	Draize test; NG	Not irritating (undiluted)
5.2.2	Eye Irritation	Rabbit	OECD TG 405	Not irritating (undiluted, 0.1 mL)
		Rabbit	OECD TG 405	Not irritating (undiluted, 0.1 mL)
5.3	Skin Sensitization	Human	Other; NG	Not sensitizing (Induction: 0.2 mL of 50% solution , semi-occlusive; Challenge: 0.2 mL of 50% solution semi-occlusive)
		Human	Other, NG	Not sensitizing (Induction: 0.2 mL of 50% solution , occlusive).
		Human	Other, Draize	Not sensitizing ((Induction: 0.5 g of 12% dilution in petrolatum)
5.4	Repeated Dose Toxicity	Rat	15 wk, oral; NG	NOAEL = 50000 ppm in diet

CAS NO: 57-55-6		SPECIES	PROTOCOL	RESULTS
	Toxicity			LOAEL = >50000 ppm in diet
		Rat	140 days, drinking water; NG	NOAEL = 13200 mg/kg LOAEL = >13200 mg/kg
		Rat	104 wk, oral, feed; NG	NOAEL = 50000 ppm in diet LOAEL = > 50000 ppm in diet
		Dog	104 wk, oral; NG	NOAEL = 2000 mg/kg LOAEL = > 5000 mg/kg
		Cat	69-94 days, oral feed; NG	NOAEL = 80 mg/kg LOAEL = 443 mg/kg
		Cat	117 days, oral feed; NG	NOAEL = <6% in diet LOAEL = 6% in diet
5.5	Genetic Toxicity In Vitro			
A.	Bacterial Test (Gene mutation)	Salmonella typhimurium	Ames test; NG	Negative with activation (TA 92, 94, 98, 100, 1535, 1537)
		Salmonella typhimurium	Ames test; NG	Negative without activation (TA 98, 100, 1535, 1537)
B.	Non-Bacterial In Vitro Test	Chinese hamster fibroblasts	Chromosomal aberration; NG	Ambiguous; postive response confounded by high concentration tested (420 mM).
		Human	Chromosomal aberration; OCED TG 473	Negative with and without activation (concentrations up to 50 mM)
5.6	Genetic Toxicity In Vivo	Rat	Cytogenetic assay; NG	Negative; (single oral doses up to 5000 mg/kg)
		Rat	Cytogenetic assay; NG	Negative; (oral doses up to 5000 mg/kg/day for 5 days)
		Mouse	Micronucleus assay; NG	Negative; (single i.p. doses up to 15000 mg/kg)
		Rat	Dominant lethal; NG	Negative (single gavage doses up to 5000 mg/kg)
		Rat	Dominant lethal; NG	Negative; (gavage doses up to 5000 mg/kg/day for 5 days)
5.7	Carcinogenicity	Rat	104 wk, oral, feed; NG	Negative (up to 50000 ppm in diet)
		Mouse	2x/wk, lifetime; dermal; NG	Negative (approx. 2, 10, and 21 mg/animal per application
		Rat	3x/wk, 10-14 mo; dermal; NG	Negative (ear painting strudy in which PG was used as a test vehicle)
5.8	Toxicity to Reproduction	Mouse	Cont. breeding; drinking water; Other, NTP	NOAEL = 5% (parents) NOAEL = 5% (F1 offspring) NOAEL = 5% (F2 offspring)
5.9	Developmental Toxicity/ Teratogenicity	Rat	GD 6-15, gavage; NG	NOAEL = 1600 mg/kg (maternal tox.) NOAEL = 1600 mg/kg (teratogenicity)

CAS NO: 57-55-6		SPECIES	PROTOCOL	RESULTS
		Rabbit	GD 6-18, gavage; NG	NOAEL = 1230 mg/kg (maternal tox.) NOAEL = 1230 mg/kg (teratogenicity)
		Mouse	GD 6-15, gavage; NG	NOAEL = 1600 mg/kg (maternal tox.) NOAEL = 1600 mg/kg (teratogenicity)
		Golden hamster	GD 6-10, gavage; NG	NOEL = 1550 mg/kg (maternal tox.) NOEL = 1550 mg/kg (teratogenicity)
5.10	Other Relevant Information	Human	5 days, i.v.; NG	Rapid clearance; half-life about 2 hr. No hemolysis or RBC effects after repeated dosing up to 7700 mg/day, i.v., for 5 days.
		Rats	Single dose, gavage; NG	Uptake and excretion followed first order kinetics.
		Rabbits	Single dose, gavage; NG	Increase in pyruvate and lactate in blood; no change in blood pH (dose, 38.66 mmol/kg)
5.11	Experience with Human Exposure	--	--	No data

SIDS Initial Assessment Report

1. Identity

Commercial propylene glycol (CAS No. 57-55-6) is manufactured by reaction of propylene oxide with water. USP-grade propylene glycol is typically 99.9% pure. It is a liquid that possesses the following physical-chemical properties and characteristics:

Property	Value
Chemical formula	CH_3-CHOH-CH_2OH
Molecular weight	76.09
Purity	>= 98%
Impurities	Dipropylene glycol
Solubility	miscible with water, acetone and chloroform
Melting point	< -60° C
Boiling point	189° C
Density	1040 mg/ml @ 20° C
Vapor pressure	0.11 hPa @ 20° C
Log Kow	-1.41 to -0.3; -0.78 preferred value
Synonyms	PG; MPG; Synonyms: 1,2-Propanendiol; 2,3-Propanediol: 1, 2-Dihydroxypropane; Methylethylene Glycol; Trimethyl Glycol; 1,2-Propylene Glycol; Monopropylene Glycol; Propane-1, 2-diol; Alpha-Propylene Glycol; Dowfrost; GR12; Sirlene; Propanediol, Solar Winter Ban, 1,2-Dihydroxypropane; 2-Hydroxypropanol; Methyethyl Glycol; Methyl Glycol. (Sources: Hazardous Substance Database (HSDB) and Chemfinder Database).

2. General Information on Exposure

2.1 Production

Propylene glycol production capacity in the US was 1312 million pounds (596 thousand tonnes) in 1998. Domestic demand was 1050 million pounds (477 thousand tonnes). In 1994, approximately 18% of US production was converted to downstream products by the manufacturers. In 1998, propylene glycol was produced in the US by The Dow Chemical Company, Eastman Chemical Company, Huntsman Corporation, Lyondell Chemical Company, and Olin Corporation. (Sources: ChemExpo Chemical Profile (1998) and US ITC, (1994) Synthetic Organic Chemical Report p 3-31).

According to the ECDIN database, in 1989 western Europe produced 708 million pounds (325 thousand tonnes) and consumed 660 million pounds (300 thousand tonnes).

2.2 Use

Propylene glycol is used as the base in the production of antifreeze, deicing solutions, and polyester compounds for industrial or commercial use, as well as solvents in liquid laundry detergents and paint manufacturing. It is also used as an additive in food, pharmaceuticals, pet foods, and tobacco processing. These uses of propylene glycol as a substance capitalize on its properties to retain moisture and act as a functional fluid. The uses of propylene glycol are listed in the following table.

USES OF PROPYLENE GLYCOL

USES	APPLICATION	FUNCTION	% PRODUCTION (1)	(2)
Intermediate	Unsaturated Polyester Resins	Resin Monomer	38%	40%
Substance Substance	Food, Pharmaceuticals Cosmetics and Personal Care	Humectant Emollient	17%	12%
Substance	Specialty Antifreeze, Aircraft Deicing, Industrial Lubricants, Inks	Lubricant, Coolant	13%	10%
Substance	Liquid Laundry Detergents	Dispersant	9%	15%
Substance	Pet Foods	Humectant	5%	6%
Substance	Tobacco Processing	Humectant	4%	3%
Substance	Paints and Coatings	Solvent	4%	4%
Substance Intermediate		Miscellaneous Plasticizer	10%	4%

(Sources: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd Ed., Volumes 1-26, NY, John Wiley and Sons 1978-1984; (1): Chemical Business, Nov. 1992, p. 36; (2): and Chemical Marketing Reporter, Vol 249, No. 7 p. 37, 2/12/96).

The list of uses of propylene glycol is extensive. Uses listed in the table above have been grouped and assigned a publicly available percentage of production. The Environmental Defense Scorecard website (Source: www.scorecard.org). for propylene glycol lists 82 consumer product types and 157 pesticidal products. Data available from the US EPA

indicate that, whereas 170 pesticidal products containing propylene glycol as an ingredient have been registered over time, in 2001 only 16 such products are registered in the US (Source: California Department of Pesticide Registration website, http://www.cdpr.ca.gov/cgi-bin/epa/chemdet.pl?pccode=068603).

2.3 Exposure

Potential worker exposure to propylene glycol is estimated to be 1,748,454 workers with a projection that 98% of potential exposures occur with trade name products containing propylene glycol, and the balance in the production of the chemical (Source: NIOSH, the National Occupational Exposure Survey (NOES), 1989). Dermal exposure is given as the most significant route of exposure in occupational settings. In the commercial service and consumer settings use as a functional fluid (paints, deicing, cosmetic creams) presents a potential for inhalation exposure in addition to dermal exposure.

In the consumer setting, exposure by ingestion is a result of the approved use of propylene glycol in food, tobacco and pharmaceutical products by the US Food and Drug Administration (FDA) (Source: FDA, GRAS list, 20 CFR 184.1666 and 21CFR 582.4666 4/1/93). Dermal exposure, and to a lesser degree inhalation exposure are to be expected where propylene glycol is formulated into cosmetic products.

The general routes of potential exposure to propylene glycol are outlined in the following table. Sources of information are listed beneath the table.

PROPYLENE GLYCOL EXPOSURE POTENTIAL

POPULATION	ROUTE(S) OF EXPOSURE	SOURCE(S)
Occupational Exposure	Dermal Inhalation	Manufacturing Industrial use as Intermediate Commercial Service
Consumer	Ingestion Dermal; Inhalation	Food and Drugs; Tobacco Cosmetics

(Sources: Clayton, G. and P. Clayton (1982) Patty's Industrial Hygiene and Toxicology, 3rd ed., NY, Wiley-Interscience, p. 3852: Patty, F (1963), Patty's Industrial Hygiene and Toxicology, Vol. II: Toxicology, 2nd ed., NY, Interscience Publishers, p. 1516); and Cassarett, L. and J. Doull (1975) Toxicology: The Basic Science of Poisons, NY, MacMillan Publishing Co., p. 516)

There are substantial data available on the concentration of propylene glycol found in cosmetic and personal care products. A Final Report on the Safety Assessment of Propylene Glycol (CTFA) provides detailed use concentration assessments for formulated cosmetics containing propylene glycol in 74 different product types. This is summarized in the following table.

COSMETIC PRODUCT FORMULATIONS CONTAINING PROPYLENE GLYCOL

PRODUCT CATEGORY	RANGE OF CONCENTRATIONS AS USED (%)				
	<1	**1-10**	**10-25**	**25-50**	**>50**
No. of Hair Care Products	183	284	157	65	1
No. of Eye Care Products	66	214	11	2	0
No. of Skin Care Products	1122	1808	55	25	20
No. of Bath Products	135	49	6	4	0
No. of Shaving Products	61	82	5	1	0

(Source: Journal of the American College of Toxicology, Vol. 13, No. 6, p. 440, 1994). Other data sources identified a concentration range (from 2.2 to 70%) of propylene glycol approved for use in specific cosmetic and medical applications. (Sources: American Medical Association, Council of Drugs (1994), AMA Drug Evaluations Annual, Chicago, IL, AMA).

The concentration of propylene glycol in branded pesticidal products is also available. This is summarized in the following table.

PESTICIDAL FORMULATIONS CONTAINING PROPYLENE GLYCOL

	RANGE OF CONCENTRATION (%)				
	<1	**1-10**	**10-25**	**25-50**	**>50**
No. of Brand Name Products	3	124	24	2	3

(Source: ED Website: www.scorecard.org)

Whereas the table above provides data for 156 branded pesticidal products, only 16 of these currently (May, 2001) maintain active registrations in the US. The 16 active registered products contain propylene glycol in the 0.1 to 10 percent range.

EPA published data on the quantities of propylene glycol in consumer products in its efforts to define parameters for the assessment of urban air toxics. The following table summarizes this data on propylene glycol.

EPA DATA ON PROPYLENE GLYCOL IN CONSUMER GOODS

PRODUCT CATEGORIES	NUMBER OF PRODUCTS	RANGE OF CONCENTRATION (%)
Paint Primers Varnishes	3	21.2 - 50.2%
Room Deodorants Disinfectants	2	Up to 100%
Personal Deodorants	1	Up to 100%
Metal Cleaners Polishes	1	Up to 100%
All-Purpose Cleaners	5	10.7 - 100%

(Source: US EPA, (1989) Compilation and Speculation of National Emissions Factor for Consumer/Commercial Solvent Use, EPA -450/2-89-008).

A use and exposure compilation for propylene glyc ol as an intermediate and substance is outlined in the following summary.

USE AND EXPOSURE SUMMARY TABLE
1,2 -PROPYLENE GLYCOL CAS NO: 57-55-6

End Use	Market Application (Source)	Function	Settings	Exposure Routes
Intermediate	Raw Material for Polypropylene Adipate (1,2,4)	Polymeric Plasticizer	INDUS	DERM
Intermediate	Raw Material for 2-Methyl-piperazine (1)	Corrosion Inhibiter	INDUS	DERM
Intermediate	Raw Material for 1,2-Propylene-diamine	Chemical Intermediate	INDUS	DERM
Intermediate	Raw Material for Hydroxylated Polyester Resins (1)	Oil-free Alkyd, Resin Functionality	INDUS	DERM
Intermediate	Raw Material for Unsaturated Polyester Resins (UPE) (1,3,4)	End-Group Functionality	INDUS	DERM
Substance	Veterinary Germicide (1,3)	Anti-bacterial Anti-viral	COMM CONS	INHL DERM
Substance	Foods, Pet food, Tobacco (1,2,3,4)	Humectant, Emulsifier	INDUS CONS	ORAL DERM INHL
Substance	Cosmetic and Pharmaceutical (2,4)	Emollient Creams	CONS	DERM
Substance	Food Colors and Flavors (2,4)	Solvent	INDUS COMM CONS	ORAL DERM
Substance	Aircraft Deicing Fluid (1,4)	Freezing Point Depression	INDUS	DERM INHL
Substance	Drug Formulation (1,3)	Solvent, Humectant Emulsifying Agent	CONS	DERM ORAL
Substance	Dentifrices (1)	Humectant	CONS	DERM ORAL

End Use	Market Application (Source)	Function	Settings	Exposure Routes
Substance	Functional Fluid in Latex Paints, Vehicle Coolant, Refrigeration Equipment (1,3,4) Antifreeze Heat Transfer Film Lapping	Freeze-thaw Stability	INDUS COMM CONS	DERM

Sources: **1**. Kirk – Othmer Encyclopedia of Chemical Technology (1978-84) **2.** Chemical Products Synopsis: Propylene Glycol (1984) **3.** The Merck Index – Encyclopedia of Chemicals, Drugs & Biologicals, 11th ed. (1989) **4**. Hawley's Condensed Chemical Dictionary, 12th ed. (1993).

3. Environment

3.1 Environmental Exposures

Because of its low vapor pressure, propylene glycol is not expected to volatilize. As a consequence, photodegradation is a relatively unimportant means of removing propylene glycol from the environment, although reaction with hydroxyl radicals in air has been estimated to be rapid (Atkinson *et al.*, 1985).

Removal of propylene glycol from aquatic and terrestrial environment occurs by biodegradation. It is readily biodegradable by unadapted sludge under aerobic conditions (79% in 20 days; Price *et al.*, 1974), while breakdown in acclimated systems is rapid (84-99% in 20-24 hr; Martino et al., 1990). It is also removed by soil microcosms under aerobic (Klecka *et al.*, 1993) and anaerobic (Klier *et al.*, 1997) conditions.

No tests of bioaccumulation were reported in fish, however a BCF of 1.40 was calculated using a log K_{ow} of -0.78 and the method of Bysshe (1982).

3.2 Environmental Partitioning

Based on the EPIWIN Level III Fugacity Model propylene glycol is expected to partition primarily to soil and water.

Compartment	Percent
Air	2.98
Water	48.8
Soil	48.1
Sediment	0.0729

3.3 Effects on the Environment

The acute toxicity of propylene glycol toward aquatic species has been well studied using guideline protocols and a range of fish, invertebrates, and algae. Representative results are presented below, and demonstrate that it has a very low order of toxicity in the environment.

Organism	**Duration** hr	**LC_{50} / EC_{50}** mg/l	**NOEC** mg/l	**Source**
Fish				
Oncorrhynchus mykiss	96	51600[1]	42000	Boeri and Ward, 1990a
Pimephales promelas	96	51400[1]	26000	Boeri and Ward, 1990b
Pimephales promelas	96	46500[1]	36000	Weinberg *et al.*, 1993

Invertebrate				
Daphnia magna	48	43500[2]	28500	Boeri and Ward, 1990c
Ceriodaphnia dubia	48	18340	13020	Pillard, 1995
Mysidopsis bahia	96	18800[3]	<9500	Boeri and Ward, 1990d
Algae				
Selenastrum capricornutum	96	19000[4]	15000	Boeri and Ward, 1990e
Skeletonema costatum	96	19100[4]	<5300	Boeri and Ward, 1990f

Notes :
[1] = OECD 203 guideline study
[2] = OECD 202 guideline study
[3] = EPA OTS 797.1930
[4] = OECD 201 guideline study

Repeat toxicity data are also available for *Ceriodaphnia dubia*, which show an $IC25_{reproduction}$ of 13470 mg/l over 7 days, and a $NOEC_{reproduction}$ of 13020 mg/l ($NOEC_{mortality}$ = 29000 mg/l) (Pillard, 1995).

Using an assessment factor of 100 and the value from the 48-hr invertebrate *Ceriodaphnia dubia* study (EC_{50}=18,340 mg/L), a predicted no effect concentration (PNEC) of 183 mg/L is obtained.

4. Human Health

There are extensive toxicity data available for propylene glycol, although the age of the database is considerable and many of the studies originate from the 1930's - 1960's. Although many investigations were conducted before standardized testing guidelines were established, the reporting of methods and results is sufficiently robust to make the findings valuable for an initial hazard assessment.

4.1 Toxicity Studies

4.1.1 Acute Toxicity

The acute oral toxicity of propylene glycol has been investigated extensively over the past 60 years in a range of species, including rats, mice, guinea pigs, rabbits, and dogs (summarized by Laug *et al.*, 1939; Ruddick, 1972; Clark et al., 1979). The lowest oral LD_{50} values range between 18 and 24.9 grams (5 relevant and different species). Representative data indicate oral LD_{50} values of 24900 mg/kg bw in the mouse, 22000 mg/kg bw in the rat, 18000 mg/kg bw in the rabbit, 19700 mg/kg bw in guinea pig and 20000 mg/kg bw in the dog. The acute dermal toxicity of propylene glycol in rabbits was 20800 mg/kg bw (20.8 grams; NPIRI, 1974).

Overall propylene glycol is not acutely harmful after ingestion or skin contact.

4.1.2 Irritation and sensitization

Results from guideline studies (OECD 405 method) demonstrate that undiluted propylene glycol is minimally irritating to the eye (Murman, 1984a; Jacobs, 1992), producing no more than slight transient conjunctivitis which resolves by 24-48 hr. Results from a Guideline 404 skin irritation test (Murman, 1984b), along with earlier data (Clarke *et al.*, 1979), show it is not a skin irritant, producing a negligible response after 4 hr occluded contact.

Results from human patch testing show no sensitization potential after semi-occlusive- (Consumer Product Testing Co., 1999a) or occlusive- (Mazulli and Maibach, 1973; Consumer Product Testing Co., 1999b) epicutaneous application to the skin of volunteers (in excess of 300 subjects in total).

These studies demonstrate that it is not irritating to skin or eye, nor does it cause sensitization by skin contact.

4.1.3 Repeated dose toxicity

Early studies (Seidenfield *et al.*, 1932) showed no toxicologically adverse changes in rats given 10% propylene glycol in drinking water for 140 days, equivalent to a NOAEL of 13200 mg/kg bw/day. Although higher treatment levels were included in this investigation (25% and 50% in drinking water), they provide no meaningful information since the animals died midway through the study (69 days) from dehydration and starvation.

Chronic feeding studies in rats (Gaunt *et al.*, 1972) demonstrated only minimal changes following administration of up to 5% w/w in the diet, equivalent to a NOAEL of 1700 mg/kg bw/day in males and 2100 mg/kg/day in females. Dogs tolerated dietary administration of 8% w/w in diet over 2 years (NOAEL equivalent to 2000 mg/kg bw/day), although mild hematological changes (slightly decreased hemoglobin, hematocrit and total erythrocyte counts, slightly increased reticulocyte count) were apparent in animals fed 20% w/w propylene glycol, equivalent to a LOAEL of 5000 mg/kg bw/day (Weil *et al.*, 1971). Both studies included a wide range of toxicological parameters (including clinical chemistry, hematology, urinalysis, necropsy examination, histopathological evaluation), and the main findings are clearly reported, making them suitable for hazard evaluation purposes.

In comparison to the foregoing, cats appear to be more responsive with a species-specific increase in Heinz bodies reported after dietary administration over 2-3 months (Quast *et al.*, 1979). Increased hemosiderin deposits were also noted in liver and spleen, but appeared secondary to Heinz body formation. The NOAEL for Heinz body formation was 80 mg/kg bw/day, with a LOAEL of 443 mg/kg bw/day. No other systemic effects were seen in cats at doses up to 4239 mg/kg bw/day (the maximum used in the investigation), including no evidence of hemolytic anemia. Results from another feeding study in cats (Bauer *et al.*, 1992) reported a LOAEL for decreased number and survival of erythrocytes of 3700 mg/cat/day. This was based on ingestion of 6% propylene glycol in feed, and was estimated to range between 741 - 1600 mg/kg bw/day.

Principle features of these repeat-dose studies are summarized below :

Species	Treatment	NOAEL/LOAEL (mg/kg bw/day)	Comments	Source
Rat	1% - 50% in drinking water for 140 d	NOAEL = 13200 (equivalent to 10% in water)	Animals from higher exposure groups died from starvation and dehydration.	Seidenfield and Hanzlik, 1932
Rat	0.625% - 5% in feed for 104 wk	$NOAEL_{males}$ = 1700 $NOAEL_{females}$ = 2100 (equivalent to 5% in feed)	No systemic effects	Gaunt *et al.*, 1972
Dog	8% or 20% in feed for 104 wk	LOAEL = 5000 (equivalent to 20% in feed) NOAEL = 2000 (equivalent to 8% in feed)	Minor red cell effects in dogs fed 20% propylene glycol over 2 years.	Weil *et al.*, 1971
Cat	80 - 4239 mg/kg/d by administration in diet for 2-3 months	LOAEL = 443 NOAEL = 80	Heinz body formation and secondarily hemosiderin deposition in liver.	Quast *et al.*, 1979
Cat	6% or 12% in feed for 117 d	LOAEL = 741 - 1600 NOAEL = <741 - 1600	Heinz bodies plus reduced red cell survival.	Bauer *et al.*, 1992.

In conclusion, studies in laboratory animals demonstrate that propylene glycol is very well tolerated by rats and dogs after repeat ingestion, with NOAELs in the range 2000 - 13200 mg/kg bw/day and above. Cats also tolerate the daily ingestion of multi-gram amounts with no adverse histopathological changes, however species-specific hematological changes (Heinz body formation) are apparent at lower exposures (NOAEL 80 mg/kg bw/day).

4.1.4 Genotoxicity

4.1.4.1 Genotoxicity *in vitro*

Two Ames assays with and without activation at dose levels up to 10000 µg/plate were negative using indicator strains TA92, TA94, TA 98, TA100, TA1535 and TA1537 (Pfieffer and Dunkelberg, 1980; Ishidate *et al.*, 1984). Satisfactory results were obtained with positive test substances included in these assays.

No increase in chromosomal aberrations was recorded in an OECD 473 guideline study, when human lymphocytes were exposed to 6.25, 25 or 50 mM propylene glycol in the absence and presence of a metabolic activation system (Erdoelchemie, 1990). A satisfactory response was achieved with EMS and mitomycin c.

In contrast to the above, Ishidate *et al.* (1988) reported a positive chromosomal aberration result when propylene glycol (32 mg/ml, equivalent to 420 mM) was incubated with Chinese hamster fibroblasts in the absence of external metabolic activation. The result appears unreliable, however, since the concentration used was significantly greater than the 10 mM maximum currently recommended by testing guidelines (set to avoid osmotic effects destabilising the test system). The test system also showed clear evidence of cytotoxicity at this concentration, again undermining confidence in the result.

4.1.4.2 Genotoxicity *in vivo*

No increase in chromosomal aberrations in bone marrow was found in male rats given 30, 2500 or 5000 mg/kg bw propylene glycol by gavage either once or on five consecutive days (Litton Bionetics, 1974). A satisfactory response was obtained with triethylene melamine (positive control substance). Similarly, there was no increase in micronucleated polychromatic erythrocytes harvested from mouse bone marrow 18 hr after a single ip injection of propylene glycol at 2500, 5000, 10000 or 15000 mg/kg bw (Hayashi *et al.*, 1988). Although no positive control was included in this study, positive results were obtained with other substances included in the test battery thereby validating the sensitivity of the assay.

The potential of propylene glycol (30, 2500 or 5000 mg/kg bw, by gavage) to induce heritable mutations in germ cells was assessed in studies conducted by Litton Bionetics (1974) involving one or five consecutive daily treatment. Triethylene melamine, used as positive control in the acute test, gave a satisfactory result. While occasional statistically-significant differences were noted in mid- and high dose animals from both phases of the investigation, comparison with historic data demonstrated that this was a consequence of unrepresentative control data rather than a substance-specific effect. Overall it was concluded that propylene glycol had no capacity to induce heritable mutations in the male rat.

Based on the weight of evidence, together with knowledge of its chemical structure and metabolic fate, propylene glycol is not genotoxic.

4.1.5 Carcinogenicity

The carcinogenic potential of propylene glycol has been investigated in two long term feeding studies (see section 4.1.3 for details of study design). No increase in tumors was recorded in rats receiving the equivalent of 1700 (males) or 2100 (females) mg/kg bw/d over two years (Gaunt *et al.*, 1972). Tumor incidences were also unchanged in male and female Beagle dogs ingesting 20% propylene glycol in diet (equivalent to 5000 mg/kg bw/day), again over two years (Weil *et al.*, 1971). Although the treatment regime used in

the latter study was inconsistent with current dietary guidelines (i.e., exceeded 5% in feed), inclusion of an appropriate caloric control group, together with extensive reporting of findings, suggests that these findings are reliable and suitable for hazard evaluation.

Skin painting studies with propylene glycol have shown no increase in dermal tumors in female mice after chronic treatment with 2, 10 or 21 mg/day over a lifetime (Stenbeck and Shubik, 1974). In a non-standard investigation, Wallenius and Lekholm (1973) used propylene glycol as vehicle (dose not specified) in an ear painting study in rats. No tumors were apparent by visual or microscopic examination after 10-14 months treatment.

There is no evidence to suggest that propylene glycol has any carcinogenic potential.

4.1.6 Reproductive/Developmental Toxicity

The impact of propylene glycol on reproductive performance in male and female mice has been assessed using a continuous breeding protocol (Morrissey *et al.*, 1989; Lamb *et al.*, 1997). Propylene glycol was administered in drinking water (1-5%), with received doses of approx. 1800, 4800 or 10100 mg/kg bw/d for up to 98 days. There was no treatment-related effect on growth or viability in the F1 and F2 generations, or on reproductive performance in the F0 or F1 generations.

Effects on fetal development have been investigated in pregnant rats, mice, hamsters and rabbits (Food and Drug Research Laboratories, 1973). Appropriate positive control substances were included in these studies (asprin for rats, mice and hamsters, 6-aminonicotinamide for rabbits). Orally administered propylene glycol (gavage) was well tolerated with no adverse effect on pregnancy parameters or maternal or fetal survival at any treatment level. There was no evidence of teratogenicity at any dose level.

The following NOAELS and LOAELS were obtained :

Species	Treatment mg/kg bw/d	Treatment period	Maternal		Fetal	
			LOAEL	NOAEL	LOAEL	NOAEL
Rat	16.0, 74.3, 345, 1600	GD 6-15	>1600	1600	>1600	1600
Rabbit	12.3, 57.1, 267, 1230	GD 6-18	>1230	1230	>1230	1230
Mouse	16.0, 74.3, 345, 1600	GD 6-15	>1600	1600	>1600	1600
Hamster	15.5, 72.0, 334.5, 1550	GD 6-10	>1550	1550	>1550	1550

In conclusion, propylene glycol is not a reproductive or developmental toxicant.

4.1.7 Toxicokinetics

Absorption of orally administered propylene glycol from the gastrointestinal tract, and its removal from the body, follow first order kinetics (Morshed *et al.*, 1988). Clearance from blood is rapid in humans, with a mean half-life of approx. 2 hr (Speth *et al.*, 1987). Its metabolism is inhibited by pyrazole, indicating a role for alcohol dehydrogenase in this process. Once absorbed it is readily converted into lactic and pyruvic acids (Morshed *et al.*, 1991), which then enter the general metabolic pool.

4.2 Human Health Assessment

Propylene glycol does not present an acute, chronic, reproductive, or developmental hazard. Acute toxicity is very low, with LD_{50} values exceeding 19000 mg/kg after ingestion or skin contact. It is not a skin or eye irritant, and does not cause sensitization. The weight of the evidence indicates that it is not genotoxic *in vitro* or *in vivo*. Adequate long-term feeding studies are available which indicate that it does not represent a cancer hazard.

5.0 Conclusions and Recommendations

5.1 Conclusions

Propylene glycol is a liquid at room temperature, it has a low vapor pressure, and is miscible with water. Releases to the environment are expected to partition primarily to water and soil where they will be readily degraded. It is not expected to bioaccumulate, based upon a calculated BCF of around 1. Testing in a range of aquatic species showed a low hazard concern. A PNEC of 190 mg/l was obtained from an algal EC_{50} of 19000 mg/l. The mammalian acute toxicity of propylene glycol is low, with values around 20000 mg/kg bw reported in tests in a range of species (rats, mice, guinea pig, rabbit, and dog). It is not a skin sensitizer or skin irritant, and is only minimally irritating to the eye. Longer-term studies demonstrate a low concern for chronic, reproductive, and developmental effects. Propylene glycol is not genotoxic or carcinogenic.

Propylene glycol is a high production volume chemical, with global production on the order of 2000 million pounds (1000 thousand tonnes). Propylene glycol is used as the base in the production of antifreeze, deicing solutions, and polyester compounds for industrial or commercial use, as well as solvents in liquid laundry detergents and paint manufacturing. It is also used as an additive in food, pharmaceuticals, pet foods, and tobacco processing. These uses of propylene glycol as a substance capitalize on its properties to retain moisture and act as a functional fluid. It is estimated that 98% of potential occupational exposures in the US occur with trade name products containing propylene glycol, and the balance in the production of the chemical. In the commercial service and consumer settings there is a potential for inhalation and dermal exposure. In the consumer setting, exposure by ingestion is a result of the approved use of propylene glycol in food, tobacco and pharmaceutical products by the US FDA.

5.2 Recommendations

The chemical is currently a low priority for further work.

6. References

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SIDS DOSSIER
Propylene Glycol CAS No. 57-55-6

1.0 GENERAL INFORMATION

1.0.1 SUBSTANCE INFORMATION

A. CAS-Number: 57-55-6

B. Name *(IUPAC name)*: propane-1,2-diol

C. Name *(OECD name)*: propylene glycol

D. CAS Descriptor

E. EINECS-Number

F. Molecular Formula $C_3H_8O_2$

G. Structural Formula CH_3-CHOH-CH_2OH

H. Substance Group

I. Substance Remark

J. Molecular Weight 76.09

1.0.2 OECD INFORMATION

A. Sponsor Country:

Name: United States of America
Contact point: Oscar Hernandez
EPA/Office of Toxic Substances RAD (7403M)
1200 Pennsylvania Ave, NW
Washington, D.C. 20460
Telephone: (202) 564-7649
Fax: (202)-564-7450

B. Lead Organisation:

Name: American Chemistry Council
Contact person: Anne LeHuray
Address: American Chemistry Council
1300 Wilson Boulevard
Arlington, VA 22209
703-741-5630
LeHuray_Anne@americanchemistry.com

1.1 GENERAL SUBSTANCE INFORMATION

1.1.1 Type of Substance element [ ]; inorganic [ ]; natural substance [ ]; organic [X]; organometallic [ ]; petroleum product [ ]

1.1.2. Physical State *(at 20°C and 1.013 hPa)*
gaseous [ ]; liquid [X]; solid [ ]

1.1.3. Purity > 98 percent (no indication as to whether this is on a weight by weight basis)

1.2 SYNONYMS:
1,2-Dihydroxypropane, 1,2-Propylene glycol, 2,3-Propandiol, 2-Hydroxypropanol, Isopropylene glycol, Methylethyl glycol, Methylethylene glycol, Monopropylene glycol, PG, Propylene glycol, Sirlene, Dowfrost

1.3 IMPURITIES

Dipropylene glycol

1.4 ADDITIVES

1.5 QUANTITY

Propylene glycol production capacity in the US was 1312 million pounds (596 thousand tonnes) in 1998. Domestic demand was 1050 million pounds (477 thousand tonnes). In 1994, approximately 18% of US production was converted to downstream products by the manufacturers. In 1998, propylene glycol was produced in the US by The Dow Chemical Company, Eastman Chemical Company, Huntsman Corporation, Lyondell Chemical Company, and Olin Corporation. (Sources: ChemExpo Chemical Profile (1998) and US ITC, (1994) Synthetic Organic Chemical Report p 3-31).

According to the ECDIN database, in 1989 western Europe produced 708 million pounds (325 thousand tonnes) and consumed 660 million pounds (300 thousand tonnes).

1.6 LABELLING AND CLASSIFICATION

Labelling
Type:
Specific limits:
Symbols:
Nota:
R-phrases:
S-phrases:
Text of S-phrases:
Remarks:

Classification
Type:
Category of danger:
R-phrases:
Remarks:

1.7 USE PATTERN

1.7.1 GENERAL

USES OF PROPYLENE GLYCOL

USES	APPLICATION	FUNCTION	% PRODUCTION (1)	(2)
Intermediate	Unsaturated Polyester Resins	Resin Monomer	38%	40%
Substance Substance	Food, Pharmaceuticals Cosmetics and Personal Care	Humectant Emollient	17%	12%
Substance	Specialty Antifreeze, Aircraft Deicing, Industrial Lubricants, Inks	Lubricant, Coolant	13%	10%
Substance	Liquid Laundry Detergents	Dispersant	9%	15%
Substance	Pet Foods	Humectant	5%	6%
Substance	Tobacco Processing	Humectant	4%	3%
Substance	Paints and Coatings	Solvent	4%	4%
Substance Intermediate		Miscellaneous Plasticizer	10%	4%

(Sources: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd Ed., Volumes 1-26, NY, John Wiley and Sons 1978-1984; (1): Chemical Business, Nov. 1992, p. 36; (2): and Chemical Marketing Reporter, Vol 249, No. 7 p. 37, 2/12/96.)

1.7.2. USES IN CONSUMER PRODUCTS

The Environmental Defense Scorecard website for propylene glycol lists 82 consumer product types and 157 pesticidal products. See www.scorecard.org for this information. Use concentration assessments for formulated cosmetics containing propylene glycol in 74 different product types (from another data source) are summarized below.

COSMETIC PRODUCT FORMULATIONS CONTAINING PROPYLENE GLYCOL

PRODUCT CATEGORY	RANGE OF CONCENTRATIONS AS USED (%)				
	<1	1-10	10-25	25-50	>50
No. of Hair Care Products	183	284	157	65	1
No. of Eye Care Products	66	214	11	2	0
No. of Skin Care Products	1122	1808	55	25	20
No. of Bath Products	135	49	6	4	0
No. of Shaving Products	61	82	5	1	0

(Source: Journal of the American College of Toxicology, Vol. 13, No. 6, p. 440, 1994.) Other data sources identified a concentration range (from 2.2 to 70%) of propylene glycol approved for use in specific cosmetic and medical applications. (Source: American Medical Association, Council of Drugs (1994), AMA Drug Evaluations Annual, Chicago, IL, AMA.)

The concentration of propylene glycol in branded pesticidal products is also available. This is summarized in the following table.

PESTICIDAL FORMULATIONS CONTAINING PROPYLENE GLYCOL

	RANGE OF CONCENTRATION (%)				
	<1	**1-10**	**10-25**	**25-50**	**>50**
No. of Brand Name Products	3	124	24	2	3

(Source: ED Website: www.scorecard.org)

Whereas the table above provides data for 156 branded pesticidal products, only 16 of these currently (May, 2001) maintain active registrations in the US. The 16 active registered products contain propylene glycol in the 0.1 to 10 percent range.

EPA published data on the quantities of propylene glycol in consumer products in its efforts to define parameters for the assessment of urban air toxics. The following table summarizes this information.

EPA DATA ON PROPYLENE GLYCOL IN CONSUMER GOODS

PRODUCT CATEGORIES	NUMBER OF PRODUCTS	RANGE OF CONCENTRATION (%)
Paint Primers Varnishes	3	21.2 - 50.2%
Room Deodorants Disinfectants	2	Up to 100%
Personal Deodorants	1	Up to 100%
Metal Cleaners Polishes	1	Up to 100%
All-Purpose Cleaners	5	10.7 - 100%

(Source: US EPA, (1989) Compilation and Speculation of National Emissions Factor for Consumer/Commercial Solvent Use, EPA-450/2-89-008.)

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

No data

1.9 SOURCES OF EXPOSURE

No data

1.10 ADDITIONAL REMARKS

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

Value	-59 degree C
Method	
GLP:	no data
Reference:	Sax, N.I. (1979): Dangerous properties of industrial materials, 5th Edition, van Reinhold Company, New York, S. 943.

2.2 BOILING POINT

Value	189 degree C
Pressure:	1013 hPa
Decomposition	
GLP:	no data
Reference:	Weast, R.C. (1988): Handbook of Chemistry and Physics, 1st Edition, CRC, Boca Raton, S. C-457.

Value	187.9 degree C
Pressure:	1013 hPa
Decomposition	
GLP:	no data
Reference:	Ullmanns Encyclopedia of Technical Chemistry, 4th Edition, 1980, S. 425-432.

Value	188 degree C
Pressure	
Decomposition	
GLP:	no data
Reference:	DOW Deutschland, Inc., 1999. Safety Data Sheet.

Value	185 degree C
Pressure	
Decomposition	
GLP:	no data
Reference:	Arco Chemical Company, 1993. Material Safety Data Sheet.

2.3 DENSITY

Value	1.04 g/cm^3
Temperature:	20 degree C
GLP:	no data
Reference:	DOW Deutschland, Inc., 1999. Safety Data Sheet.

2.4 VAPOUR PRESSURE

Value	0.11 hPa
Temperature:	20 degree C
GLP:	no data
Reference:	Ullmanns Encyclopedia of Technical Chemistry, 4th Edition, 1980, S. 425-432.

Value	0.3 mbar
Temperature:	20 degree C
GLP:	no data
Reference:	DOW Deutschland, Inc., 1997. Safety Data Sheet.

Value	ca. 0.133 hPa
Temperature:	21 degree C
GLP:	no data
Reference:	Arco Chemical Company, 1993. Material Safety Data Sheet.

2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

log P_{ow}	-0.92
Temperature	degree C
GLP:	no data
Reference:	Pomona College Database. 1991. Medicinal Chemistry Project.

2.6 WATER SOLUBILITY

Described as miscible

GLP:	no data
Reference:	DOW Deutschland, Inc. 1999. Safety Data Sheet. Ullmanns Encyclopedia of Technical Chemistry, 4th Edition, 1980, S. 425-432.

2.7 FLASH POINT *(liquids)*

Value	103 degree C
Type:	closed cup
GLP:	no data
Method:	Closed Cup test. DIN 51758.
Reference:	Ullmanns Encyclopedia of Technical Chemistry, 4th Edition, 1980, S. 425-432.

Value	103 degree C
Type:	closed cup
GLP:	no data
Method:	Closed Cup test. Pensky Martens
Reference:	DOW Deutschland, Inc., 1999. Safety Data Sheet.

2.8 AUTO FLAMMABILITY *(solid/gases)*

Value	371 degree C
Pressure	
GLP:	no data
Reference:	Arco Chemical Company. 1993. Material Safety Data Sheet,

2.9 FLAMMABILITY

No data

2.10 EXPLOSIVE PROPERTIES

Result:	lower limit : 2.6 VOL% in air; upper limit: 12.5 Vol% in air
Reference:	Dow Europe SA, 1999. Material Safety Data Sheet.

2.11 OXIDIZING PROPERTIES

No data

2.12 ADDITIONAL REMARKS

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1.1 Photodegradation

Type: air; Sensitizer: OH^-

Conc. of Sensitizer: 500000 molecule/cm^3

Result:

Degradation: $t_{1/2}$ ~ 32 hrs

Rate Constant: 0.0000000000012 cm^3/(molecule*sec)

GLP: no data

Remark: Sun Indirect Photolysis: Propylene Glycol hydrolysis

By photochemically-produced hydroxy radicals is rapid in air.

Reference: Atkinson, R. A. *et al.*, (1985). Chem. Rev. pp. 60-201.

Type: water; Sensitizer: OH

Test condition: Concentration of sensitizer: 10^{-17} mol/litre ; pH = 7

GLP: no data

Result:

Degradation: $t_{1/2}$ ~ 2.3 yrs

Rate constant: 0.94 10^9 litre/ molecule.sec

Remark: Indirect photolysis: Propylene Glycol hydrolysis by photochemically-produced hydroxy radicals is slow in water.

Reference: Anbar, M., Neta, P., (1967). *Int. J. Appl. Radiation and Isotopes*, 18: 498-523.

Type: water; Sensitizer: OH-

Conc. of sensitizer: 10^{-17} mol/litre; pH = 7

GLP: no data

Result:

Degradation: $t_{1/2}$ ~ 1.3 yrs

Rate constant: 1.68 10^9 litre/molecule.sec

Remark: Indirect photolysis: Propylene Glycol hydrolysis by photochemically-produced hydroxy radicals is slow in water.

Reference: Dorfman, LM, Adam, GE, Washington National Bureau of Standards, p51, NSRD-NBS-46 (NTIS COM-73-50623).

3.1.2 Stability in Water

Remark:	Propylene Glycol is expected to degrade rapidly in water from biological processes but is not expected to be significantly influenced by hydrolysis, oxidation, volatilization, bioconcentration, or absorption to sediment.
Reference:	Hazardous Substances Database, (HSDB) 1994.

3.1.3 Stability in Soil

Remark:	Propylene Glycol is expected to biodegrade rapidly in soil.
Reference:	Hazardous Substances Database, (HSDB) 1994.

3.2 MONITORING DATA (ENVIRONMENT)

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL OMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

3.3.1 Transport Between Environmental Compartments

Type:	Adsorption [ ]: Desorption [ ]; Volatility [ ]: Other [X]
Media:	water - air
Result:	Henry Law Constant: 1.2 10^{-8} cu m/mole
Remark:	This HLC indicates that Propylene Glycol will tend to stay in water and not migrate to air.
Reference:	Simmons, P. et al., (1976). Int Tech. Conf. RTP, NC: Amer. Assoc.Text. 212-217.

3.3.2 Theoretical Distribution (Fugacity Calculation)

Model: EPIWIN (Version 3.10) - Level III Fugacity Model

Inputs: Inputs to the model were as follows:

Henry's Law constant:	1.74 x 10^{-7} atm-m^3/mole
Vapor pressure:	0.0825 mm Hg (~ 0.11 hPa)
Log K_{ow} :	-0.92
Soil K_{oc} :	0.0493
Emissions to air, water, and soil compartments:	1000 kg/hr

Results:

Compartment	**Percent**
Air	2.98
Water	48.8
Soil	48.1
Sediment	0.0729

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

No data available

3.5 BIODEGRADATION

Type:	aerobic
Inoculum:	*Pseudomonas* sp.
Test condition:	Pseudomonas predominantly in sludge. Aeration tank activated sludge waste water feed incubated at pH 9 for 24 hours.
Concentration:	700 mg/l
GLP:	no data
Results:	
Degradation:	100 % after 24 hour
Remark:	Rapid biodegradation was observed. Degradation products: Acetic acid, formaldehyde.
Reference:	Gorban NS, et al., (1972). *Probl. Okhr. Vod.* 1: 91-97.

Type:	aerobic
Inoculum:	*Pseudomonas graveoleus* and *Pseudomonas fluorescens*
Method:	Aeration tank inoculated with microbes.
Concentration:	700 mg/l
GLP:	no data
Results:	Degradation observed with both pseudomonas strains.
Reference:	Gorban, NS, Petrenko, MB, (1972). *Mikrobiol. Zh.* 34:571-575.

Type:	aerobic
Inoculum:	*Flavobacterium* sp.
GLP:	no data
Results:	
Deg.prods:	Lactaldehyde, propionaldehyde, pyruvate, carbon dioxide, n-propanol.
Remark:	Degradation pathway influenced by degree of aeration.
Reference:	Willetts, A., (1979). *Biochim. Biophys. Acta* 588: 302-309.

Type:	aerobic
Inoculum:	Bacterium strain SA-1; Bacterium isolated from soil, aerobic conditions, 30 deg. C, 4-5 day incubation.

GLP:	no data
Results:	
Deg.prods:	Lactaldehyde, lactic acid, pyruvic acid.
Reference:	Tanaka Y. et al., (1975). *Hakko Kogaku Zasshi* 53: 354-362.
Type:	aerobic
Inoculum:	activated sludge, domestic, adapted
Method:	Continuously aerated batch reactors (2 litres) with 2000-2500 mg solid/ l water, varying pH, acclimation/ non acclimation, high dose/ low dose.
Concentration:	2400 mg/l
GLP:	no data
Results:	Rapidly biodegradable.
Degradation:	Acclimated biomass is very efficient in biodegrading; 100 % after 24 hour propylene glycol; unacclimated biomass is less efficient, removing 50% in 3 days.
Reference:	Roy F. Weston Inc, report, unpublished and sponsored by Arco Chemical Company, 1990.
Type:	aerobic
Inoculum:	other bacteria; Concentration: not reported
Results:	
Degradation:	10-40% after: 7 days
GLP:	no data
Remark:	Of the glycol based solutions tested for biodegradation, propylene glycol was the most recalcitrant. Over a 7-day period, an average glycol metabolism of 1000 to 4000 mg/L/7 days was calculated.
Reference:	Strong-Gunderson, J.M., S. Wheelis, S.L. Carroll, M.D. Waltz, and A.V. Palumbo. (1995). Degradation of high concentrations of glycols, antifreeze, and deicing fluids, In: Microbial Processes for Bioremediation.
Type:	aerobic
Inoculum:	other bacteria
GLP:	no data
Remark:	This study assessed the effect of temperature on propylene glycol biodegradation rates. It was generally found that although pH and moisture were held constant, microbial activity consistently varied with temperature. The authors noted that the metabolic activity of the bacteria, but not relative numbers of bacteria, varied with temperature.
Reference:	Davis-Hoover, W.J. and S.J. Vesper. (1995).Temperature effects on propylene glycol- contaminated soil cores. In: Hinchee, R. E., C. M. Vogel and F. J. Brockman (Ed.). Bioremediation, 3 (8). Microbial Processes For Bioremediation; Selected Papers From The Third

	International In Situ and On-Site Bioreclamation Symposium, San Diego, California, USA, April 1995. X+361P. Battelle Press: Columbus, Ohio, USA. ISBN 1-57477-009-8.; 0: 329-333.
Type:	aerobic
Inoculum:	other bacteria
Concentration:	3476.5 ppm; 4179.7 ppm
Results:	
Degradation:	3.5-20.0 mg/kg/day
GLP:	No data
Remark:	An 89% propylene glycol-based deicer solution was applied to a sandy loam soil microcosm and found to have a biodegradation rate of 3.5 mg/kg-day at –2°C. The authors noted that propylene glycol was mineralized to carbon dioxide with no lag period observed. It was concluded that biodegradation will play a major role in removing residual levels of glycols from soils adjacent to airport runways.
Reference:	Klecka, G.M., C.L. Carpenter, and B.D. Landenberger. (1993). Biodegradation of aircraft deicing fluids in soil at low temperatures. *Ecotoxicology and Environmental Safety* 25: 280-295.
Type:	anaerobic
Inoculum:	*Clostridium* sp.
Test condition:	Test was conducted at 22-37 deg. C and pH 7.4- 7.6.
GLP:	no data
Results:	
Deg. Prod:	Corresponding acid and alcohol.
Reference:	Gaston, LW, Stadtman, ER, (1963). *J. Bacteriol*. 85: 356-362.
Type:	anerobic
Inoculum:	none
Procedure:	PG incubated in closed system with sandy loam or sand without oxygen for up to 105 days.
Concentration:	1,000 and 10,000 mg/kg
GLP:	yes
Results:	
Degradation:	100 % after 14 days for 1000 mg/kg and 98 % after 105 days for 10,000 mg/kg in sandy loam.
Rate:	71 mg/kg day. In sand, rate = 10 mg/kg/day

Remark:	Authors conclude that high concentrations of propylene glycol released into a soil environment can be expected to biodegrade.
Reference:	Klier, N.J., and P.A. Goodman. (1997). Anaerobic Biodegradation of Propylene Glycol in Soil. The Dow Chemical Company, Midland, Michigan.
Type:	anaerobic
Inoculum :	"Enriched methane cultures".
Method:	Hungate serum bottle technique, 50 ml inoculum, 100 mg acetate, 25 mg MPG (500 mg/l), 6 injections of MPG.
Concentration:	500 mg/l
GLP:	no data
Results:	
Degradation:	100 %
Remark:	Rapid biodegradation was observed. Degradation appears after a lag period of 4 days, at removal rate 125 mg/l/day
Reference:	Chou WL, et al., (1979). *Biotechnol. Bioeng. Symp.* 8: 39-414.
Type:	unspecified
Inoculum:	*Alcaligenes* MC11, TE8, PE18 and *Corynebacterium*, OEH8.
Method:	Microbes isolated from soil except PE18; 30 deg. C, 6 day duration, shaken.
Concentration:	1% substrate as sole carbon source.
GLP:	no data.
Result:	
Degradation:	MC11/ growth; TE8/ slight growth; PE18/ no growth; OEH8/ slight growth.
Reference:	Harada T., Nagashima Y., (1975). *J. Ferment. Technol*. 53: 218-222.
Type:	unspecified
Inoculum:	*Pseudomonas* sp.
Method:	Growth
GLP:	no data
Remark:	Degradation observed - doubling time 7 hours.
Reference:	Bolbot JA, Anthony C, (1980). *J. Gen. Microbiol*. 120:

245-254.

Type: unspecified

Inoculum: not specified

Concentration: 1% MPG

Method: 30 deg. C, 48 hours

GLP: no data

Results:

Degradation: 90 % after 48 hour

Remark: Rapid biodegradation was observed. Degradation products: Lactic acid

Reference: Ishii M, et al., (1959). *Nippon Nogei Kagaku Kaishi* 33: 889-893.

Type: unspecified

Inoculum: *Corynebacterium* sp.;

Test condition: 20-30 deg.C, pH 7-9

Method: Growth

GLP: no data

Remark: Degradation observed.

Reference: Kawai F. *et al.*, (1977). *J. Ferment. Technol.* 55: 89-96.

Type: unspecified

Inoculum: 23 strains of bacteria, 25 strains of yeast and 17 strains of fungi.

Method: Propylene Glycol used as sole carbon source; bacteria and strains incubated for 10 days at 30 deg. C, fungi for 20 days at room temperature.

GLP: no data

Remark: 83% of microbes were able to use PG as sole carbon source (8/23 bacteria, 18/25 yeasts, 10/17 fungi)

Reference: Yanagi M, Onishi G, (1971). *J. Soc. Cosmet. Chem*. 94: 796-798.

Type: unspecified

Inoculum: Filtered sewage seed. BOD test measurement at 5, 10, 15 and 20 days in salt water and fresh water.

GLP: no data

Results: BOD_5 = 62%, BOD_{20} = 79% (fresh water); BOD_5 = 55%, BOD_{20} = 83% (salt water).

Reference:	Price, K.S., *et al.*, (1974). Brine Shrimp Bioassay and Seawater BOD of Petrochemicals. *Journal of Water Pollution Control* Fed. Vol. 46: 63-77.
Type:	unspecified
Inoculum:	Activated sludge seed + PG + nutrients in Warburg respirometer.
GLP:	no data
Results:	BOD_{40} = 78 %
Reference:	Helfgott TB *et al.*, EPA-600/2-77-174. ADA, OK: US EPA
Type:	unspecified
Inoculum:	
Method:	not specified.
GLP:	no data
Results:	BOD = 95% after 6 hours
Reference:	Grunwald A *et al.*, (1984). *Vodni Hospod*. 34: 247-252
Type:	unspecified
Inoculum:	*Mycobacterium* sp.
Test condition:	Propylene Glycol used as sole carbon source by all *M. smegmatis* strains, most *M. fortuitum* and some *M. phlei* strains.
GLP:	no data
Results:	not given
Reference:	Tsukamura M., (1966). *Am. Rev. Resp. Dis.* 94: 796-798.

3.6 BOD_5,COD OR RATIO BOD_5/COD

BOD_5/COD

Method:	Standard dilution 5-day BOD water ; Concentration 3700 mg/l
GLP:	no data
Results:	BOD_5 = 1170 mg/l COD = 2600 mg/g BOD_5/COD = .45
Reference:	Roy F. Weston Inc. report, sponsored by ARCO Chemical Company, 1990.

BOD5/COD Ratio

Method:	Filtered sewage seed- 5 days at 20 deg. C.

GLP: no data

Result: BOD_5 = 64% BODT

COD = 97% CODT

BOD_5/COD = .67

Reference: Bridie AL *et al.* 1979a. *Water Res*. 13: 627-630.

BOD

Method: Activated sludge or digested sludge inocula- no degradation in sterile controls.

GLP: no data

Result: BOD_4= 100%, aerobic.

BOD= 100% in 4-9 days, anaerobic.

Reference: Kaplan DL *et al.*, (1977). Environ. Organics USEPA-66/2-77-174.

BOD_5

Method: Standard dilution BOD water.

GLP: no data

Result: BOD_5 = 2.2% at day 5, 56.7% at day 10 and 80% at day 50.

Reference: Lamb CB, Jenkins GF, (1952). Proceedings 8th Industrial Waste Conference, Purdue University pp. 326-329.

BOD_5

Method: Standard dilution 5-day BOD water.

GLP: no data

Result: BOD_5 = 26% in 5 day; seawater: 59.5% in 5 days.

Reference: Takemoto S *et al.*, (1981). *Suishitsu Odaku Kenkyu* 4:80-90.

BOD_5

Method: not specified

GLP: no data

Result: BOD_5 = 74.5% in 5 days.

Reference: Wagner R, (1976). *Vom Wasser* 47:241-265.

3.7 BIOACCUMULATION

Remark: BCF calculated from Log K_{ow} of -0.92. BCF<1

Reference: Lyman WJ *et al.*, (1982). Handbook of Chemical Property Estimation Methods, McGraw-Hill, New York.

4. ECOTOXICOLOGICAL DATA

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type:	static
Species:	*Pimephales promelas*
Method:	OECD Guideline 203; Exposure Period 96 hour
Analyt.	
Monitoring:	yes
GLP:	yes
Results:	NOEC = 41,000 mg/l
	LC_{50} = 51,400 mg/l
Reference:	ARCO Chemical Company. 1990a. Static Acute Toxicity of Propylene Glycol to the Fathead Minnow, *Pimephales promelas*. Enviro Systems (Study No. 8930-A). Feb. 7. Unpublished report.

Type:	static
Species:	Fathead Minnow *(Pimephales promelas)*
Exposure	
Period:	96 hours
GLP:	yes
Results:	NOEC = 12,960 mg/l
	LC_{50} = 46,500 mg/l
Reference:	Weinberg, J.T., H.D. Kirk, J.A. Miller, M.F. Servinski. (1993). Evaluation of the acute toxicity of industrial grade propylene glycol to representative freshwater organisms. Unpublished report of The Dow Midland Company. Midland, Michigan, 48674.

Type:	other
Species:	*Pimephales promelas*
Method:	American Society for Testing & Materials. ASTM Standard E729-80, Standard Practice for Conducting Acute Toxicity Tests with Fishes, Macroinvertebrates and Amphibians. Philadelphia, Penn., 1980; Exposure Period 96 hour
GLP:	no data
Results:	NOEC < 47,829 mg/l
	LC_{50} = 54,650 mg/l
	LC_{100} = 65,610 mg/l
Reference:	DOW (1981): Report ES-462.
Type:	static
Species:	Fathead Minnow *(Pimephales promelas)*

Exposure Period:	48 hour
GLP:	no data
Results:	NOEC: 52,930 mg/l
	LC_{50}: > 62,000 mg/l
Reference:	Pillard, D.A. (1995). Comparative toxicity of formulated glycol deicers and pure ethylene and propylene glycol to *Ceriodaphnia dubia* and *Pimephales promelas*. *Environ. Toxicol. Chem.* 14:311-315.
Type:	static
Species:	Fathead Minnow *(Pimephales promelas)*
Exposure Period:	7 days
GLP:	no data
Results:	NOEC: < 11,530 mg/l for growth; LC_{50}: 55,770
Reference:	Pillard, D.A. (1995). Comparative toxicity of formulated glycol deicers and pure ethylene and propylene glycol to *Ceriodaphnia dubia* and *Pimephales promelas*. *Environ. Toxicol. Chem.* 14:311-315.
Type:	static
Species:	*Oncorhynchus mykiss*
Method:	OECD Guideline 203; Exposure Period 96 hour
Analyt. Monitoring:	yes
GLP:	yes
Results:	NOEC = 42,000 mg/l
	LC_{50} = 51,600 mg/l
Reference:	ARCO Chemical Company. 1990b. Static Acute Toxicity of Propylene Glycol to the Rainbow Trout, *Oncorhynchus mykiss*. Enviro Systems (Study No. 8928-A). Feb. 7. Unpublished report.
Type:	static
Species:	*Cyprinodon variegates*
Method:	OECD Guideline 203; Exposure Period 96 hour
Analyt. Monitoring:	yes
GLP:	yes
Results:	NOEC < 16,000 mg/l
	LC_{50} = 23,800 mg/l
Reference:	ARCO Chemical Company. 1990c. Static Acute Toxicity of Propylene Glycol to the Fathead Minnow, *Pimephales promelas.* Enviro Systems (Study No. 8930-A0). Feb. 7. unpublished report.

Type:	NA
Species:	*Carassius auratus*
Method:	Static-tank acute toxicity test. Standard methods for the examination of water and wastewater. American Public Health Association, New York. Method No. 231; Exposure Period 24 hour
GLP:	no data
Results:	LC_{50} > 5000 mg/l
Reference:	Bridie, A.L. *et al.* 1979b. Water Res. 13: 623-626.

Type:	other
Species:	*Salmo gairdneri*
Method :	Standard Methods for the Examination of Water and Wastewater. 13th Edition. American Public Health Association, 1971. Exposure Period 24 hour
GLP:	no data
Results:	LC_0 = 50,000 mg/l
Reference:	Majewski, H.S. *et al.* (1978): *Water Res.* 13: 217-221.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Species:	*Daphnia magna*
Method	OECD Guideline 202, part 1; Exposure Period 48 hour
Analyt. Monitoring:	yes
GLP:	yes
Results:	NOEC = 28,500 mg/l EC_{50} = 43,500 mg/l
Reference:	ARCO Chemical Company. 1990d. Static Acute Toxicity of Propylene Glycol to the Daphnid, *Daphnia magna.* Enviro Systems (Study No. 8926-A). Feb. 8.

Species:	*Daphnia magna*
Method:	American Society for Testing & Materials. ASTM Standard E729-80, Standard Practice for Conducting Acute Toxicity Studies with Fishes, Macroinvetebrates and Amphibians. Philadelphia, Penn., 1980; Exposure Period 48 hour
GLP:	no data
Results:	NOEC < 4295 mg/l EC_{100} = 50,000 mg/l
Reference:	DOW (1981): Report ES-462.

Species: *Artemia salina*

Exposure Period: 24 hour

GLP: no data

Results: EC_{50} = 10,000 mg/l

Reference: Price, K.S., *et al.*, (1974). Brine Shrimp Bioassay and Seawater BOD of Petrochemicals. *Journal of Water Pollution Control* Fed. Vol. 46: 63-77.

Species: *Mysidopsis bahia*

Method: US EPA FIFRA Guideline 72-3 (TSCA 797.1950); Exposure Period 96 hour

Analyt. Monitoring: yes

GLP: yes

Results: NOEC < 9500 mg/l

LC_{50} = 18800 mg/l

Reference: ARCO Chemical Company. 1990e. Static Acute Toxicity of Propylene Glycol to the Mysid, *Mysidopsis bahia*. EnviroSystems (Study No. 8934-A). Feb. 8.

Species: Water Flea *(Ceriodaphnia dubia)*

Method: static; Exposure Period: 48 hour

GLP: no data

Results: NOAEC = 13,020 mg/l

EC_{50} = 18,340 mg/L

Reference: Pillard, D.A. (1995). Comparative toxicity of formulated glycol deicers and pure ethylene and propylene glycol to *Ceriodaphnia dubia* and *Pimephales promelas*. *Environ. Toxicol. Chem.* 14:311-315.

4.3 TOXICITY TO AQUATIC PLANTS e.g. Algae

Species: *Skeletonema costatum*

Method: OECD Guideline 201; Endpoint: growth rate; Exposure Period 14 day

Analyt. Monitoring: yes

GLP: yes

Results: NOEC < 5300 mg/l

EC_{50} = 19,100 mg/l (at 96 hours)

Reference:	ARCO Chemical Company. 1990f. Static Acute Toxicity of Propylene Glycol to the Marine Algae, *Skeletonema Costatum*. EnviroSystems. (Study No. 8960-A), Feb. 7. unpublished report.
Species:	*Selenastrum capricornutum*
Method:	OECD Guideline 201; Endpoint growth rate; Exposure Period 14 day
Analyt.	
Monitoring:	yes
GLP:	yes
Results:	NOEC = 15,000 mg/l
	EC_{50} = 19,000 mg/l (at 96 hours)
Reference:	ARCO Chemical Company. 1990g. Static Acute Toxicity of Propylene Glycol to the Freshwater Alga, *Selenastrum Capricornutum*. EnviroSystems (Study No.8959-A), Feb. 8. Unpublished report.

4.4 TOXICITY TO BACTERIA

Species:	Bacterium *Pseudomona putida*
Method:	other; Exposure Period: no data
GLP:	no data
Results:	NOAEC = 20,000 mg/l
Reference:	Hanstveit, A.O., and M.A.H.L. Pullens. (1982). The Effect of Propylene Glycol on the Growth of the bacterium *Pseudomonas Putida*. Unpublished report of Dow Chemical Europe.

4.5 CHRONIC TOXICITY

4.5.1. Chronic Toxicity to Fish

No data available

4.5.2. Chronic Toxicity to Aquatic Invertebrates

Species:	Water Flea *(Ceriodaphnia dubia)*
Method:	Static; Exposure Period: 7 days
GLP:	no data
Results:	NOAEC = 13,020 mg/l for reproduction
Reference:	Pillard, D.A. (1995). Comparative toxicity of formulated glycol deicers and pure ethylene and propylene glycol to *Ceriodaphnia dubia* and *Pimephales promelas*. *Environ. Toxicol. Chem.* 14: 311-315.

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil-dwelling Organisms

No data available

4.6.2 Toxicity to Terrestrial Plants

No data available

4.6.3 Toxicity to other Non-mammalian Terrestrial (Including Avian) Species

No data available

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data available

4.8 BIOTRANSFORMATION AND KINETICS

No data available

4.9 ADDITIONAL REMARKS

5. MAMMALIAN TOXICITY

5.1 ACUTE TOXICITY

5.1.1 Acute Oral Toxicity

Species:	rat
Method:	details not given
GLP:	no data
Results:	LD_{50} = 21,000 to 30,000 mg/kg
Effects:	Details not Reported.
Reference:	Ruddick, J.A. (1972). Toxicology, Metabolism and Biochemistry of 1, 2-Propanediol. *Tox. Appl. Pharmacol.* 21, 102-111.
	Laug, *et al.* (1939). *J. Ind. Hyg. Tox.* Vol. 21, pgs. 173-201.

Species:	rat
Method:	details not given
GLP:	no data
Results:	LD_{50} = 20,300 to 24,000 mg/kg
Reference:	Clark CR *et al.*, (1979): *Toxicol. Appl. Pharmacol*. 51:529-535

Species:	rat
Method:	details not given
GLP:	no data
Results:	LD_{50} = 33,500 mg/kg
Effects:	Only minimal kidney changes were observed.
Reference:	Weatherby, J.H., and H.B. Haag. (1938). Toxicity of propylene glycol. *J. Am. Pharm. Assoc.* 27:466-471.

Species:	female rat
Method:	Single oral dose; details not given
GLP:	no data
Results:	at 730 or 2940 mg/kg, statistically significant and progressive decrease was noted in hemoglobin, packed cell volume and red cell counts, whereas an increase reticulocyte counts, plasma hemoglobin, and osmolality were also observed. In addition, electron microscope morphology revealed rough cell surface, ruptured membranes and increased cell adherence.
Reference:	Saini, M., Amma, M.K., Dash, S. and Nagpaul, J.P. (1996). Hematological alterations in propylene glycol-dosed female rats are minimal. *Vet. Hum. Toxicol.* 38: 81-85.

Species:	mouse

Method:	details not given
GLP:	no data
Results:	LD_{50} = 23900 cc/kg (24.9 mg/kg)
Reference:	J. A. Ruddick. (1972). Toxicology, Metabolism and Biochemistry of 1, 2-Propanediol. *Tox. Appl. Pharmacol.* 21, 102-111.
	Laug, *et al.* (1939). *J. Ind. Hyg. Tox.* 21: 173-201.
Species:	mouse
Method:	oral dose; details not given
GLP:	no data
Results:	Ataxia was observed in the 4.0 g/kg dose group. At 10.4 g/kg, observed effects included: ataxia, moderated decrease of spontaneous motor activity, body/limb tone, and respiration, 60% fall in treadmill performance, and 3° C fall in body temperature.
Reference:	Singh, P.P., Junnarkar, A.Y., Seshagirirao, C., Kaushai, R., Naidu, M.U.R., Tripathi, R.K. and Shridhar, D.R. (1982). A pharmacological study of propane-1,2-diol. *Arzheim.- Forsch.* 32:1443-1446.
Species:	guinea pig
Method:	details not given
GLP:	no data
Results:	LD_{50} = 18,900 mg/kg
Reference:	J. A. Ruddick. (1972). Toxicology, Metabolism and Biochemistry of 1, 2-Propanediol. *Tox. Appl. Pharmacol.* 21: 102-111.
	Laug, *et al.* (1939). *J. Ind. Hyg. Tox*. 21: 173-201.
Species:	guinea pig
Method:	details not given
GLP:	no data
Results:	LD_{50} = 18350 mg/kg
Effects:	Observed effects included CNS depression or narcosis.
Reference:	Smyth, H.F., Jr., J. Seaton, and L. Fischer. (1941). The single dose toxicity of some glycols and derivatives. *J. Ind. Hyg. Tox.*. 23:259-268.
Species:	rabbit
Method:	details not given
GLP:	no data
Results:	LD_{50} = 18000 to 19000 mg/kg
Reference:	J. A. Ruddick. (1972). Toxicology, Metabolism and Biochemistry of 1, 2-Propanediol. *Tox. Appl. Pharmacol*. 21, 102-111.
	Laug, *et al.* (1939). *J. Ind. Hyg. Tox.* 21: 173-201.

Species:	rabbit
Method:	details not given
GLP:	no data
Results:	Minimum Lethal Dose (MLD) = 20,000 mg/kg
Effects:	increased respiratory rate, loss of equilibrium, profound CNS depression, analgesia, respiratory effects, and coma.
Reference:	Braun, H.A., and G.F. Cartland. (1936). The toxicity of propylene glycol. *J. Am. Pharm. Assoc*. 25:746-748.

Species:	dog
Method:	details not given
GLP:	no data
Results:	LD_{50} = 20000 mg/kg
Effects:	Symptoms of acute intoxication with propylene glycol are those of central nervous system depression or narcosis. No system or organ has been established as a target for the acute oral lethal effects of propylene glycol.
Reference:	J. A. Ruddick. (1972). Toxicology, Metabolism and Biochemistry of 1, 2-Propanediol. *Tox. Appl. Pharmacol*. 21, 102-111. Laug, *et al.* (1939). *J. Ind. Hyg. Tox.* 21: 173-201.

Species:	horse
Method:	case report
GLP:	no data
Results:	7.9 g/kg (7.6 ml/kg) lethal dose: case report
Effects:	pain, ataxia, salivation, and excessive sweating within 10-15 minutes with death following increasing ataxia and respiratory arrest. Post mortem observations revealed microscopic hepatic and renal lesions (renal infarcts).
Reference:	Dorman, D.C., and W.M. Haschek, (1991). Fatal propylene glycol toxicosis in a horse. *J. Am. Vet. Med. Assoc.* 198:1643-1644.

Species:	Charles River Rat
Method:	oral gavage 3 times/day for 2 days, twice on 3rd day to groups of 10 rats at 0.75, 1.5 or 3.0 ml/kg/dose
GLP:	no data
Results:	One rat administered 0.75 ml/kg displayed slight hyperemia of the GI tract. One rat exposed to 1.5 ml/kg had severe hyperemia of the GI tract. Two rats given 3.0 ml/kg displayed slight hyperemia of the GI tract. The other rats displayed no irritation. Rats given 3 ml/kg either as 50% or 75% in water had no irritation. Propylene glycol was less irritating than glycerin or sorbitol.

Reference:	Staples, R., A. Misher, and J.J. Wardell. (1964). Gastrointestinal irritant effect of glycerol as compared with sorbitol and propylene glycol in rats and dogs. *J. Pharm. Sci*. 56:398- 400.
Species:	Mongrel dogs
Method:	oral gavage 3 times/day for 2 days, twice on 3rd day to groups of 1 dog at 0.75, 1.5 or 3.0 ml/kg/dose
GLP:	no data
Results:	At 0.75 and 3.0 ml/kg: stomach and duodenum appeared "normal". At 1.5 ml/kg the dog displayed slight hyperemia.
Reference:	Staples, R., A. Misher, and J.J. Wardell. (1964). Gastrointestinal irritant effect of glycerol as compared with sorbitol and propylene glycol in rats and dogs. *J. Pharm. Sci*. 56:398- 400.

5.1.2 Acute Inhalation Toxicity

No data available

5.1.3 Acute Dermal Toxicity

Species:	rabbit
Method:	not specified
GLP:	no data
Results:	LD_{50} = 20,800 mg/kg
Reference:	Raw Mater. Data Handb. (1974), Vol. 1, pg. 101, 1974, as cited in the RTECS.

5.1.4 Acute Toxicity, Other Routes of Administration

Species:	rat
Route:	i.p.
Method:	details not given
GLP:	no data
Results:	LD_{50} = 6660 mg/kg.
Reference:	*Kriobiol Kriomed*. 1981. 9: 36, as cited in RTECS.

Species:	rat
Route:	i.p
Method:	details not given
GLP:	no data
Results:	LD_{50} = 13000 mg/kg.
Reference:	Thomas JF *et al.*, (1949). *J. Ind. Hyg. Toxicol.* 31:256-257; cited in Ruddick JA, 1972, *Toxicol. Appl. Pharmacol*. 21: 102-111.

Species: mouse
Route: i.p
Method: details not given
GLP: no data
Results: LD_{50} = 9718 mg/kg
Effects: Lungs, Thorax or Respiration (Chronic pulmonary edema or congestion). Kidney, Ureter, Bladder (Changes in both tubules and glomeruli). Blood (Changes in spleen).
Reference: Fed. Proc. Fed. Am. Soc. Exp. Biol. 1947. 6: 342, as cited in RTECS.

Species: mouse
Route: i.p.
Method: details not given
GLP: no data
Results: LD_{50} = 10900 mg/kg.
Reference: Davis DJ, Jenner PM, (1959). *Toxicol Appl. Pharmacol.* 1: 556-558; as cited in Ruddick JA, 1972, *Toxicol. Appl. Pharmacol*. 21: 102-111.

Species: rat
Route: s.c.
Method: details not given
GLP: no data
Results: LD_{50} = 22,500 mg/kg.
Reference: Interagency Collab. Group Environ. Carcinog. [17JUN74], as cited in RTECS.

Species: rat
Route: s.c.
Method: details not given
GLP: no data
Results: LD_{50} = 28000 mg/kg
Reference: Thomas JF, *et al.*, (1949). *J. Ind. Hyg. Toxicol*. 31:256-257 as cited in Ruddick JA, (1972). *Toxicol. Appl. Pharmocol.* 21:102-111.

Species: mouse
Route: s.c.
Method: details not given
GLP: no data

Results: LD_{50} = 17370 mg/kg

Effects: Behavioral (Change in motor activity; Muscle contraction or spasticity). Lungs, Thorax or Respiration (Cyanosis).

Reference: *Kriobiol Kriomed.* 1981. 8: 46, as cited in RTECS.

Species: guinea pig

Route: s.c.

Method: details not given

GLP: no data

Results: LD_{Lo} = 15500 mg/kg

Reference: National Technical Informational Services [PB280-477], as cited in the RTECS.

Species: rat

Route: i.v.

Method: details not given

GLP: no data

Results: LD_{50} = 6423 mg/kg

Reference: *Arzneim-Forsch*. 1976. 26: 1581, as cited in RTECS.

Species: mouse

Route: i.v.

Method: details not given

GLP: no data

Results: LD_{50} = 6630 mg/kg

Reference: *Arzneim-Forsch.* 1976. 26: 1581, as cited in RTECS.

Species: dog

Route: i.v.

Method: details not given

GLP: no data

Results: LD_{50} = 25 cc/kg (26000 mg/kg)

Reference: National Technical Information Services [PB280-477], as cited in RTECS.

Hanzlik, P.J. Newman, H.W., Van Winkle, W., Jr., Lehman, A.J., and Kennedy, N.K. (1939): Toxicity, fats and excretion of propylene glycol and other glycols. *J. Pharmacol. Exp. Therap.* 67: 101-113.

Species: rabbit

Route: i.v.

Method: details not given

GLP: no data

Results: LD_{Lo} = 4200 mg/kg

Effects: Behavioral (Somnolence; Coma). Lungs, Thorax, or Respiration (Respiratory stimulation).

Reference: *J. Pharmacol. Exp. Ther*. 1932. 44: 109, as cited in RTECS.

Species: other

Route: i.v.

Method: details not given

GLP: no data

Results: LD_{Lo} = 27000 mg/kg.

Reference: *J. Pharmacol. Exp. Ther*. 1937. 60: 312, as cited in RTECS.

Species: rabbit

Route: i.v.

Method: rabbits given single IV dose of 2-5 cc/kg; observed for 2 to 46 days.

GLP: no data

Results: Doses of 4 or 5 cc/kg caused hemolysis; hemoglobin casts and disoloration on kidneys.

Reference: Kesten, H.D., Mulinos, M.G., and Pomerantz, L., (1939). Pathologic effects of certain glycols and related compounds. *Arch. Pathol*. 27: 447-465.

Species: rat

Route: i.m.

Method: no details

GLP: no data

Results: LD_{50} = 14000 mg/kg

Reference: Interagency Collab Group Environ Carcinog [17JUN74], as cited in the RTECS.

Species: rat

Route: i.m.

Method: details not given

GLP: no data

Results: LD_{50} = 20000 mg/kg.

Reference: Thomas JF et al. (1949). *J. Ind. Hyg. Toxicol*. 31: 256-257; as

cited in Ruddick JA, (1972). *Toxicol. Appl. Pharmacol*. 21:102-111.

Species:	rabbit
Route:	i.m.
Method:	details not given
GLP:	no data
Results:	LD_{Lo} = 6300 mg/kg
Effects:	Behavioral (Somnolence; Coma). Lungs, Thorax, or Respiration (Respiratory stimulation).
Reference:	*J. Pharmacol. Exp. Ther*. 1932. 44: 109, as cited in RTECS.

5.2 CORROSIVENESS/IRRITATION

5.2.1 Skin Irritation/Corrosion

Species:	human
Method:	Dose: 500 mg/7 days
GLP:	no data
Results:	slightly irritating
Reference:	*J. Invest. Dermatol*. 1970. 55: 190, as cited in RTECS.

Species:	human
Method: duration.	Patch-test. 15 microlitre 100% PG per test chamber, 48 hour
GLP:	no data
Results:	not irritating
Reference:	Willis, C.M. et al. (1989): *J. Invest. Dermatol.* 93: 695-699.

Species:	human
Method:	6 volunteers, pads containing the test substance were fixed to the forearm for 2 hours, observation time: 7 days.
GLP:	no data
Results:	not irritating
Reference:	Kimmerle G., Untersuchungen der Bayer AG, Briefbericht vom 30 Januar 1967.

Species:	human
Method:	100% open patches, 100% occluded patches, single or multiple days; visual examination and skin-fold thickness determinations.
GLP:	no data
Results:	Humans displayed no effects as a result of open or occluded exposure to propylene glycol for up to 10 days.

Reference:	Wahlberg, J.E., and G. Nilsson. (1984). Skin irritancy from propylene glycol. *Acta Dermato-Venereol.* 64:286-290, as cited in CIR, 1994.
Species:	rabbit
Method:	OECD Guideline 404
GLP:	no data
Results:	not irritating; Scores according to 79/831/EEC: Redness: mean = 0; Edema: mean = 0
Reference:	Huels AG. 1984a. Pruefung der akuten Hautreizwirkung von 1,2-Propylenglykol. Huels report No. 0211. Unpublished.
Species:	rabbit
Method:	0.5 ml, max. 72 hour duration.
GLP:	no data
Results:	not irritating
Reference:	Clark, C.R. *et al.* (1979): *Toxicol. Appl. Pharmacol.* 51: 529-535.
Species:	rabbit
Method:	Dose: 0.5 ml propylene glycol on both intact and abraded skin
GLP:	no data
Results:	non-irritating
Reference:	Catanzaro, J.M., and J.G. Smith. (1991). Propylene glycol dermatitis. *J. Am. Acad. Dermatol.* 24: 90-95.
Species:	rabbit
Method:	no details given
GLP:	no data
Results:	not irritating
Reference:	Drill, V. (1950). Chronic skin absorption of dipropylene glycol methyl ether (50B), Propylene Glycol, D-17, P-2,000, and P-15-200 in rabbits. Wayne University, College of Medicine, Department of Pharmacology. Submitted to Dow Chemical Company.
Species:	rabbit
Method:	100% open patches, 100% occluded patches, single or multiple days; visual examination and skin-fold thickness determinations.
GLP:	no data
Results:	Rabbits displayed no effects as a result of open or occluded exposure to propylene glycol for up to 10 days.
Reference:	Wahlberg, J.E., and G. Nilsson. (1984). Skin irritancy from propylene glycol. *Acta Dermato-Venereol.* 64:286-290, as cited in CIR, 1994.

Species:	guinea pigs
Method:	100% open patches, 100% occluded patches, single or multiple days; visual examination and skin-fold thickness determinations.
GLP:	no data
Results:	Guinea pigs displayed no effects as a result of open exposure to propylene glycol for up to 10 days; when propylene glycol was applied under occlusive patches increased skin-fold thickness was seen from 7 to 10 days after application.
Reference:	Wahlberg, J.E., and G. Nilsson. (1984). Skin irritancy from propylene glycol. *Acta Dermato-Venereol.* 64:286-290, as cited in CIR, 1994.

Species:	SKH1 hr/hr hairless mice
Method:	cup holding 0.3 cc PG glued to skin for 24 hours; mice killed and skin examined micrscopically
GLP:	no data
Results:	Propylene glycol (vehicle control) reported to "have no discernable effects on the skin"; however, no data were presented on untreated skin for comparison to PG data.
Reference:	Phillips, C.A. and Michniak, B.B. (1995). Topical application of Azone analogs to hairless mouse skin: histopathological study. *Int. J. Pharmaceut*. 125: 63-71.

5.2.2 Eye Irritation/Corrosion

Species:	rabbit
Method:	OECD Guideline 405
GLP:	no data
Results:	not irritating. Scores according to 79/831/EEC: Cornea: mean = 0; Iris: mean = 0; Conjunctiva: Redness: mean = 0.5; Chemosis: mean = 0
Reference:	Jacobs, G.A. (1992). OECD eye irritation tests on propylene glycol and Solketal. *J. Am. Coll. Toxicol*. 11: 739.

Species:	rabbit
Method:	OECD Guideline 405
GLP:	no data
Results:	not irritating. Scores according to 79/831/EEC: Cornea: mean = 0; Iris: mean = 0; Conjunctiva: Redness: mean = 0; Chemosis: mean = 0
Reference:	Huels AG. 1984b. Pruefung der akuten Augen-und Schleimhautreizwirkung von 1,2-Propylenglykol. Huels report No. 0212. Unpublished.

Species:	rabbit

Method:	Dose: 100 mg.
GLP:	no data
Results:	mild irritation.
Reference:	*Food Chem. Toxicol.* 1982. 20: 573, as cited RTECS.
Species:	rabbit
Method:	Dose: undiluted or 50% aqueous solution
GLP:	no data
Results:	non-injurious - Pain, conjunctivitis and lachrymation did ensue after instillation, however these effects were considered transient.
Reference:	none given, 1953.
Species:	rabbit
Method:	Dose: 500 mg/24 hours.
GLP:	no data
Results:	Effects: Mild.
Reference:	*Food Chem. Toxicol.* 1982. 20: 573, as cited in RTECS.
Species:	rabbit
Method:	0.1 ml., 1, 24, 48, 72, 92 hour duration.
GLP:	no data
Results:	not irritating
Reference:	Clark, C.R. et al. (1979): *Toxicol. Appl. Pharmacol.* 51: 529-535.
Species:	rabbit
Method:	2 rabbits, one drop of the substance in the conjunctival sac of the eye, observation time: 7 days.
GLP:	no data
Results:	not irritating
Reference:	Kimmerle G., Untersuchungen der Bayer AG, Briebericht vom 30 Januar 1967.
Species:	rabbit
Method:	500 mg observation time: 24 hours.
GLP:	no data
Results:	mild irritation
Reference:	Org. Latky. 1986. *Prehled Prumyslove Toxikol*. p 206, as cited in RTECS.

5.3 SKIN SENSITISATION

Species:	human
Method:	12% PG contained in Cream. 204 test persons.
GLP:	no data
Results:	not sensitizing
Reference:	Marzulli, F.N. and Maibach, H.I. (1973): *J. Soc. Cosmet. Chem*. 24: 399-421.

Species:	mouse (Mouse ear swelling test)
Method:	application to both sides of the right ear on days 0 and 2; sc injection of Complete Freund's adjuvant Day 2; challenge application to both sides of left ear Day 9; measured thickness of left ear day 9 (before treatment) and Day 10. Female Balb/c mice, number not given.
GLP:	no data
Results:	not sensitizing; no increase in skin thickness.
Reference:	Descotes, J. (1988): Identification of contact allergens: the mouse ear sensitization assay. *J. Toxicol. Cut. Ocular Toxicol*. 7: 263-276.

5.4 REPEATED DOSE TOXICITY

5.4.1 Oral Studies

Species:	male/female rats, strain not reported
Method:	not reported
Exposure	
Period:	140 days
Concentrations:	0, 1, 2, 5, 10, 25, and 50% PG in drinking water
GLP:	no data
Results:	Animals died within 69 days in both highest doses groups.
NOAEL:	10%
Reference:	Seidenfeld, M.A. and Hanzlik, P.J. (1932): *J. Pharmacol. Exp. Therap.* 44: 109. Cited in: Patty's Industrial Hygiene And Toxicology, 3rd Edition, Vol. 2C, 1982, John Wiley & Sons, New York, S., pgs. 3853-3857.

Species:	male/female dogs, Strain not reported
Method:	not reported
Exposure	
Period:	access to propylene glycol for hour twice daily for five to nine months
Concentrations:	5, 10 % PG in drinking water (no control group)

GLP:	no data
Results:	This study assessed kidney and liver function in male and female dogs. No functional deficits were observed.
NOEL:	not established
Reference:	Van Winkle, W., and Newman. H.W. (1941). Further results of continued administration of propylene glycol. *Food Res.* 6:509-516.
Species:	male/female rats, strain not reported
Method:	not reported
Exposure	
Period:	2 years, continuous treated diets
Concentrations:	0, 6250, 12,500, and 50,000 ppm in food
GLP:	no data
Results:	No damaging effects observed.
NOEL:	50,000 ppm (corresponds to 2500 mg/kg/day for rats)
Remark:	An ADI of 25 mg/kg/day has been proposed for humans.
Reference:	Gaunt I.F. *et al.* (1972). *Food Cosmet. Toxicol*. 10: 151-162.
Species:	male/female albino rat
Method:	administered in feed for 2 years; one pup from each litter placed in each treatment group; 20 litters used.
Exposure	
Period:	2 years
Concentrations:	0, 24,500 and 49,000 ppm in food
GLP:	no data
Results:	No effects were noted for growth rate, food and water consumption, survival, gross and microscopic lesions in lung, heart, liver, spleen, kidney, adrenal glands, and testis. Slight liver damage was observed but no statistical analysis was performed.
NOEL:	not established
Reference:	Morris, H.J., A.A. Nelson, and H.O. Calvery. (1942). Observations on the chronic toxicities of propylene glycol, ethylene glycol, diethylene glycol, ethylene glycol mono-ethyl-ether, and diethylene glycol mono-ethyl-ether. *J. Pharmacol. Exper. Therap.* 74:266- 273.
Species:	rat
Method:	administered in feed; pair fed or *ad libitum*
Exposure	
Period:	up to 24 weeks
Concentrations:	0, as replacement for carbohydrate: 25, 50, 75 or 100% of normal carbohydrate in diet
GLP:	no data

Results:	When PG replaced all or 75% of carbohydrate in diet, rats died after 4 or 14 weeks. At 50% replacement, no deaths, reduced weight gain; at 25% replacement essentially normal. Effect appeared to be due to reduced food consumption. When pair-fed, PG (25% carbohydrate replacement) exposed rats gained better than non-exposed.
Reference:	Hanzlik, P.J. Newman, H.W., Van Winkle, W., Jr., Lehman, A.J., and Kennedy, N.K.. (1939): Toxicity, fats and excretion of propylene glycol and other glycols. *J. Pharmacol. Exp. Therap*. 67: 101-113.
Species:	male/female dog
Method:	not reported
Exposure	
Period:	2 years, continuous treated diets
Concentrations:	0, 2000, and 5000 mg/kg in food
GLP:	no data
Results:	5000 mg/kg caused reversible hematological effects.
NOEL:	2000 ppm
Reference:	Weil, C.S. *et al.* (1971): *Food Cosmet. Toxicol*. 9: 479-490.
Species:	male/female cat
Method:	not reported
Exposure	
Period:	16 weeks, continuous treated diets
Concentrations:	0, 60,000 and 120,000 ppm (6%and 12%) in food
	Compound
intake:	0, 3780 and 10,140 mg/kg/day
GLP:	no data
Results:	Observed effects included: no treatment-related effects on hematocrit or hemoglobin levels; dose-responsive significant decrease in the numbers of erythrocytes in both groups; significant increases in numbers of aggregate reticulocytes in the 12% group, significant increases in Heinz bodies in both groups, and dose-responsive decrease in erythrocyte survival.
NOEL:	not established
Reference:	Bauer, M.C., Weiss, D.J., and V. Perman. (1992). Hematologic alterations in adult cats fed 6% or 12% propylene glycol. *Am. J. Vet. Res.* 53:69-72.
Species:	male cat
Method:	not reported
Exposure	
Period:	94 days, continuous treated diets
Concentrations:	0, 80, 443, 675, 1763, and 4239 mg/kg/day (in feed)

GLP:	no data
Results:	Slight increase in the formation of Heinz bodies at 443 mg/kg/day. At 675 mg/kg/day and above increase in Heinz bodies and increased hemosiderin pigment in Kupffer cells of liver and reticuloendothelial cells of the spleen. No other treatment-related effects seen even at 4239 mg/kg/day.
NOEL:	80 mg/kg
Reference:	Quast, J.F., Humiston, C.G., Wade, C.E., Beyer, J.E., Albee, R.R., Scheutz, D.J., and Morden, D.C. (1979). Results of a toxicology study in cats fed diets containing propylene glycol for up to three months. Unpublished report from The Dow Chemical Co., pp. 1-86.
Species:	Dog, Sex not reported
Method:	dogs given “divided doses”, but frequency not stated
Exposure	
Period:	duration not reported
Doses:	9 cc/kg in 6 doses; 8 cc/kg in 4 doses; or 20 cc/kg in 2 doses (by gavage)
GLP:	no data
Results:	No adverse effects
Reference:	Hanzlik, P.J. Newman, H.W., Van Winkle, W., Jr., Lehman, A.J., and Kennedy, N.K.. (1939): Toxicity, fats and excretion of propylene glycol and other glycols. *J. Pharmacol. Exp. Therap*. 67: 101-113.

5.4.2 Inhalation Studies

Species:	male/female Sprague-Dawley rat
Method:	not given
Exposure	
Period:	6 hours/day, 5 days/week, 90 days
Concentrations:	0, 160, 1000, 2200 mg/m^3 in atmosphere; nose only exposure
GLP:	no data
Results:	During second week and following, nose bleeding occurred as a result of dehydration effect from Propylene Glycol on nasal tissue. At highest dose, reduction of body weight and decrease in food intake by female rats was observed. No clear dose related changes of clinical-chemical and hematological parameters were detected. Neither organs (liver, kidneys, spleen and lungs) nor blood examined showed any sign of toxicological effects.
NOEL :	1000 mg/ m^3
Reference:	Suber, R.L. *et al.* (1989): *Fd. Chem. Toxic.* 29: 573-583.
Species:	male/female white rat, strain not reported
Method:	not reported

Exposure

Period: 18 months, frequency and daily duration not reported

Concentrations: 0, 170-350 mg/m^3 (100+% saturation)

GLP: no data

Results: Rats exposed to propylene glycol gained weight more rapidly than control rats, however no change in breeding, litter size, appearance and weight gain in pups was observed. In addition, no signs of conjunctival irritation or abnormal findings in aspirated urine were noted. Microscopic examination of the lungs revealed localized infection in rats exposed for eight months or longer (n=2) and in 25% of controls. No pathological changes were observed in the kidneys, liver, or spleen

NOEL: not reported

Reference: Robertson, O.H., Loosli, C.G., Puck, T.T., Wise, H., Lemon, H.M. and Lester, W., Jr. (1947). Test for the chronic toxicity of propylene glycol on monkeys and rats by vapor inhalation and oral administration. *J. Pharmacol. Exp. Therap*. 91:52-76.

Species: *Macacus rhesus* Monkey, Sex not reported

Method: not reported

Exposure

Period: 12 months, frequency and daily duration not reported

Concentrations: 0, 100-220 mg/m^3 (60% saturation); 230-350 mg/ m^3 (100% saturation)

GLP: no data

Results: Monkeys exposed to propylene glycol vapors had a slightly greater increase in red blood cells and distinctly higher hemoglobin content than did the control animals, however no changes in weight or abnormalities upon microscopic examination of urine were observed. Pathological examinations revealed infection with parasites, lung mites, and lung infections isolated by macrophage spheres. No bladder or kidney stones were noted. No gross or microscopic changes were seen in the liver, kidneys, spleen, mesenteric glands, and adrenals.

NOEL: not reported

Reference: Robertson, O.H., Loosli, C.G., Puck, T.T., Wise, H., Lemon, H.M. and Lester, W., Jr. (1947). Test for the chronic toxicity of propylene glycol on monkeys and rats by vapor inhalation and oral administration. *J. Pharmacol. Exp. Therap*. 91:52-76.

5.5 GENETIC TOXICITY *IN VITRO*

5.5.1 Bacterial *In Vitro* Tests

Type: Ames test

System of Testing: *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537 without metabolic activation

Concentration:	not given
GLP:	no data
Result:	Negative
Reference:	Pfieffer, E.H. and Dunkelberg, H. (1980): *Food Cosmet. Toxicol.* 18: 115-118.

Type:	Ames test
System of Testing:	*Salmonella typhimurium*, TA 92, TA 94, TA 98, TA 100, TA 1535, TA 1537 with metabolic activation
Concentration:	up to 10 mg/plate
GLP:	no data
Result:	Negative
Reference:	Ishidate, M., Sofuni, K., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., and Matsuoka, A. (1984): *Food Cosmet. Toxicol.* 22: 623-636.

5.5.2 Non-bacterial *In Vitro* Tests

Type:	Chromosomal aberrations *in vitro*
Method:	OECD Guide-line 473
System of Testing:	Human Lymphocytes with and without metabolic activation
Concentration:	476, 1910, 3810 µg/l
GLP:	yes
Result:	Negative. In two parallel studies, propylene glycol caused no statistically significant increase in the proportion of metaphase figures containing chromosomal aberrations. Propylene Glycol has shown no evidence of clastogenic activity.
Reference:	EC Erdolchemie GmbH. 1990. HRC report No. CLD 49/30349. Unpublished results.

Type:	Chromosomal aberrations *in vitro*
System of Testing:	Human embryonic lung cultures (WI-38); no data on metabolic activation
Concentration:	0.001, 0.01, and 0.1 µg/ml
GLP:	no
Results:	No significant aberrations in the anaphase chromosomes.
Reference:	Litton Bionetics, Inc. 1974. Mutagenic Evaluation of Compound FDA 71-56, Propylene Glycol. PB-245 450. March 5.

Type:	Chromosomal aberrations *in vitro*
System of Testing:	Chinese hamster fibroblast cell line; no metabolic activation system was used.
Concentration:	32 gm/l

GLP: no data

Result: Increased aberrations were found only at the highest concentration. Concentration exceeded recommended maximum for affecting osmolality (maximum recommended 10 mM; PG 420 mM).

Reference: Ishidate, M., Sofuni, K., Yoshikawa, K., Hayashi, M., Nohmi, T., Sawada, M., and Matsuoka, A. (1984): *Food Cosmet. Toxicol.* 22: 623-636.

Type: DNA damage and repair assay, *in vitro*

System of Testing: alkaline elution in CH V79 cells with and without metabolic activation

Concentration: not given

GLP: no data

Result: Negative

Reference: Swenberg, J.A. *et al.* (1976): *Biochem. Biophys. Res. Commun.* 72: 732-738.

Type: Cell Transformation, Clonal Assay, *in vitro*.

System of Testing: Syrian Hamster Embryo (SHE) Cells, concentration not given, metabolic activation not stated

GLP: no data

Result: Negative

Reference: *Mutat. Res*. 1983. 114: 283-385, as Cited in the GENE-TOX database.

Type: Sister Chromatid Exchange assay, *in vitro*

System of Testing: human fibroblasts

GLP: no data

Result: Negative

Reference: Tucker, J.D., Auletta, A., Cimino, M.C., Dearfield, K.L., Jacobson-Kram, D., Tice, R.R., and Carrano, A.V. (1993): Sister-chromatid exchange: second report of the Gene-Tox program. *Mutat. Res.* 297:101-180. (Summary of original article: Sasaki, M., Sugimura, K., Yoshida, M.A., and Abe, S. (1980). Cytogenetic effects of 60 chemicals on cultured human and Chinese hamster cells. *La Kromosomo II*, 20: 574-584.)

5.6 GENETIC TOXICITY *IN VIVO*

Type: Host mediated assay for in-vivo and in-vitro mutagenicity evaluation.

Species: mouse

Method: not specified

Route of Administration:	gavage
Doses:	30, 2500, and 5000 mg/kg (five exposures)
GLP:	no
Result:	No clear increase in *Salmonella* TA-1530 and G-46 mutant frequencies. *Saccharomyces* D-3 showed some increased recombinant frequencies. *In vitro Salmonella* tests were negative and *Saccharomyces* were positive.
Reference:	Litton Bionetics, Inc. 1974. Mutagenic Evaluation of Compound FDA 71-56, Propylene Glycol, (PB-245 450). March 5.

Type:	Cytogenetic assay, bone marrow metaphase
Species:	rat
Method:	not specified
Route of Administration:	oral unspecified
Doses:	30, 2500, and 5000 mg/kg (five exposures).
GLP:	no
Result:	No detectable significant aberrations of rat bone marrow metaphase chromosomes.
Reference:	Litton Bionetics, Inc. 1974. Mutagenic Evaluation of Compound FDA 71-56, Propylene Glycol. (PB-245 450) March 5.

Type:	Micronucleus assay
Species:	male mouse
Method:	not specified
Route of Administration:	i.p.
Doses:	0, 2500, 5000, 10,000 and 15,000 mg/kg (single exposure)
GLP:	no data
Results:	No formation of micronuclei.
Reference:	Hayashi, M. *et al.* (1988): *Food Chem. Toxicol.* 22: 487-500.

Type:	Dominant lethal assay
Species:	male/female rat
Method:	not specified
Route of Administration:	gavage
Doses:	30, 2500, and 5000 mg/kg (five exposures)

GLP:	no
Result:	Not Mutagenic.
Reference:	Litton Bionetics, Inc. 1974. Mutagenic Evaluation of Compound FDA 71-56, Propylene Glycol. (PB-245 450) March 5.
Type:	Dominant lethal assay
Species:	male mouse
Method:	male mice treated once; each mated with 3 females/week for 8 weeks; pregnant females examined for preimplantation loss and early resorptions. Propylene glycol was the control for this study.
Route of Administration:	intraperitoneal injection
Exposure Period:	single dose
Doses:	10 mg/kg single exposure
GLP:	no data
Remark:	There were no untreated animals for comparison, but early resorptions and preimplantation losses were not increased (increases were observed in the positive control). No mutagenic result for the applied concentration.
Reference:	Kennedy Jr., G.L., Arnold, D.W., Keplinger, M.L. and Calandra, J.C. (1975): Investigation of hexachlorophene for dominant lethal effects in the mouse. *Toxicology* 5: 159-162
Type:	Cell kinetic assay
Species:	male Oslo mice (hairless)
Method:	not specified
Route of Administration:	subcutaneous injection
Doses:	0.2 ml propylene glycol 3 times/week for 3 months
GLP:	no data
Results:	Observed effects included: an increase in proportion of diploid cells, a slight decrease in the number of tetraploids, and almost a complete disappearance of all octaploid cells. In addition, it was also noted that some bladder epithelial cells were killed and the mechanism of repeated DNA synthesis was altered.
Reference:	Farsund, T. (1978). Cell kinetics of mouse urinary bladder epithelium. VI. Changes in the proportions of cells with various nuclear DNA content after repeated doses of propylene glycol (1,2-propanediol). *Virchows Arch. B Cell Pathol.* 27(1):1-6.

5.7 CARCINOGENICITY

Species:	male/female CD rat
Method:	Groups of 30 male and 30 female (120-150 g) at initiation

Route of Administration:	oral feed
Exposure Period:	2 years
Doses:	0, 6250, 25,000 and 50,000 ppm daily
GLP:	no data
Result:	No tumors were observed.
Reference:	Gaunt, I.F. *et al* (1972): *Food Cosmet. Toxicol.* 10: 151-162.
Species:	male/female rat
Method:	one pup from each litter assigned to each treament group, 20 litters used.
Route of Administration:	oral feed
Exposure Period:	2 years
Doses:	0, 24,500 and 49,000 ppm
GLP:	no data
Results:	No increase in tumors. Limited value small group sizes
Reference:	Morris, H.J., A.A. Nelson, and H.O. Calvery. (1942). Observations on the chronic toxicities of propylene glycol, ethylene glycol, diethylene glycol, ethylene glycol mono-ethyl-ether, and diethylene glycol mono-ethyl-ether. *J. Pharmacol. Exper. Therap.* 74:266- 273.
Species:	female Swiss mouse from the Eppley colony
Method:	twice weekly application of 0.02 ml on back for life; 50 female mice/group
Route of Administration:	dermal
Exposure Period:	lifetime
Doses:	0, 10, 50 % PG in acetone or 100% PG twice weekly
GLP:	no data
Result:	No skin tumors were observed.
Reference:	Stenback F, and Shubik P. (1974): *Toxicol. Appl. Pharmacol*.30:7-13.
Species:	female Sprague-Dawley rat
Method:	PG applied to left ear as control for 4-nitrocholinoline N-oxide applied to right ear.
Route of	

Administration:	dermal
Exposure	
Period:	10-14 Months
Doses:	100% PG thrice weekly; amount not specified
GLP:	no data
Result:	No skin tumors were observed in the left ears.
Reference:	Wallenius, K. and Lekholm, U. (1973): Influence of saliva on epidermal cancer in rat induced by water- or fat-soluble carcinogens. *Odont. Revy*. 24: 115-126.
Species:	male/female dog
Method:	not specified
Route of	
Administration:	oral feed
Exposure	
Period:	2 years
Doses:	0, 2 and 5 g/kg in daily feed
GLP:	no data
Result:	No tumors were observed.
Reference:	Weil, C.S. *et al.* (1972): *Food Cosmet. Toxicol*. 10: 479-490.

5.8 TOXICITY TO REPRODUCTION

Type:	Fertility
Method:	not specified
Species:	male/female rat
Route of	
Administration:	oral feed
Doses:	0, up to 30 % PG in daily feed daily for 20 week test period, 3 generations
GLP:	no data
Results:	Below 7.5% PG in feed, no toxicological effects occurred. By increasing the concentrations in the diet, decreased food intake, reduced growth and average smaller litters appeared. Fewer young were raised compared with the control. A diet containing 30% of PG caused an absence of offspring in the third generation.
Reference:	Guerrant NB *et al.*, (1947): *Bull. Natl. Formulary Comm*.15: 205-229, cited in Federal Register, Vol. 42. pgs. 30865-30866. June 17, 1977. PB-223-822.
Type:	Fertility

Method:	not specified
Species:	male/female CD-1 mouse
Route of Administration:	drinking water
Doses:	0, 1.0, 2.5 and 5 % PG in drinking water daily 98 days repeated after a break of 21 days
GLP:	no data
Result:	Exposure to Propylene Glycol up to 5 % did not have any influence on fertility. The number bringing forth litters of youngs, the quantity of breeding, the average weight and the number of viviparous were comparable to the control groups. No significant differences were found in the average weight of the last litter, nor in the average weights of the dams. No sperm changes were observed.
Reference:	Gulati DK *et al.*, (1985): NTP-84-FACB-038, S, 1-316.

Type:	Fertility
Method:	not specified
Species:	female mouse
Route of Administration:	oral unspecified
Doses:	0.1 ml 50% solution of PG in water single day
GLP:	no data
Results:	The amount of mating was reduced by 30 % and the litter of young by 15%. The animals visibly swelled with intestinal gases; they recovered after exposure.
Reference:	Emmens CW (1971): *J. Reprod. Fert.* 26:175-182

Type:	Fertility
Method:	RACB Procedure (Reproductive Assessment by Continuous Breeding)
Species:	male/female CD-1 mice
Route of Administration:	as part of a series of studies; report says “in feed or drinking water”, but does not specify route for each chemical.
Doses:	1.0 or 2.5, or 5.0% daily 98 days (estimated by authors at 1820, 4800 and 10,100 mg/kg/day)
GLP:	probably GLP, but not stated.
Results:	Experimental design was a continuous breeding reproductive study. No significant adverse reproductive effects were observed for the parent (F_0) or second generation (F_1). However, observed effects did include mating and fertility indices, mean number of live pups for litter, proportion of pups born live, and sex of pups born live.
Reference:	Morrissey, R.E., J.C. Lamb IV, R.W. Morris, R.E. Chapin, D.K. Gulati, and J.J. Heindel. (1989). Results and evaluations of 48

continuous breeding reproduction studies conducted in mice. *Fund. Appl. Toxicol.* 13: 747-777.

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Type:	Teratology
Method:	FDA Segment I study
Species:	female Wistar rat
Route of Administration:	gavage
Doses: period	0, 16, 74.3, 345, and 1600 mg/kg of PG daily days 6-15 of gestation
GLP:	no data
Results:	No effect on the nesting behavior and the maternal or fetal survival. No difference in abnormalities. No teratogenic effects.
Reference:	FDA. 1973. Teratologic Evaluation of FDA 71-56 (Propylene glycol). FDA report No. FDABF GRAS-141, pp. 1-56.

Type:	Teratology
Method:	FDA Segment I study
Species:	female CD-1 mouse
Route of Administration:	gavage
Doses: period	0, 16, 74.3, 345, and 1600 mg/kg of PG daily days 6-15 of gestation
GLP:	no data
Results:	No effect on the nesting behavior and the maternal or fetal survival. No difference in abnormalities. No teratogenic effects.
Reference:	FDA, (1973) Teratologic Evaluation of FDA 71-56 (Propylene glycol). FDA report No. FDABF GRAS-141, pp. 1-56.

Type:	Teratology
Method:	FDA Segment I study
Species:	female Dutch rabbit
Route of Administration:	oral feed
Doses: period	0, 12.3, 57.1, 267 and 1230 mg/kg of PG daily days 6-18 of gestation
GLP:	no data
Results:	No effect on the nesting behavior and the maternal or fetal survival. No difference in abnormalities. No teratogenic effects.

Reference:	FDA, (1973) Teratologic Evaluation of FDA 71-56 (Propylene glycol). FDA report No. FDABF GRAS-141, pp. 1-56
Type:	Teratology
Method:	FDA Segment I study
Species:	female golden hamster
Route of Administration:	oral gavage
Doses:	0, 15.5, 72, 334.5 and 1550 mg/kg of PG daily days 6-10 of gestation period.
GLP:	no data
Results:	No effect on the nesting behavior and the maternal or fetal survival. No difference in abnormalities. No teratogenic effects.
Reference:	FDA, (1973) Teratologic Evaluation of FDA 71-56 (Propylene glycol). FDA report No. FDABF GRAS-141, pp. 1-56.
Type:	Developmental *In Vitro*
Method:	not specified
Species:	murine preimplantation embryos
Route of Administration:	*in vitro*
Doses:	0.05 to 1.0% (w/v) propylene glycol for 24 hours, observed for 6 days
GLP:	no data
Results:	propylene glycol neither accelerated nor inhibited development.
Reference:	Kowalczyk, C.L., Stachecki, J.J., Schultz, J.F, Leach, R.E. and Armant, D.R. (1996). Effects of alcohols on murine preimplantation development: Relationship to relative membrane disordering potency. *Alcoholism Clinical and Experimental Research.* 20: 566-571.
Type:	Developmental: Chick Embryo
Method:	*in vitro*
Species:	chicken (eggs)
Route of Administration:	injection into air sac or yolk
Doses:	0.05 ml PG once over the period of 0-7 days of incubation.
GLP:	no data
Results:	If PG was injected into the air sac on day 0 or 1, there was no effect. If later, there was increased embryo mortality; the severity peaked from injection on day 4. The toxicity appeared to stem from diffusion of PG into the developing vascular system causing edema. 21 % of the embryos that survived injection on day 4 developed unilateral micromelian. Similar effects were seen from injection of many other

diols as well as glycerol. An injection of 0.05 ml of PG in the yolk-sac of chicken embryos on day 0, 1, 2, 3, or 4 of incubation did not have any teratogenic or toxic effect.

Reference: Gebhardt, D.O.E. (1968) The teratogenic action of propylene glycol (Propanediol-1,2) and propanediol-1,3 in the chick embryo. *Teratology* 1: 153-162.

Type: Developmental: Chick Embryo

Method: chick embryos injected with teratogen day 4 of incubation; fetuses examined Day 19

Species: White Leghorn chicken (egg)

Route of Administration: injection into yolk sac on day 4 of incubation

Doses: 0.2 ml PG, as solvent for known teratogens

GLP: no data

Results: Less teratogenicity of known human teratogens when dissolved in DMSO or PG than when dissolved in water.

Reference: Landauer W, and Salam N (1972): Aspects of dimethylsulfoxide as solvent for teratogens. *Dev. Biol*. 28:35-46.

Type: Developmental

Method: not specified

Species: Hydra

Route of Administration: in water

Doses: not specified

GLP: no data

Results: For PG, an A/D quotient of 1.3 has been calculated. Short-time screening tests with increased concentration of PG in water showed that a quotient of about 1 will not lead to developmental effect. This has been validated by tests on animals.

5.10 OTHER RELEVANT INFORMATION

Type: Metabolism

Remark: Once absorbed into the body, propylene glycol is excreted unchanged into the urine and also metabolized to lactic and pyruvic acids. These acids are normal body constituents and are further broken down to carbon dioxide and water. PG can also be glucuronidated.

Reference: Yu, D.K. and Sawchuk, R.J. (1987). Pharmacokinetics of Propylene Glycol in the Rabbit. *J. of Pharmacokin. and Biopharm*. 15: 453-471.

Reference: Rowe, V.K. and Wolf, M.A. (1982). Glycols. In: Patty's Industrial Hygiene and Toxicology. 3rd Edition. Vol. 2C, page 3861.

Type: Metabolism

Remark: Propylene Glycol was administered rectally to 10 adults and to 4 children at doses of 8.64 g and 173 mg/kg, respectively. Peak concentrations for adults were 199 mg/l 1.5 hr after administration. Peak concentrations in the children were calculated to be 171 mg/l 1.0 hr after administration. In adults and children, the average terminal half-lives were determined to be 2.8 hr and 2.6 hr, respectively. Finally, total body clearance for adults and children were calculated to be (CI/F) 0.20 1/hr/kg and 0.21 l/hr/kg while the apparent volume of distribution (VD/F) was determined to be 0.79 l/kg and 0.77 l/kg, respectively.

Reference: Kolloffel, W.J., Weekers, L.E., and Goldhoorn, P.B. (1996). Pharmacokinetics of propylene glycol after rectal administration. *Pharm. World Sci.* 18: 109-113.

Type: Protective Properties

Remark: When 0.25 µmol of hydrocortisone succinate sodium (HC) was administered to 15-day-old hen's fertile eggs, almost all of the lenses of the embryos developed cataracts 48 hours after treatment. However, administration of PG (1.5 mmol/egg) at 3, 10, and 20 hr after HC treatment repressed the decline of glutathione and the elevation of lipid peroxide levels in the lens due to exposure to HC and effectively prevented the HC-induced cataract formation. During normal metabolic activities, PG is known to be converted to lactate and pyruvate producing NADH. Propylene Glycol is also known to be protective against x-ray radiation.

Reference: Nishigori, H., J.W. Lee, and M. Iwatsur. (1995). Glucocorticoid-induced cataract of the developing chick embryo-prevention by propylene glycol. *Ophthalmic Res*. 27: 350-355.

Type: Protective Properties

Remark: A study by Thompson *et al.* 1995, assessed the association between acetaminophen hepatotoxicity and its biotransformation to the reactive metabolite N-acetyl-p-benzoquinone imine. It has been suggested that Cytochrome P450 (forms CYP2E1 and CYP1A2) is responsible for triggering bioactivation. Fasted male NMRI mice were pretreated with 10 ml of 50% v/w propylene glycol/kg or fluvoxamine (10 mg/kg) at -80 and -20 minutes in order to inhibit CYP2E1 and CYP1A2 activities, respectively. Mice were dosed with 300 mg/kg acetaminophen and were sacrificed 0.5 or 4 hr thereafter. Thompson *et al.* noted that propylene glycol or propylene glycol plus fluvoxamine reduced acetaminophen hepatotoxicity. Authors concluded that hepatotoxicity is associated with bioactivation of acetaminophen by CYP2E1.

Reference: Thomsen, M.S., S. Loft, D.W. Roberts, and H.E. Poulsen. (1995). Cytochrome P4502E1 inhibition by propylene glycol prevents acetaminophen (paracetamol) hepatotoxicity in mice without cytochrome P4501A2 inhibition. *Pharmacol. Toxicol.* 76: 395-399.

5.11 EXPERIENCE WITH HUMAN EXPOSURE

5.11.1 Case Reports of Irritation/Sensitization

Remark: Propylene Glycol may cause skin irritation in some individuals when high concentrations are held in contact with skin under closed conditions.

References: Trancik, R. J. and H. I. Maibach. (1982). Propylene Glycol: Irritation or Sensitization? *Contact Dermatitis* 8: 185-189. Motoyoshi, K. *et al.* (1984). The safety of propylene glycol and other humectants. *Cosmetics and Toiletries* 99: 83-91.

Remark: The primary irritation potential of propylene glycol was evaluated using human volunteers. Individuals were exposed to 0.2 ml of a 25% solution of propylene glycol in distilled water for 24 hours via semi-occluded patches. Of the 33 subjects tested, thirteen exhibited mild to moderate erythema at the 30 minute evaluation. Three of these individuals responses had subsided by the 24 hour evaluation. The ten remaining subjects exhibited mild erythema and four subjects with mild erythema and peeling at the 24 hour evaluation.

Reference: Acklin, A., and Plaza, M.E. (1995). Evaluation of Primary Irritation Potential in Humans. Hill Top Research, Inc. Report No. 94-1373-70. Submitted to Dow Chemical Company.

Remark: Human volunteers (n=866) were exposed to standard skin patch tests. Of those tested, 16% demonstrated a positive reaction. Positive reactions ranging from simple erythema to erythema with induration and vesiculation, however 89 out of the 138 reactors had a concomitant skin condition (dermatitis venenata). Subsequent “open” tests of the 23 patients exhibiting positive reactions in the “closed” tests resulted in only 17 reactions in the “open” test.

Reference: Warshaw, T.G., and F. Herrmann. (1952). Studies of skin reactions to propylene glycol. *J. Invest. Dermatol*. 19: 423-430.

Remark: This is a review of the irritant and sensitization reports on propylene glycol in human use. Some humans exposed to amounts of propylene glycol exhibited contact dermatitis and primary skin irritations. In addition, an increase in number of irritant responses with increasing concentrations of propylene glycol was also noted. The incidence of allergy caused by propylene glycol is uncertain; studies range from 0 to 12% of tested subjects sensitized.

Reference: Catanzaro, J.M., and J.G. Smith. (1991). Propylene glycol dermatitis. *J. Am. Acad. Dermatol*. 24: 90-95.

Remark: After application of a topical calcipotriene ointment containing propylene glycol, a 78-year-old woman developed a pruritic exacerbation of her methotrexate-dependent psoriasis.

Reference: Fisher, D.A. (1997). Allergic contact dermatitis to propylene glycol in calcipotriene ointment. *CUTIS*. 60: 43-44.

Remark: Contact sensitization was diagnosed in a 60-year-old patient after being exposed to propylene glycol-based electrode gel.

Reference: Uter, W., and Schwanitz, H.J. (1996). Contact dermatitis from propylene glycol in ECG electrode gel. *Contact Dermatitis.* 34: 230-231.

Remark: Contact dermatitis from exposure to propylene glycol was reported in a 61-year-old man. Patient was patch tested with a 0.5% aqueous solution and subsequently developed a positive reaction.

Reference: El Sayed, F., Bayle-Lebey, P., Marguery, M.C. and Bazex, J. (1995). Contact dermatitis from propylene glycol in Rifocine. *Contact Dermatitis.* 33: 127-128.

Remark: *Case I* - A 36-year-old woman received injectable Valium before undergoing a minor surgical procedure and reported a pruritic vulvitis the following day. Further evaluation revealed a positive reaction to a 5% percent patch test of propylene glycol.

Case II - A 29-year-old woman suffered from severe vulvitis following delivery of her first child. The patient had a history of dermatitis as a result of exposure to products containing propylene glycol.

Case III - A 55-year-old man reported a severe allergic contact dermatitis to halcinonide. Results of the patch test indicated that the patient was allergic to propylene glycol.

Case IV - A 27-year-old woman developed swelling, itching, and redness after exposure to an electrolyte jelly for two to three weeks. The patient demonstrated a positive patch test reaction when tested for propylene glycol.

Reference: Fisher, A.A. (1995). Systemic contact dermatitis due to intravenous valium in a person sensitive to propylene glycol. CUTIS 55: 327-328.

5.11.2 Case Reports of Adverse Effects

Remark: As part of a vitamin C treatment, a 15-month old boy was given 7.5 ml of propylene glycol containing 250 mg vitamin C (three times/day). On day 8 of treatment, an irregular apical heart rate (sinus arrhythmia) was evident. On days 10-13, the boy had three episodes of unconsciousness and had tachypnea and diaphoresis. All symptoms receded when vitamin C treatment was suspended.

Reference: Martin, G., and Finberg, L. (1970). Propylene glycol: A potentially toxic vehicle in liquid dosage form. *J. Pediatr.* 77: 877-878.

Remark: Propylene glycol intoxication was reported in a 2-year-old child. Additional symptoms included central nervous depression and a severe metabolic acidosis.

Reference: Glover, M.L., and Reed, M.D. (1996). Propylene glycol: The safe diluent that continues to cause harm. *Pharmacotherapy.* 16: 690-693.

Remark: Based upon a case study, a 16-year-old boy suffered from acute renal failure after being administered large doses of pentobarbital and phenobarbital, both of which were solubilized with propylene glycol.

The author suggests that the reversible acute renal failure caused by propylene glycol is attributable to proximal renal tubular cell injury.

Reference: Yorgin, P.D., Theodorou, A.A., Amira, A.U., Davenport, K., Boyer-Hassen, L.V. and Johnson, M.I. (1997). Propylene glycol-induced proximal renal tubular cell injury. *American Journal of Kidney Diseases.* 30: 134-139.

Remark: After coming in contact with an unknown quantity of propylene glycol, an individual (age and sex not reported) initially became comatose with metabolic acidosis. Patient responded to bicarbonate therapy.

Reference: Cate, J.C., IV, and Hendrick, R. (1980). Propylene glycol intoxication and lactic acidosis. *New Engl. J. Med.* 303: 1237.

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I U C L I D Data Set

Existing Chemical	:	ID: 57-55-6
CAS No.	:	57-55-6
EINECS Name	:	propane-1,2-diol
EINECS No.	:	200-338-0
TSCA Name	:	1,2-Propanediol
Molecular Formula	:	C3H8O2

Producer Related Part

Company	:	ACC Propylene Oxide/Propylene Glycol Panel
Creation date	:	29.05.2001

Substance Related Part

Company	:	ACC Propylene Oxide/Propylene Glycol Panel
Creation date	:	29.05.2001
Memo	:	
Printing date	:	30.05.2001
Revision date	:	
Date of last Update	:	30.05.2001
Number of Pages	:	1
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD AND COMPANY INFORMATION

Type :
Name : Lyondell Chemical Company
Partner :
Date :
Street : 1221 McKinney Street Suite 1600
Town : 77010 Houston Texas
Country : United States
Phone : 713-652-7200
Telefax :
Telex :
Cedex :
30.05.2001

Type :
Name : Huntsman Corporation
Partner :
Date :
Street : 500 Huntsman Way
Town : 84108 Salt Lake City, Utah
Country : United States
Phone : 1-800-421-2411
Telefax : 801-584-5781
Telex :
Cedex :
30.05.2001

Type :
Name : The Dow Chemical Company
Partner :
Date :
Street : 2030 Dow Center
Town : 48674 Midland, MI
Country : United States
Phone : 517-636-1000
Telefax : 517-636-4033
Telex :
Cedex :
30.05.2001

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

Substance type : organic
Physical status : liquid
Purity : >= 98 % w/w
Source : A.K. Mallett Surrey
Flag : Critical study for SIDS endpoint
23.05.2001

1.1.0 DETAILS ON TEM PLATE

1.1.1 SPECTRA

1.2 SYNONYMS

1.3 IMPURITIES

1.4 ADDITIVES

1.5 QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

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. HARMLES S

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 : < -60 °C
Sublimation :
Method :
Year : 1993
GLP : no data
Test substance : no data
Source : A.K. Mallett Surrey
Flag : Critical study for SIDS endpoint
29.05.2001 (43)

Value : < -57 °C
Sublimation :
Method :
Year : 1952
GLP : no data
Test substance : no data
Source : A.K. Mallett Surrey
Flag : Critical study for SIDS endpoint
29.05.2001 (21)

2.2 BOILING POINT

Value : = 187.4 °C at
Decomposition :
Method :
Year : 1952
GLP : no data
Test substance : no data
Source : A.K. Mallett Surrey
Flag : Critical study for SIDS endpoint
29.05.2001 (21)

Value : = 187.9 °C at
Decomposition :
Method :
Year : 1993
GLP : no data
Test substance : no data
Source : A.K. Mallett Surrey
Flag : Critical study for SIDS endpoint
29.05.2001 (43)

Value : = 188.2 °C at
Decomposition :
Method :
Year : 1979
GLP : no data
Test substance : no data
Source : A.K. Mallett Surrey
Flag : Critical study for SIDS endpoint
29.05.2001 (39)

Value : = 189 °C at
Decomposition :

Method :
Year : 1983
GLP : no data
Test substance : no data
Source : A.K. Mallett Surrey
Flag : Critical study for SIDS endpoint
29.05.2001 (46)

2.3 DENSITY

Type : density
Value : = 1.032 g/cm3 at ° C
Method :
Year : 1952
GLP : no data
Test substance : no data
Source : A.K. Mallett Surrey
Flag : Critical study for SIDS endpoint
29.05.2001 (21)

Type : relative density
Value : ca. 1.036 at ° C
Method :
Year :
GLP : no data
Test substance : no data
Source : A.K. Mallett Surrey
Flag : Critical study for SIDS endpoint
29.05.2001 (43) (46)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = .11 hPa at 20° C
Decomposition :
Method
Year : 1993
GLP : no data
Test substance : no data
Source : A.K. Mallett Surrey
Flag : Critical study for SIDS endpoint
29.05.2001 (43)

Value : = .08 at ° C
Decomposition :
Method
Year : 1952
GLP : no data
Test substance : no data
Remark : Note: value given as mm Hg
Source : A.K. Mallett Surrey
Flag : Critical study for SIDS endpoint
29.05.2001 (20)

2.5 PARTITION COEFFICIENT

Log pow	:	ca. -1.41 - -.3 at ° C
Method		
Year	:	1983
GLP	:	no data
Test substance	:	no data
Source	:	A.K. Mallett Surrey
Flag	:	Critical study for SIDS endpoint

29.05.2001 (44)

2.6.1 WATER SOLUBILITY

Value	:	at ° C
Qualitative	:	other: described as 'soluble'
Pka	:	at 25 ° C
PH	:	at and ° C
Method	:	
Year	:	1983
GLP	:	no data
Test substance	:	no data
Source	:	A.K. Mallett Surrey
Flag	:	Critical study for SIDS endpoint

29.05.2001 (46)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type : air
Light source :
Light spect. : nm
Rel. intensity : based on Intensity of Sunlight
Remark : Atmospheric oxidation (25 degrees C) [AopWin v1.90]:
Hydroxyl radicals reaction:
Overall OH rate constant = 12.8199 E-12 cm3/molecule-sec
Half-life = 0.834 days (12hr day; 1.5E6 OH/cm3)
Half-life = 10.012 hr
Source : A.K. Mallett Surrey
Reliability : (2) valid with restrictions
23.05.2001 (18)

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETW EEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level III
Media :
Air (level I) :
Water (level I) :
Soil (level I) :
Biota (level II / III) :
Soil (level II / III) :
Method : other: calculated
Year :
Method : Melting Point (deg C): -59
Boiling Point (deg C): 189
Vapor Pressure (mm Hg): 0.0826
Log Kow (octanol-water): -0.92

Default emissions of 1000 kf/h for air, water and soil
(provided by EPIWIN).
Result : Concentration (percent)
Half Life (hours)
Emissions (kg/h)

Air
2.98
21.4
1000

Water
48.8
208

1000

Soil
48.1
208
1000

Sediment
0.0729
832
0

Henry's Law Constant 1.74E-007 atm-m3/mole (EPIWIN estimate)

River
Lake

Water depth (meters)
1
1

Wind Velocity (m/sec)
5
0.5

Current velocity (m/sec)
1
0.05

HALF-LIFE (hours)
2936
3.21E+004

HALF-LIFE (days)
122.3
1338

HALF-LIFE (years)
0.335
3.662

Source : A.K. Mallett Surrey

Conclusion : According to EPIWIN, assuming equal emission to air, water and soil, this chemical will concentrate mostly in water (48.8%) and soil (48.1%).

This chemical will take about 122 days to volatilize from a model river, and 1338 days to volatilize from a model lake.

Reliability : (4) not assignable
Calculated result, reliability dependent on input data.

24.05.2001 (12)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge, domestic, non-adapted
Contact time	:	20 day
Degradation	:	= 79 % after 20 day
Result	:	readily biodegradable
Kinetic of test substance	:	5 day = 62 **%** 10 day = 68 **%** 15 day = 75 **%** 20 day = 79 **%** **%**
Deg. Product	:	not measured
Method	:	other: Amer Pub Hlth Assoc (1971) 'Standard methods for the examination of waste-water', 13th ed.
Year	:	1974
GLP	:	no
Test substance	:	no data
Method	:	Origin of sample Unadapted settled domestic waste water, filtered through glass wool, was used in these studies. Degradation testing The tests were conducted in BOD bottles, half filled with aerated dilution water containing minerals and buffer (no further details available). Propylene glycol was added to a final concentration of 3, 7 and 10 mg/l. Experiments were conducted once (3 mg/l) or in duplicate (7 and 10 mg/l). Each test ran for 20 days. Dissolved oxygen (DO) was measured on days 5, 10, 15 and 20 using a DO meter. When DO fell below 4.0 mg/l the contents were re-aerated (by opening and agitating aseptically).
Result	:	Results are represented as '% bio-oxidation', and show 62% degradation by unadapted sludge within 5 days. (The concentration of propylene glycol giving this result is not stated.)
Source	:	A.K. Mallett Surrey
Conclusion	:	Under the conditions of this study, propylene glycol was readily degraded by unacclimated sludge.
Reliability	:	(2) valid with restrictions Non-guideline study, pre-GLP, some shortcomings in reporting but generally acceptable.
Flag	:	Critical study for SIDS endpoint

29.05.2001 (37)

Type	:	aerobic
Inoculum	:	other: soil microcosm
Concentration	:	399mg/l related to Test substance related to
Contact time	:	111 day
Degradation	:	= 100 % after 12 day
Result	:	other: degradable by soil microorganisms (see results)
Deg. Product	:	
Method	:	other: experimental study
Year	:	1993
GLP	:	no data
Test substance	:	other TS: deicing fluid containing 89% propylene glycol

Method : Origin of sample
Soil (characterised as sandy loam) was collected from an area adjacent to an airport runway. The upper 2 - 5 cm of topsoil was cleared, and the next 30 cm collected with a shovel. The soil was sieved (<2 mm retained) and stored at 4 degrees C.

Degradation test
Soil microcosms were prepared by transferring 20 g of soil into a 160 ml sterile serum bottle, to which sterile aqueous deicing fluid was added to a final concentration of 0.05% or 0.5% product v/w. No aeration was used, since preliminary calculations indicated that the bottles contained excess oxygen. Soil blanks (to compensate for CO2 production from endogenous sources) were prepared by addition of sterile water with no additional substrate. Heat-killed (autoclaved) soil was included as a further control. The tests were conducted at 8.2 degrees C.

Analytical methods
Microcosms were periodically sacrificed and analysed for disappearance of propylene glycol (GD-FID) and production of CO2 (carbon analyser).

Statistics
Degradation rates were determined by linear regression analysis, after correction for substrate disappearance or CO2 production by the controls.

Remark : The antibacterial properties of propylene glycol, or of other unspecified components present in the deicer, may have hindered biodegradation in the high-concentration incubations.

Result : Analysed concentrations of propylene glycol in the incubations (GC-FID) were 399 and 4933 mg/kg. Regression analysis gave a biodegradation rate (active sample - control) of 41.4 and 20.0 mg/kg soil/day, respectively.

Graphical data indicate complete removal of the propylene glycol from incubations containing 399 mg/kg within 12 days. 57% of the THoD was recovered after 34 days.

Removal from incubations containing 4933 mg/kg was slower, with 76% degraded and 44% of the THoD recovered after 111 days.

In heat-killed controls, 91% recovery of propylene glycol was achieved after 111 days with negligible production of CO2.

Source : A.K. Mallett Surrey

Conclusion : Under the conditions of the test, propylene glycol was degraded by soil microorganisms.

Reliability : (2) valid with restrictions
Non-guideline pre-GLP study using non-standard substrate (deicing fluid), with graphical presentation of results.
Good analytical methodology.

Flag : Critical study for SIDS endpoint
24.05.2001 (22)

Type : aerobic

Inoculum	:	other: unadapted and adapted sludge
Concentration	:	220mg/l related to Test substance 2400mg/l related to Test substance
Contact time	:	24 hour(s)
Degradation	:	= 84 - 95 % after 24 hour(s)
Result	:	readily biodegradable
Deg. Product	:	not measured
Method	:	
Year	:	1990
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Origin of sample Seed samples were obtained from a local municipal treatment works and from an industrial WWTP. These were combined to give a diverse microbial population representative of treatment facilities that receive both municipal and industrial waste. Sludge acclimation The combined seed was mixed with a 1:300 volume dilution of a 1:1:1 v/v mixture of propylene glycol, ethylene glycol and diethylene glycol supplemented with dibasic diammonium phosphate at 20 degrees C. The mixed liquor was monitored on a daily basis for pH, temperature, dissolved oxygen (DO) and DO uptake (before and after feeding). These parameters were used to monitor the acclimation process. Acclimation was accomplished by gradually increasing the proportion of diluted glycols in the feed while the proportion of primary effluent was correspondingly decreased. Degradation testing Studies were conducted using both unacclimated and acclimated sludge samples. The tests were conducted in a cylindrical reactor (volume 10 l, containing 8 l of liquor) with continuous aeration and mixing at approx 20 degrees C. The concentration of substrate and other parameters (temperature, pH) were varied in subsequent experiments. Analysis Real-time monitoring was conducted for temperature, pH, DO uptake, total suspended solids (TSS), volatile suspended solids (VSS) and COD.
Result	:	Kinetic data are presented graphically in the report. Acclimation In the fully acclimated system, COD was 4000 mg/l in the feed and < 450 mg/l in the supernatant (n = 2 runs) and DO uptake was 3-21 mg/l/hr pre-feeding reaching a maximum of 222-338 mg/l/hr post feeding. (The period of time required for acclimation was not reported.) Batch reactor degradation Biodegradation of 1400 mg/l propylene glycol by unacclimated sludge at 20.4 degrees showed a reduction in COD from 4700 mg/l to 1900 mg/l over 33 hr (60% reduction). Biodegradation of 2400 mg/l propylene glycol by acclimated

sludge at 19.3 degrees C showed a reduction in COD from 2900 mg/l to 149 mg/l over 24 hr (95% reduction). Degradation of 940 mg/l under comparable conditions gave a 99.7% reduction in COD over 20hr, while an 84% reduction in COD was achieved at a starting concentration of 220 mg/l propylene glycol.
When the initial substrate concentration was 1000 mg/l and the temperature decreased to 10.2 degrees C, COD decreased from 4800 mg/l to 2000 mg/l over 48 hr (58% reduction) with acclimated sludge.

Source : A.K. Mallett Surrey
Conclusion : Under the conditions of these tests, propylene glycol was readily degraded by unacclimated and acclimated sludge.
Reliability : (2) valid with restrictions
Well documented non-guideline study, extensive reporting of results, however no information on GLP status.
Flag : Critical study for SIDS endpoint
24.05.2001 (27)

Type : anaerobic
Inoculum : other: soil microcosm
Contact time :
Degradation : % after
Result : other: degraded to methane by soil microorganisms under anaerobic conditions (see results)
Deg. Product :
Method : other: experimental study
Year : 1997
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Method : Origin of sample
Two different soil types were used, Tappan sandy loam and a surface sand (Midland County, MI). The top 10- 12 cm of soil and vegetation was cleared, and the next 10-12 cm collected into plastic bags, heat sealed and stored at 4 degrees C.

Degradation test
Soil microcosms were prepared by transferring 50 g of soil and 80 ml of sterile water into a 160 ml sterile serum bottle in an anaerobic chamber (70% N2, 28% CO2, 2% H2). Propylene glycol was added at initial concentrations in the range 100 - 10000 ppm. The bottles were then sealed and incubated in the dark at 25 degrees plus or minus 1 degree C. Heat-killed (autoclaved) soil, with no added propylene glycol, was included as a control.

Analytical methods
Duplicate reaction mixtures were analysed over time for disappearance of test substance (GC-FID) and formation of degradation products (CH4).

Statistics
No specific methods are described.
Remark : Clear interpretation of these results is hampered by probable microbial contamination of at least some of the heat-killed control incubations.
Result : Tappan sandy loam
In microcosms amended with 100 mg/kg propylene glycol, complete loss of substrate occurred by day 30, with complete

conversion to gaseous products by day 60. Headspace chromatography confirmed that methane was the only headspace gas present, with propionic acid identified as precursor.

Complete loss of propylene glycol also occurred after 14 days in incubations containing 1000 mg/kg. In contrast, 96% of the substrate remained in the heat-killed samples at day 30. The biodegradation rate was approx. 71 mg/kg/day. Gas production showed 52% of the maximum theoretical yield by day 105.

A longer incubation time was required for complete removal in microcosms amended with 10000 mg/kg propylene glycol. After 105 days, 98% had been degraded. However significant losses were also noted in the controls (48% at day 105) indicating potential microbial contamination. No significant gas production was found at this concentration. This was considered to be a result of the accumulation of toxic concentrations of propionic acid in the system, which decreased the pH from ~7.0 to 6.5.

Surface sand
In microcosms amended with 1000 mg/kg propylene glycol, 96% of the test compound was degraded by day 104 compared to 27% in the heat-inactivated controls. This indicates a biodegradation rate of approx 10 mg/kg/day.

Removal of 10000 mg/kg was comparable to that seen in the heat-killed controls ie 36% versus 21% at day 105.

No gas production was detectable in the sand microcosms during the time period of the tests.

Source : A.K. Mallett Surrey
Conclusion : Under the anaerobic conditions of the test, propylene glycol was degraded to methane by microorganisms present in sandy loam, whereas comparable activity was not detected in samples of surface sand.
Reliability : (2) valid with restrictions
Well documented non-guideline study, extensive reporting of results, however no information on GLP status. Suspected microbial contamination of blanks limits reliability overall.
Flag : Critical study for SIDS endpoint
29.05.2001 (23)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

BCF : = 1.4
Remark : Calculation : Log BCF = 0.76*(log Kow)*(-0.23)
[Calculated using the prefered value of log Kow = -0.78.]
Source : A.K. Mallett Surrey
Reliability : (4) not assignable
Calculated result, reliability dependent on input data.
Flag : Critical study for SIDS endpoint

29.05.2001 (8)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	m = 42000
LC0	:	m = 42000
LC50	:	c = 51600
LC100	:	m = 63500
LC50 24hr	:	c = 79700
LC50 48hr	:	c = 79700
LC50 72hr	:	c = 51600
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1990
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Test organisms Juvenile rainbow trout were acclimated for 14 days in 100% dilution water under flow through conditions (temp 11-13.5 degrees C, dissolved oxygen >9.1 mg/l). They were fed a commercial fish food once or twice daily before the test. Control fish had an average total length of 40.7 mm, and an average weight of 0.64 g at the end of the test. Test conditions Dilution water was collected from wells at the laboratory, and adjusted to a hardness of 44 mg/l CaCO3, stored in polyethylene tanks and aerated until use. It had a pH of 7.3, and conductivity of 926 umhos/cm. A preliminary toxicity screening test was used to establish the concentration range to be used in the main study. The main test was conducted at a target temperature of 12 plus or minus 2 degrees C. Nominal concentrations of propylene glycol were 0 (control), 15000, 24000, 38000, 60000 and 96000 ppm. Twenty fish were randomly and equally distributed between two replicate tanks per treatment. The tank volume was 19.6 l and contained 15 l of test media. The vessels were randomly arranged in a water bath throughout the test. The average loading rate was 0.43 g/l. A 16 hr light and 8 hr dark cycle was applied. No aeration was necessary to maintain oxygen levels within acceptable limits. The fish were not fed during the study. Observations Dissolved oxygen, pH and conductivity were monitored daily, while temperature was measured continuously in one tank throughout the test. The number of surviving organisms and the occurrence of sub-lethal effects (loss of equilibrium, erratic swimming, loss of reflex, excitability, discoloration, change in behaviour) were determined visually initially and after 24, 48, 72 and 96 hr. Dead fish were removed when first observed.

Analytical methods
The actual concentration of propylene glycol in the test vessels was determined by HPLC with reverse phase column and differential refractometer detection.

Statistics
LC50 values were computed using standard techniques (Stephan, CE, 1993. Computer program for the calculation of LC50 values, US EPA, Duluth MN)

Result : The test material remained fully dissolved throughout the study. Conductivity was in the range 421 - 960 umho/cm, pH 7.3 - 8.4, temperature 11.5 - 11.6 degrees C and dissolved oxygen 11.8 - 8.0 mg/l.

Mean measured concentrations (with nominal in parenthesis), were 16000 (15000), 26000 (24000), 42000 (38000), 63500 (60000) and 100000 (96000) mg/l.

No mortality or other effects were reported for fish exposed to concentrations up to and including 42000 mg/l.

At 63500 mg/l 10/10 test organisms showed loss of equilibrium, lethargy and gasping at 24 hr and 48 hr, with 100% mortality after 72 hr.

The 100000 mg/l series showed 100% mortality at 24hr.

Source : A.K. Mallett Surrey
Conclusion : The 96 hr LC50 for propylene glycol in Oncorhynchus mykiss was calculated as 51600 mg/l (95% CI 42000 - 63500 mg/l).
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
23.05.2001 (2)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : no
NOEC : m = 36000
LC0 : m = 36000
LC50 : c = 46500
LC100 : m = 60000
LC50 24hr : c = 67400
LC50 48hr : c = 46500
LC50 72hr : c = 46500
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 1993
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Method : Test organisms
Juvenile fathead minnows were acclimated for 14 days before the study commenced. They were fed a commercial fish food at least once daily during the holding period (unfed for 48 hr prior to test). Mortality did not exceed 3% in the 5 days before testing commenced. The mean length and weight of the control organisms at the end of the test was 23.6 mm and 194 mg, respectively.

Test conditions
Dilution water was limed and flocculated with ferric chloride to a hardness of 75 mg/l CaCO3 by the local supplier. Prior to use in the laboratory it was sand filtered, pH-adjusted with CO2, carbon filtered and UV-irradiated.

A preliminary toxicity screening test was used to establish the concentration range to be used in the main study.

The main test was conducted at a target temperature of 22 plus or minus 1 degrees C. The vessels were housed in a circulating water bath throughout the test. A 16 hr light and 8 hr dark cycle was applied.

Nominal concentrations of propylene glycol were 0 (control), 12960, 21600, 36000, 60000 and 100000 mg/l. Ten fish were randomly distributed into single replicate tanks per treatment. The tank volume was 12 l and contained 10 l of test media, fitted with glass covers to prevent evaporation. The loading of the vessels was 0.19 g fish.

Observations
Dissolved oxygen, pH and temperature was measured initially and daily thereafter in all tanks containing surviving fish.

The number of surviving organisms and the occurrence of sub-lethal effects (swimming at the surface, loss of equilibrium, lethargy, hyperactivity, erratic movement) were determined visually throughout the test. Dead fish were removed when observed.

Statistics
A computer program was used to calculate the LC50/EC50 values and corresponding 95% confidence intervals. This included probit analysis, moving average angle analysis and binominal probability.

Result : The test material remained fully dissolved throughout the study. Dissolved oxygen was in the range 8.4 - 9.1 mg/l, temperature was 21.5 - 22.4 degrees C and pH was 7.3 - 7.9 during the 96 hr of the test.

No treatment-related mortality or effects occurred in fish exposed to concentrations up to and including 36000 mg/l. (Note : a single fish was found dead at the 72 hr time point in the 21600 mg/l tank, however the absence of any further deaths in this tank at 96 hr, plus the absence of any mortality in the 36000 mg/l tank suggests this was unrelated to treatment.)

At 60000 mg/l there were 3/10 deaths at the 24 hr time-point, with the surviving fish exhibiting erratic swimming behaviour. There was 100% mortality at the 48 hr observation period.

There was 100% mortality at 24hr in fish exposed to 100000 mg/l.

Source : A.K. Mallett Surrey

Conclusion : The 96 hr LC50 for propylene glycol in Pimephales promelas

was calculated as 46500 mg/l (95% CI 36000 - 60000 mg/l).

Reliability : (1) valid without restriction
Well documented guideline study, lack of clarity over GLP status is only shortcoming.

Flag : Critical study for SIDS endpoint

29.05.2001 (48)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : yes
NOEC : m = 26000
LC0 : m = 41000
LC50 : c = 51400
LC100 : m = 64500
LC50 24hr : c = 77800
LC50 48hr : c = 54000
LC50 72hr : c = 51400
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 1990
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Method : Test organisms
Juvenile fathead minnows were acclimated for 38 days in 100% dilution water under flow through conditions (temp 21.5 - 22.8 degrees C, dissolved oxygen >8.0 mg/l in the 14 days before the study commenced). They were fed a commercial fish food once or twice daily before the test. Control fish had an average total length of 31.3 mm, and an average weight of 0.30 g at the end of the test.

Test conditions
Dilution water was collected from wells at the laboratory, and adjusted to a hardness of 44 mg/l CaCO3, stored in polyethylene tanks and aerated until use. It had a pH of 7.9, and conductivity of 1234 umhos/cm.

A preliminary toxicity screening test was used to establish the concentration range to be used in the main study.

The main test was conducted at a target temperature of 22 plus or minus 2 degrees C. Nominal concentrations of propylene glycol were 0 (control), 15000, 24000, 38000, 60000 and 96000 ppm. Twenty fish were randomly and equally distributed between two replicate tanks per treatment. The tank volume was 19.6 l and contained 15 l of test media. The vessels were randomly arranged in a water bath throughout the test. The average loading rate was 0.20 g/l. A 16 hr light and 8 hr dark cycle was applied. No aeration was necessary to maintain oxygen levels within acceptable limits. The fish were not fed during the study.

Observations
Dissolved oxygen, pH and conductivity were monitored daily, while temperature was measured continuously in one tank throughout the test.

The number of surviving organisms and the occurence of

sub-lethal effects (loss of equilibrium, erratic swimming, loss of reflex, excitability, discoloration, change in behaviour) were determined visually initially and after 24, 48, 72 and 96 hr. Dead fish were removed when first observed.

Analytical methods
The actual concentration of propylene glycol in the test vessels was determined by HPLC with reverse phase column and differential refractometer detection.

Statistics
LC50 values were computed using standard techniques (Stephan, CE, 1993. Computer program for the calculation of LC50 values, US EPA, Duluth MN)

Result : The test material remained fully dissolved through-out the study. Conductivity was in the range 655 - 1435 umho/cm, pH 7.8 - 8.4, temperature 20.4 - 23.7 degrees C and dissolved oxygen 19.2 - 5.6 mg/l.

Mean measured concentrations of propylene glycol (with nominal in parenthesis), were 16000 (15000), 26000 (24000), 41000 (38000), 64500 (60000) and 104000 (96000) mg/l.

No mortality occurred in fish exposed to concentrations up to and including 41000 mg/l, however 1/10 and 5/10 from replicates at this concentration were lethargic 24 hr into the test (normal behaviour thereafter).

At 64500 mg/l, 20-60% of the test organisms were lethargic at the 24 hr time-point. Mortality was 10%, 90% and 100% at the 24hr, 48hr and 72 hr time-points, respectively.

All test organisms were dead at 24hr in tanks containing 104000 mg/l.

Source : A.K. Mallett Surrey
Conclusion : The 96 hr LC50 for propylene glycol in Pimephales promelas was calculated as 51400 mg/l (95% CI 41000 - 64500 mg/l).
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
23.05.2001 (3)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : yes
NOEC : m = 28500
EC0 : m = 28500
EC50 : c = 43500
EC100 : m = 66500
EC50 24hr : c = 70700
Method : OECD Guide-line 202, part 1 "Daphnia sp., Acute Immobilisation Test"
Year : 1990
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Test organisms
Juvenile daphnids (from a single source) were bred and acclimated at the laboratory. Control daphnia had an average weight of 0.19 mg at the end of the test.

Test conditions
Dilution water was collected from wells at the laboratory, and adjusted to a hardness of 180 mg/l CaCO3, stored in polyethylene tanks and aerated until use. It had a pH of 7.2, and conductivity of 347 umhos/cm.

A preliminary toxicity screening test was used to establish the concentration range to be used in the main study.

The main test was conducted at a target temperature of 20 plus or minus 1 degree C. The vessels were housed in an incubator throughout the test. A 16 hr light and 8 hr dark cycle was applied. Aeration was not required.

Nominal concentrations of propylene glycol were 0 (control), 15000, 24000, 38000, 60000 and 96000 ppm. Twenty daphnids were randomly and equally distributed into two replicate tanks per treatment. The tank volume was 250 ml, containing 200 ml of test medium. The loading rate was approx 0.0095 g/l.

Observations
Dissolved oxygen, pH, salinity and temperature was measured initially and daily thereafter in all tanks containing surviving organisms.

The number of surviving organisms and the occurrence of sub-lethal effects (loss of equilibrium, erratic swimming, loss of reflex, excitability, discoloration or change in behaviour) were determined visually throughout the test. Dead organisms were removed when observed.

Analytical methods
The actual concentration of propylene glycol in the test vessels was determined by HPLC with reverse phase column and differential refractometer detection.

Statistics
LC50 values were computed using standard techniques (Stephan, CE, 1993. Computer program for the calculation of LC50 values, US EPA, Duluth MN)

Result : The test material remained fully dissolved throughout the study. Dissolved oxygen was in the range 6.7 - 8.7 mg/l, temperature was 20.2 - 20.5 degrees C, pH was 7.2 - 8.4 and conductivity was 198 - 765 umhos/cm during the test.

Mean measured concentrations (with nominal in parenthesis), were 14500 (15000), 28500 (24000) 41000 (38000) 66500 (60000) and 94000 (96000) mg/l.

No treatment-related mortality or effects occurred in daphnids exposed to concentrations up to and including 28500 mg/l.

At 41000 mg/l there was 30 - 50% mortality at the 48 hr time-point.

At 66500 mg/l there was 20 -50% mortality at the 24 hr time-point and 100% mortality at 48hr.

At 94000 mg/l no organisms survived to 24 hr.

Source : A.K. Mallett Surrey
Conclusion : The 48 hr LC50 for propylene glycol in Daphnia magna was calculated as 43500 mg/l (95% CI 41000 - 66500 mg/l).
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
29.05.2001 (5)

Type : static
Species : other: Mysidopsis bahia
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : yes
NOEC : m < 9500
EC0 : m < 9500
EC50 : c = 18800
EC100 : m = 41000
EC50 24hr : c = 31000
EC50 48hr : c = 27300
EC50 72hr : c = 23400
Method : EPA OTS 797.1930
Year : 1990
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Method : Test organisms
Juvenile mysids (from a single source) were bred at the laboratory and acclimated for 14 days at 21.1 - 22.8 degrees C before the study commenced. They were fed Artemia salina at least once daily during the holding period, and once daily during the test. Control mysids had an average weight of 2.4 mg at the end of the test.

Test conditions
Dilution water was seawater collected from the Atlantic Ocean (Hampton, NJ). It was adjusted to salinity 11-17 parts per thousand and stored in polyethylene tanks, where it was aerated. It had a pH of 7.8.

A preliminary toxicity screening test was used to establish the concentration range to be used in the main study.

The main test was conducted at a target temperature of 22 plus or minus 2 degrees C. The vessels were housed in a circulating water bath throughout the test. A 16 hr light and 8 hr dark cycle was applied. Aeration was required after 48 hr exposure to maintain dissolved oxygen at an acceptable level.

Nominal concentrations of propylene glycol were 0 (control), 10000, 16000, 25000, 40000 and 100000 ppm. Twenty mysids were randomly and equally distributed into two replicate tanks per treatment. The tank volume was 2 l, containing 1 l of test medium. The loading rate was approx 0.024 g/l.

Observations
Dissolved oxygen, pH, salinity and temperature was measured initially and daily thereafter in all tanks containing surviving organisms.

The number of surviving organisms and the occurrence of sub-lethal effects (loss of equilibrium, erratic swimming, loss of reflex, excitability, discoloration or change in behaviour) were determined visually throughout the test. Dead organisms were removed when observed.

Analytical methods
The actual concentration of propylene glycol in the test vessels was determined by HPLC with reverse phase column and differential refractometer detection.

Statistics
LC50 values were computed using standard techniques (Stephan, CE, 1993. Computer program for the calculation of LC50 values, US EPA, Duluth MN)

Result : The test material remained fully dissolved through-out the study. Salinity was in the range 11 - 15 pp thousand, pH 7.7 - 8.0, temperature 21.5 - 222.2 degrees and dissolved oxygen 6.5 - 8.5 mg/l.

Mean measured concentrations of propylene glycol (with nominal in parenthesis), were 9500 (10000), 15500 (16000), 25000 (25000), 41000 (40000) and 64500 (64000) mg/l.

No mortality occurred in the control tanks.

At 9500 mg/l and 15500, 1 or 2 organisms per tank had died at the 72 hr and 96 hr time-points.

At 25000 mg/l, 1 or 2 organisms were dead at the 24 hr observation period, increasing to 60 - 90% mortality at 96 hr.

At 41000 mg/l and above, 100% mortality occurred after 24 hr.

Source : A.K. Mallett Surrey
Conclusion : The 96 hr LC50 for propylene glycol in Mysidopsis bahia was calculated as 18800 mg/l (95% CI 15900 - 22000 mg/l).
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
29.05.2001 (4)

Type : static
Species : Ceriodaphnia sp. (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : yes
NOEC : c = 13020
EC50 : c = 18340
Method : other: Weber, C (1991) EPA 600/4-90/027, US-EPA Cincinnati OH
Year : 1995
GLP : no data
Test substance : other TS: Sigma Chemical Co

Method	:	Test organisms Juvenile cerids were bred and acclimated at the laboratory. Organisms were less than 24 hr old at the start of the test. Test conditions Dilution water was moderately hard reconstituted water, with a hardness of 86 mg/l CaCO3 and an alkalinity of 62 mg/l CaCO3. A preliminary toxicity screening test was used to establish the concentration range to be used in the main study. The main test was conducted at 25 degrees C with a 16 hr light and 8 hr dark cycle. There were four replicates each containing five organisms per test chamber. The range of exposure concentrations is not reported. The cerids were not fed during the study. Observations Dissolved oxygen, pH and conductance were measured. Analytical methods The actual concentration of propylene glycol in the test vessels was determined using EPA method 8015 (GC-FID). Statistics LC50 values were determined by binomial, probit or trimmed Spearman-Karber methods.
Result	:	Oxygen concentration was 6.3 - 7.2 mg/l, pH 7.5 - 8.2 and conductance 264 - 322 umho/cm. The 48hr LC50 was reported as 18340 mg/l, and the NOAEC 13020 mg/l.
Source	:	A.K. Mallett Surrey
Conclusion	:	The 48 hr LC50 for propylene glycol in Ceriodaphnia dubia was calculated as 18340 mg/l.
Reliability	:	(2) valid with restrictions Non-guideline study, GLP status unclear, some shortcomings in descriptive methodology and reporting of results but generally acceptable. Non-guideline study, GLP status unclear, some shortcomings in descriptive methodology and reporting of results but generally acceptable.
Flag	:	Critical study for SIDS endpoint

29.05.2001 (36)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum sp. (Algae)
Endpoint	:	growth rate
Exposure period	:	14 day
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	m = 15000
EC50 48 hr	:	c = 34100
EC50 72 hr	:	c = 24200
EC50 96 hr	:	c = 19000
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"

Year : 1990
GLP : yes
Test substance : as pres cribed by 1.1 - 1.4
Method : Test organisms
Algae were obtained from the Culture Collection of Algae at the University of Texas, Austin. The culture was transferred to sterile enriched media and grown under conditions identical to those used for this test.

Test conditions
Water used for acclimation of test organisms and for all toxicity testing was sterile enriched media (US-EPA, 1978, EPA-600/9-78-018), adjusted to pH 7.5.

The definitive test was conducted at a target temperature of 24 plus or minus 2 degrees C. Nominal concentrations of propylene glycol were 6250, 12500, 25000, 50000 and 100,000 ppm. One thousand algal cells were equally and randomly distributed among three replicates per concentration. The test was performed in 250 ml glass Erlenmeyer flasks containing 100 ml of test solution. The flasks were capped with an inverted beaker, and randomly arranged on a rotary shaker in an incubator. A 24 hr light period was used.

Observations
The temperature of the incubator was recorded daily, and pH m easured in each vessel at the start and end of each test.

The number of algal cells/ml was determined by direct microscopic count using a hemocytometer. Determinations were recorded daily during the first 96 hr, and every 48 hr thereafter.

Analytical methods
The actual concentration of propylene glycol in the test vessels was determined by HPLC with reverse phase column and differential refractometer detection.

Statistics
LC50 values were computed using standard techniques (Stephan, CE, 1993. Computer program for the calculation of LC50 values, US EPA, Duluth MN). Shapiro-Wilk's test was used to determine if cell growth after 14 days was normally distributed, and Bartlett's test to determine if variances were homogeneous.

Remark : Raw data included in the report indicates that the 24 hour EC50 of <5200 mg/l is the consequence of an initial 'lag' in cell growth in the low exposure series, which had resolved by day 3. A similar 'lag' was present also in the 15000 mg/l series.

Selected mean data: cells/ml on days 0, 1, 2, 3, 4 and 14
Control: 1000, 34000, 41000, 334000, 728000 and 4710000
5200mg/l: 1000, 11000, 30000, 338000, 637000 and 3552000
15000 mg/l: 1000, 11000, 40000, 273000, 553000 and 3373000

Result : The test material remained fully dissolved throughout the study.

Mean measured concentrations of propylene glycol (with

nominal values in parenthesis), were 5200 (6250), 15000 (12500), 26000 (25000), 53000 (50000) and 100000 (100000) mg/l.

The tested concentrations of propylene glycol were not stimulatory toward the alga at the concentrations used.

The calculated EC50 values (with 95% CI) were as follows :

24 hr < 5200 mg/l
48 hr 34100 (29100 - 40600) mg/l
72 hr 24200 (22100 - 26500) mg/l
96 hr 19000 (16700 - 21400) mg/l
14 d 18100 (15500 - 20900) mg/l

The 14 day NOEC was 15000 mg/l

Source : A.K. Mallett Surrey
Conclusion : The 96 hr EC50 (growth) for propylene glycol in Selenastrum capricornutum was calculated as 19000 mg/l (95% CI 16700 - 21400 mg/l).
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
29.05.2001 (7)

Species : Skeletonema costatum (Algae)
Endpoint : growth rate
Exposure period : 14 day
Unit : mg/l
Analytical monitoring : yes
NOEC : m < 5300
EC50 48 hr : c = 19000
EC50 72 hr : c = 19300
EC50 96 hr : c = 19100
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 1990
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Method : Test organisms
Algae were obtained from the Culture Collection of Algae at the University of Texas, Austin. The culture was transferred to sterile enriched media and grown under conditions identical to those used for this test.

Test conditions
Water used for acclimation of test organisms and for all toxicity testing was sterile enriched media, adjusted to a salinity of 30 parts per thousand.

The definitive test was conducted at a target temperature of 20 plus or minus 2 degrees C. Nominal concentrations of propylene glycol were 6250, 12500, 25000, 50000 and 100,000 ppm. One thousand algal cells were equally and randomly distributed among three replicates per concentration. The test was performed in 250 ml glass Erlenmeyer flasks containing 100 ml of test solution. The flasks were capped with an inverted beaker, and randomly arranged on a rotary shaker in an incubator. A 14 hr light / 10 hour dark period was used.

Observations
The temperature of the incubator was recorded daily, and pH measured in each vessel at the start and end of each test.

The number of algal cells/ml was determined by direct microscopic count using a hemocytometer. Determinations were recorded daily during the first 96 hr, and every 48 hr thereafter.

Analytical methods
The actual concentration of propylene glycol in the test vessels was determined by HPLC with reverse phase column and differential refractometer detection.

Statistics
LC50 values were computed using standard techniques (Stephan, CE, 1993. Computer program for the calculation of LC50 values, US EPA, Duluth MN). Shapiro-Wilk's test was used to determine if cell growth after 14 days was normally distributed, and Bartlett's test to determine if variances were homogeneous.

Result : The test material remained fully dissolved throughout the study.

Mean measured concentrations of propylene glycol (with nominal values in parenthesis), were 5300 (6250), 12000 (12500), 25000 (25000), 51000 (50000) and 97000 (100000) mg/l.

The tested concentrations of propylene glycol were not stimulatory toward the alga at the concentrations used.

The calculated EC50 values (with 95% CI) were as follows :

24 hr 31500 (27600 - 36200) mg/l
48 hr 19000 (16600 - 21600) mg/l
72 hr 19300 (16900 - 21800) mg/l
96 hr 19100 (17200 - 21000) mg/l
14 d <5300 mg/l

The 14 day NOEC was less than 5300 mg/l, the lowest tested concentration.

Source : A.K. Mallett Surrey
Conclusion : The 96 hr EC50 (growth) for propylene glycol in Skeletonema costatum was calculated as 19100 mg/l (95% CI 17200 - 21000 mg/l).
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
23.05.2001 (6)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species	:	Ceriodaphnia sp. (Crustacea)
Endpoint	:	reproduction rate
Exposure period	:	
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	c = 13020
IC25	:	c = 13470
Method	:	other: Weber, C (1989) EPA 600/4-89/001, US-EPA Cincinnati OH
Year	:	1995
GLP	:	no data
Test substance	:	other TS: Sigma Chemical Co
Method	:	Test organisms Juvenile cerids were bred and acclimated at the laboratory. Organisms were less than 24 hr old at the start of the test. The cerids were fed (yeast-trout chow-Cerophyl plus Selenastrum capricornutum) daily during the study. Test conditions Dilution water was moderately hard reconstituted water, with a hardness of 86 mg/l CaCO3 and an alkalinity of 62 mg/l CaCO3. Tests were run at 25 degrees C with a 16 hr light and 8 hr dark cycle. Ten replicates were tested for each concentration, with one organism per replicate. The concentration range used is not reported. The study was terminated when 60% of the control cerids had produced three broods. Observations Dissolved oxygen, pH and conductance were measured. Analytical methods The actual concentration of propylene glycol in the test vessels was determined using EPA method 8015 (GC-FID). Statistics The IC25 (reproduction) was calculated using EPA methods (EPA , 1988, ICp calculation program release 1.0, Duluth MN).
Result	:	Oxygen concentration was 5.2 - 7.9 mg/l, pH 7.5 - 8.3 and conductance 264 - 322 umho/cm. The NOEC for reproduction was 13020 mg/l. The NOEC for mortality was reported as 29000 mg/l. The IC25 was 13470 mg/l.
Source	:	A.K. Mallett Surrey
Conclusion	:	The IC25 (reproduction) for propylene glycol in Ceriodaphnia dubia was calculated as 13470 mg/l.
Reliability	:	(2) valid with restrictions Non-guideline study, GLP status unclear, some shortcomings in descriptive methodology and reporting of results but generally acceptable.
Flag	:	Critical study for SIDS endpoint

29.05.2001 (36)

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	:	no data
Sex	:	no data
Number of animals	:	134
Vehicle	:	no data
Value	:	= 22000 mg/kg bw
Method	:	other (calculated): because this study was conducted before any standardized guidelines were established, the question of guideline methodology and GLP conduct is not applicable.
Year	:	1939
GLP	:	no
Test substance	:	no data
Method	:	Animals and treatments Rats (sex and strain unspecified) were selected with a body weight of 250 g (range 75 g). The investigation used 2 series of animals (series A = 89 rats; series B = 45 rats). Treatment levels were 15- 25 cc/kg (approx 1500 - 26000 mg/kg) for series A and 17.6- 22.6 cc/kg (approx 18200 - 23400 mg/kg) for series B. There were 9 -10 animals per dose level, with the treatments commonly run in duplicate. Propylene glycol was administered by stomach tube following an 18 hr overnight fast. Post-mortem examination All animals that died were necropsied and those showing evidence of mechanical injury were excluded from calculation of the LD50. The liver and kidneys were examined by light microscopy (processing details etc not stated) Calculation of LD50 In brief, a straight line was fitted to a plot of the log dose versus the percentage mortality (expressed in probits) using a least-squares method. The log dose corresponding to a 50% mortality was then determined by inspection of these graphical data.
Result	:	General signs of toxicity in all species included in this study included loss of equilibrium, marked depression, analgesia, coma and finally death after a prolonged moribund state shortly after administration of large doses of propylene glycol. Gros s examination of the internal organs were essentially negative except for hemorrhagic areas in the small intestine. Microscopic changes in kidney were minimal, with nuclear pyknosis and vacuolar degeneration of the cytoplasm. A few cortical tubules contained protein debris or loose casts. The liver showed only slight congestion and hyperemia with no fatty changes. The LD50 in the rat was determined to be 21.0 cc/kg, with standard errors of 19.2- 23.0 cc/kg (equivalent to 22000 mg/kg, errors 20000 - 24000 mg/kg)
Source	:	A.K. Mallett Surrey
Conclusion	:	Based on the results of this study, an LD50 of 22000 mg/kg was determined for propylene glycol in the rat.
Reliability	:	(2) valid with restrictions Clear reporting of technical methods, data analysis (probit)

and results, but no characterization of test species or test substance.

Flag : Critical study for SIDS endpoint
24.05.2001 (25)

Type : LD50
Species : mouse
Strain : no data
Sex : no data
Number of animals : 70
Vehicle : no data
Value : = 24900 mg/kg bw
Method : other (calculated): because this study was conducted before any standardized guidelines were established, the question of guideline methodology and GLP conduct is not applicable.
Year : 1939
GLP : no
Test substance : no data
Method : Animals and treatments
Mice (sex and strain unspecified) were selected with a body weight of 20 g (range 8 g). The investigation used a total of 70 animals, with group sizes of 10 - 20 per dose. Treatment levels were 20 - 30 cc/kg (approx 21000 - 31000 mg/kg), with the test substance administered by stomach tube following an 18 hr overnight fast.

Post-mortem examination
All animals that died were necropsied and those showing evidence of mechanical injury were excluded from calculation of the LD50. The liver and kidneys were examined by light microscopy (processing details etc not stated)

Calculation of LD50
In brief, a straight line was fitted to a plot of the log dose versus the percentage mortality (expressed in probits) using a least-squares method. The log dose corresponding to a 50% mortality was then determined by inspection of these graphical data.

Result : General signs of toxicity in all species included in this study included loss of equilibrium, marked depression, analgesia, coma and finally death after a prolonged moribund state shortly after administration of large doses of propylene glycol. Gross examination of the internal organs were essentially negative except for hemorrhagic areas in the small intestine. Microscopic changes in kidney were minimal, with nuclear pyknosis and vacuolar degeneration of the cytoplasm. A few cortical tubules contained protein debris or loose casts. The liver showed only slight congestion and hyperemia with no fatty changes.

The LD50 in the mouse was determined to be 23.9 cc/kg, with standard errors of 22.8 - 25.1 cc/kg (equivalent to 24900 mg/kg, errors 23700 - 26100 mg/kg)

Source : A.K. Mallett Surrey
Conclusion : Based on the results of this study, an LD50 of 24900 mg/kg was determined for propylene glycol in the mouse.
Reliability : (2) valid with restrictions
Clear reporting of technical methods, data analysis (probit) and results, but no characterization of test species or test

substance.

Flag : Critical study for SIDS endpoint
24.05.2001 (25)

Type	:	LD50
Species	:	guinea pig
Strain	:	no data
Sex	:	no data
Number of animals	:	40
Vehicle	:	no data
Value	:	= 19700 mg/kg bw
Method	:	other (calculated): because this study was conducted before any standardized guidelines were established, the question of guideline methodology and GLP conduct is not applicable.
Year	:	1939
GLP	:	no
Test substance	:	no data
Method	:	Animals and treatments Guinea pigs(sex and strain unspecified) were selected with a body weight of 300 g (range 100 g). The investigation used a total of 40 animals, with group sizes of 10 per dose. Treatment levels were 15 - 22.5 cc/kg (approx 16000 - 23400 mg/kg), with the test substance administered by stomach tube following an 18 hr overnight fast. Post-mortem examination All animals that died were necropsied and those showing evidence of mechanical injury were excluded from calculation of the LD50. The liver and kidneys were examined by light microscopy (processing details etc not stated) Calculation of LD50 In brief, a straight line was fitted to a plot of the log dose versus the percentage mortailty (expressed in probits) using a least-squares method. The log dose corresponding to a 50% mortality was then determined by inspection of these graphical data.
Result	:	General signs of toxicity in all species included in this study included loss of equilibrium, marked depression, analgesia, coma and finally death after a prolonged moribund state shortly after administration of large doses of propylene glycol. Gross examination of the internal organs were essentially negative except for hemorrhagic areas in the small intestine. Microscopic changes in kidney were minimal, with nuclear pyknosis and vacuolar degeneration of the cytoplasm. A few cortical tubules contained protein debris or loose casts. The liver showed only slight congestion and hyperemia with no fatty changes. The LD50 in the guinea pig was determined to be 18.9 cc/kg with standard errors of 17.2 - 20.7 cc/kg (equivalent to 19700 mg/kg, errors 17900 - 21500 mg/kg).
Source	:	A.K. Mallett Surrey
Conclusion	:	Based on the results of this study, an LD50 of 19700 mg/kg was determined for propylene glycol in the guinea pig.
Reliability	:	(2) valid with restrictions Clear reporting of technical methods, data analysis (probit) and results, but no characterization of test species or test substance.

Flag : Critical study for SIDS endpoint
24.05.2001 (25)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Species : rabbit
Strain : no data
Sex : no data
Number of animals :
Vehicle :
Value : = 20800 mg/kg bw
Method :
Year :
GLP : no data
Test substance : no data
Remark : Details for study not available.
Source : A.K. Mallett Surrey
Reliability : (4) not assignable
Secondary source, no information on study conduct.
Flag : Critical study for SIDS endpoint
24.05.2001 (34)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species : rabbit
Concentration : undiluted
Exposure : Occlusive
Exposure time : 4 hour(s)
Number of animals : 6
PDII : 0
Result : not irritating
EC classification :
Method : OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year : 1984
GLP : no data
Test substance : other TS: presumed as prescribed by 1.1 - 1.4
Remark : Text is in german language.
Result : No skin reactions were present in any of the six animals at 1hr, 24hr, 48hr and 72hr following removal of the patch.
Source : A.K. Mallett Surrey
Conclusion : Not irritating to rabbit skin.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
23.05.2001 (33)

Species : rabbit
Concentration : undiluted
Exposure : no data

Exposure time	:	no data
Number of animals	:	
PDII	:	
Result	:	not irritating
EC classification	:	
Method	:	Draize Test
Year	:	1979
GLP	:	no
Test substance	:	other TS: USP grade
Method	:	Only brief details a re available. Outbred female New Zealand rabbits (2- 6 kg, n = 6) were used. Skin responses were evaluated 24 hr and 72 hr after application of 0.5 ml of test substance. Dermal responses were assessed independently by 3 evaluators.
Result	:	A mean score of 0.1 is reported (mean of the 24- and 72 hr responses from 6 rabbits). (Scores of < 2.0 were described as indicating 'mild or no irritation'.)
Source	:	A.K. Mallett Surrey
Conclusion	:	Not irritating to rabbit skin.
Reliability	:	(2) valid with restrictions Near-guideline study, pre-GLP, some shortcomings in reporting but generally acceptable.
Flag	:	Critical study for SIDS endpoint

29.05.2001 (9)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure Tim e	:	
Comment	:	
Number of animals	:	6
Result	:	not irritating
EC classification	:	
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1984
GLP	:	no data
Test substance	:	no data
Remark	:	Text is in german language.
Result	:	Res ults are presented as the mean score for the 6 animals at each of the evaluation time-points. There were no corneal or iris effects (score 0). The mean score for conjunctivitis (redness, maximum possible score = 3) was 3.0 at 4hr, decreasing to 0.33, 0.0 and 0.0 at 24 hr, 48 hr and 72 hr post-treatment, respectively. An irritation index of 0.83/110 was obtained on the basis of these results.
Source	:	A.K. Mallett Surrey
Conclusion	:	Not irritating to rabbit eye.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

23.05.2001 (32)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure Time	:	
Comment	:	
Number of animals	:	6
Result	:	not irritating
EC classification	:	
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	1992
GLP	:	no data
Test substance	:	no data
Method	:	Animals and treatments Only brief experimental details are available for this study, which followed OECD guideline 405. 0.1 ml undiluted propylene glycol was applied to the lower conjunctival sac of 6 New Zealand White albino rabbits. Reactions were recorded at 4, 24, 48, 72 and 96 hr post-instillation, using the scoring system of Draize et al (1944, J Pharmac. Exp Ther, 82, 377 - 390).
Result	:	Results are presented as the mean score for the 6 animals at each of the evaluation time-points. There was no chemosis, corneal opacity or surface corneal damage in any animal at any time. The mean score for conjunctivitis (redness, maximum possible score = 3) was 1.1 at 4hr, decreasing to 0.9, 0.2 and 0.1 at 24 hr, 48 hr and 72 hr post-treatment, respectively. This had fully resolved by 96 hr. Iritis, score 0.3 (out of a maximum of 2), was recorded at the 24 hr time-point only.
Source	:	A.K. Mallett Surrey
Conclusion	:	The results from this study demonstrate that undiluted propylene glycol causes mild, fully reversible irritation of the rabbit eye.
Reliability	:	(2) valid with restrictions Guideline study but absence of information on GLP status and brief reporting limit reliability.
Flag	:	Critical study for SIDS endpoint

24.05.2001 (19)

5.3 SENSITIZATION

Type	:	Patch-Test
Species	:	human
Concentration	:	Induction 50 % semiocclusive Challenge 50 % semiocclusive
Number of animals	:	104
Vehicle	:	water
Result	:	not sensitizing
Classification	:	not sensitizing
Method	:	other: repeated insult patch test
Year	:	1999
GLP	:	yes

Test substance : as prescribed by 1.1 - 1.4

Method : Subjects
One hundred and four volunteers (male and female, age 19 - 79 yr) participated in the study. The upper back between the scapulae served as the treatment area.

Induction phase
Approx. 0.2 ml of a 50% aqueous dilution of propylene glycol was applied to 2.5 cm x 2.5 cm absorbent pad, covered with a semi-occlusive dressing. The application was repeated three times per week (Mon, Wed, Fri) for a total of 9 applications. The patches were removed after 24 hr contact (Tues, Thurs, Sat), and skin reactions evaluated 24 hr (Wed, Fri) or 48 hr (Mon) immediately prior to re-appliaction.

Challenge phase
Approx. 2 weeks after the final induction, a challenge patch was applied to a virgin site, adjacent to the induction site. This was removed after a 24 hr contact period, and reactions assessed immediately and again after 72 hr. Subjects responding at 72 hr were reassessed at 96 hr. (Note: challenge concentration is note stated.)

Scoring system
A six point scale was used to record skin responses during induction and challenge :
0 - no visible reaction
+ - barely perceptible or spotty erythema
1 - mild erythema covering most of the test site
2 - moderate erythema, possible presence of mild edema
3 - marker erythema, mild edema
4 - severe erythema, possible edema, vesiculation, bullae and/or ulceration

Statistics
No statistical methods were applied to the data.

Remark : With the exception of one hyper-responsive individual, skin responses during all stages of the study were considered within normal limits by the laboratory carrying out the investigation.

Result : General
One subject (no 18, panel 19990609) responded with varying degrees of erythema during the early stages of the study and induction was halted after the fourth application. This was considered to be an irritant hypersensitive reaction by the laboratory (based on a rapid onset plus other studies that subsequently demonstrated the individual's susceptability to other diols). This subject is excluded from the analysis presented below.

Induction
Three subjects responded with barely perceptible or mild erythema (score + or 1) on two or more occasions during the nine induction treatments. Four others responded with barely perceptible erythema (score +) on at least one occasion during induction.

Challenge
Skin reactions (barely perceptible to mild, score + to 1)

were recorded in 4/103 subjects on challenge. A barely perceptible skin response (score +) was recorded in 3 of these individuals at the 96 hr evaluation.

Source : A.K. Mallett Surrey

Conclusion : Under the conditions of the investigation, propylene glycol showed no potential to causes allergic contact sensitization.

Reliability : (1) valid without restriction
Non-guideline, GLP-compliant study, well described methods and results, large number of subjects.

Flag : Critical study for SIDS endpoint

29.05.2001 (11)

Type : Patch-Test

Species : human

Concentration : Induction 50 % occlusive epicutaneous
Challenge 50 % occlusive epicutaneous

Number of animals : 104

Vehicle : water

Result : not sensitizing

Classification : not sensitizing

Method : other: repeated insult patch test

Year : 1999

GLP : yes

Test substance : as prescribed by 1.1 - 1.4

Method : Subjects
One hundred and four volunteers (male and female, age 19 - 79 yr) participated in the study. The upper back between the scapulae served as the treatment area.

Induction phase
Approx. 0.2 ml of a 50% aqueous dilution of propylene glycol was applied to 1.9 cm x 1.9 cm absorbent pad, covered with a occlusive dressing. The application was repeated three times per week (Mon, Wed, Fri) for a total of 9 applications. The patches were removed after 24 hr contact (Tues, Thurs, Sat), and skin reactions evaluated 24 hr (Wed, Fri) or 48 hr (Mon) immediately prior to re-appliaction.

Challenge phase
Approx. 2 weeks after the final induction, a challenge patch was applied to a virgin site, adjacent to the induction site. This was removed after a 24 hr contact period, and reactions assessed immediately and again after 72 hr. Subjects responding at 72 hr were reassessed at 96 hr. (Note: challenge concentration is note stated.)

Scoring system
A six point scale was used to record skin responses during induction and challenge :
0 - no visible reaction
+ - barely perceptible or spotty erythema
1 - mild erythema covering most of the test site
2 - moderate erythema, possible presence of mild edema
3 - marker erythema, mild edema
4 - severe erythema, possible edema, vesiculation, bullae and/or ulceration

Statistics
No statistical methods were applied to the data.

Remark : With the exception of one hyper-responsive individual, skin responses during all stages of the study were considered within normal limits by the laboratory carrying out the investigation.

Result : General
One subject (no 18, panel 19990609) responded with varying degrees of erythema during the early stages of the study and induction was halted after the fourth application. This was considered to be an irritant hypersensitive reaction by the laboratory (based on a rapid onset plus other studies that subsequently demonstrated the individual's susceptability to other diols). This subject is excluded from the analysis presented below.

Induction
Thirteen subjects responded with barely perceptible or mild erythema (score + or 1) on one or more occasions during the nine induction treatments. One of these showed a moderate reaction (score 2) on one occasion.

Challenge
Skin reactions (barely perceptible to mild, score + to 1) were recorded in 3/103 subjects at the 72 hr time-point. One of these subjects showed a barely perceptible skin response (score +) at the 96 hr evaluation.

Source : A.K. Mallett Surrey

Conclusion : Under the conditions of the investigation, propylene glycol showed no potential to causes allergic contact sensitization.

Reliability : (1) valid without restriction
Non-guideline, GLP-compliant study, well described methods and results, large number of subjects.

Flag : Critical study for SIDS endpoint
29.05.2001 (10)

Type : Patch-Test
Species : human
Concentration : Induction 12 % occlusive epicutaneous
Challenge 12 % occlusive epicutaneous

Number of animals : 204
Vehicle : Petrolatum
Result : not sensitizing
Classification : not sensitizing
Method : other: modified Draize method
Year : 1973
GLP : no
Test substance : no data
Method : Only brief experimental details are available.

Subjects
The study was conducted using a panel of 204 male volunteers, age 21 - 50.

Induction
Propylene glycol (0.5 g of a 12% dilution in petrolatum) was applied to the lateral portion of the arm, covered with an

occlusive patch, and removed after 48 or 72 hr. Ten consecutive applications were administered to the same skin site. This was followed by a 2 week 'rest period' before challenge.

Challenge
The challenge patch was applied (not specified if the conditions were the same as described above), and skin reactions assessed after 72 hr.

Scoring system
A five point scale was used to assess responses during the challenge phase :
0 : no response
1 : erythema
2 : erythema and induration
3 : vesiculation
4 : bulla formation

Statistics
There was no statistical analysis of the data.

Result : None of the 204 subjects responded upon challenge.
Source : A.K. Mallett Surrey
Conclusion : Under the conditions of the investigation, propylene glycol showed no potential to cause allergic contact sensitization.
Reliability : (2) valid with restrictions
Non-guideline human volunteer study, with no information on GLP-compliance and only briefly described methods and results, benefits from inclusion of large number of subjects.
Flag : Critical study for SIDS endpoint
29.05.2001 (28)

5.4 REPEATED DOSE TOXICITY

Species : rat
Sex : male/female
Strain : other: Charles River, CD strain
Route of admin. : oral feed
Exposure period : 15 wk
Frequency of treatment : daily
Post obs. period : none
Doses : 50000 ppm
Control group : yes, concurrent vehicle
NOAEL : = 50000 ppm
LOAEL : > 50000 ppm
Method : other: because this study was conducted before any standardized guidelines were established, the question of guideline methodology and GLP conduct is not applicable.
Year : 1972
GLP : no
Test substance : other TS: British Pharmacopoeia grade
Method : Animals
15 male (bw 120 - 150g) and 15 female (bw 120 - 140g) rats

Hematology
Blood was collected (aorta) and analysed for Hb content, PCV

and counts of erythrocytes, reticulocytes and total and differential leucocytes.

Clinical chemistry
Serum was separated (aorta sample) and ASAT / ALAT activity and urea concentration determined.

Renal function
A urinary concentration test was conducted which included measurement of specific gravity, urine volume under different water loading conditions, a urinary cell count and glutamic-oxalacetic transaminase activity.

Terminal observations
The brain, heart, liver, spleen, kidneys, adrenals, gonads and pituitary were weighed at necropsy.

Statistical methods
Applied, but details not given.

Remark : Current guidelines indicate that the concentration of test substance should not exceed 5% of the diet to avoid any concerns about nutritional imbalances.

Result : Estimated received doses (mg/kg bw/day) were not provided.

There were no significant differences in serum and urinary parameters, hematological indices or organ weights between control animals and those fed a diet containing 50000 ppm propylene glycol.

No abnormalities were seen at necropsy.

Source : A.K. Mallett Surrey

Reliability : (1) valid without restriction
Non-guideline non-GLP study, with adequate and well described methods and detailed results.

Flag : Critical study for SIDS endpoint

29.05.2001 (15)

Species : rat
Sex : no data
Strain : no data
Route of admin. : drinking water
Exposure period : 140 days
Frequency of treatment : daily
Post obs. period : none
Doses : 1%, 2%, 5%, 10%, 25% and 50%
Control group : yes, concurrent vehicle
NOAEL : = 13200 mg/kg bw
LOAEL : > 13200 mg/kg bw
Method : other: because the study was conducted before any standardized guidelines were established, the question of guideline methodology and GLP conduct is not applicable.
Year : 1932
GLP : no
Test substance : no data
Method : Animals and treatments
Groups of rats (n=5, body weight approx 50g) were given free access to diet. One group was given water to drink (control), the others received an aqueous solution of 1%,

2%, 5%, 10%, 25% or 50% propylene glycol for up to 140 days.

Observations
Food and water consumption and body weight were recorded thrice weekly during the first month, and weekly thereafter.

Renal function
Urine was collected on day 141, centrifuged and examined microscopically (no further details available).

Terminal observations
Animals were killed and necropsied, and kidneys, heart, spleen and liver sampled and processed for histopathological examination using light microscopy (no further details available).

Statistical methods
None applied

Remark : No LOAEL can be derived directly from this study, since animals from the higher treatment groups died prematurely from dehydration and starvation (rather than as a consequence of toxicity linked to the test substance). No adverse effects were detected in the lower treatment groups, meaning that the LOAEL is >13200 mg/kg bw/day.

Result : General
All animals given 25% or 50% propylene glycol in water died within the first 9 days of treatment. Water consumption per animal was reported as less than 0.5 ml per day, and the authors conclude that starvation and dehydration were the cause of death. No mortality or unusual clinical signs were observed in any other treatment group.

Dose received
The amount of propylene glycol ingested by (decedent) animals from the two higher treatment groups was 3700 and 2220 mg/kg bw/day, respectively. The average daily intake reported for surviving animals was 13200, 7700, 3680 and 1600 mg/kg bw/day (for the 10%, 5%, 2% or 1% groups, respectively).

Food intake, water consumption and body weight
There were small variations in body weight between animals that survived to the end of the study, but no dose-related trend was apparent (data presented graphically in reference). Food intake for animals in the 1%, 2% and 5% groups was comparable to control, and slightly decreased in the 10% group throughout the study (data presented graphically in reference). The report contains no information on water consumption for these groups.

Renal function
There was no evidence of albuminuria, cells or casts in urine from animals given 1 - 10% propylene glycol for 20 weeks.

Histopathology
Microscopic examination of heart and spleen sections revealed no abnormality. Occasional vacuolization of epithelial cells, present in proximal convoluted tubules

from kidneys of both control and treated animals, was considered a normal event, unrelated to propylene glycol treatment, by the authors. Moderate centrilobular vacuolization occurred in both control and treated animals. Overall no macroscopic or microscopic abnormalities were reported that were linked to ingestion of propylene glycol by these animals.

Source : A.K. Mallett Surrey
Conclusion : There were no adverse or other findings in rats given propylene glycol in drinking water at dose levels equivalent to 13200 mg/kg bw/d over 140 days (NOAEL).
Reliability : (2) valid with restrictions
Non-guideline study, pre-GLP, some shortcomings in descriptive methodology and reporting of results, but generally acceptable.
Flag : Critical study for SIDS endpoint
29.05.2001 (40)

Species : rat
Sex : male/female
Strain : other: Charles River, CD strain
Route of admin. : oral feed
Exposure period : 104 wk
Frequency of treatment : Daily
Post obs. period : None
Doses : 6250, 12500, 25000 or 50000 ppm
Control group : yes, concurrent vehicle
NOAEL : = 50000 ppm
LOAEL : > 50000 ppm
Method : other: because the study was conducted before any standardized guidelines were established, the question of guideline methodology and GLP conduct is not applicable.
Year : 1972
GLP : no
Test substance : other TS: British Pharmacopoeia grade
Method : Animals
30 male (bw 120 - 150 g) and 30 female (bw 120 - 140 g) rats

General
Individual body weights were recorded at 2-wk intervals, with food intake measured over the preceding 24 hr.

Hematology
Blood was collected (tail vein) from 8 male and 8 female rats fed diets containing 0, 25000 or 50000 ppm propylene glycol at wk 13, 21, 52 and 80. Additional samples were collected from 6250 and 12500 ppm groups at wk 54. Samples were analysed for Hb content, PCV and counts of erythrocytes, and total and differential leucocytes. Reticulocyte counts were determined at wk 52, 54 and 80. Terminal observations (wk 104) were limited to Hb concentration and microscopic examination of a stained smear.

Renal function
A urinary concentration test was conducted on 6 - 10 rats from the control, 25000 and 50000 ppm groups. Measurements included specific gravity, urine volume under different

water loading conditions and a urinary cell count.

Terminal observations
Surviving animals were killed at wk 104 (exsanguination under barbiturate anesthesia) and subject to a full necropsy, including macroscopic observations and key organ weights. Samples of the following tissues were preserved for subsequent histopathological assessment : brain, heart, liver, spleen, kidneys, adrenals, gonads, stomach, small intestine, cecum, salivary gland, trachea, aorta, thymus, lymph nodes, pituitary, urinary bladder, colon, rectum, pancreas, uterus, muscle and any additional tissue that appeared abnormal.

Statistical methods
Applied, but details not given.

Remark : Current guidelines indicate that the concentration of test substance should not exceed 5% of the diet to avoid any concerns about nutritional imbalances.

Result : General
The appearance and behavior of the animals was unremarkable, with no treatment-related effect on survival.

Dose received
Mean daily intake of propylene glycol was calculated as 200, 400, 900 and 1700 mg/kg bw/day in males, and 300, 500, 1000 and 2100 mg/kg bw/day in females.

Food intake, body weight
There was no significant effect on food intake (data not presented) or bw gain, although there was an apparent dose-related trend toward lower bw in treated animals of both sexes (approx 10 - 12% reduction at wk 104 in the top dose).

Hematology
Parameters were comparable in treated and control rats.

Renal function
Results from renal function tests showed no significant differences in concentrating / diluting ability between treated and control animals. There was no treatment-related effect on urinary cell excretion.

Organ weights
Absolute and relative organ weights were similar in treated and control animals, with no statistically significant differences.

Histopathology
There was a wide range of histological abnormalities, particularly in kidney (nephropathy), liver (fatty change, portal lymphocyte infiltration, hepatocyte vacuolation, bile duct proliferation) and lung (chronic infection, pneumonia), although the incidence was similar in treated and control animals. These lesions were consistent with those generally seen in aging rats. [See 'Carcinogenicity' section for tumor details.]

Source : A.K. Mallett Surrey

Conclusion	:	No evidence of systemic toxicity was detected under the conditions of this study following chronic dietary administration up to 50000 ppm (approx 1700- 2100 mg/kg bw/day)to rats over two years.
Reliability	:	(1) valid without restriction Non-guideline non-GLP study, with adequate and well described methods and detailed results.
Flag	:	Critical study for SIDS endpoint

29.05.2001 (15)

Species	:	dog
Sex	:	male/female
Strain	:	Beagle
Route of admin.	:	oral feed
Exposure period	:	104 weeks
Frequency of treatment	:	daily
Post obs. period	:	none
Doses	:	2000 mg/kg bw/d (8% in diet), 5000 mg/kg bw/day (20% in diet)
Control group	:	other: diet plus isocaloric controls (dextrose)
NOAEL	:	= 2000 mg/kg bw
LOAEL	:	= 5000 mg/kg bw
Method	:	other: because this study was conducted before any standardized guidelines were established, the question of guideline methodology and GLP conduct is not applicable.
Year	:	1971
GLP	:	no
Test substance	:	other TS: met Food Chemicals Codex- and United States Pharmacopoeia XVII specifications.
Method	:	Animals and treatments There were five male and five female beagle dogs, age 10-14 months at start of treatment, per treatment group. They were fed diets designed to deliver 0, 2000 or 5000 mg propylene glycol /kg bw/day. A second series of animals was given an isocaloric amount of dextrose mixed with food (2540 and 6350 mg/kg bw/day) and served as another set of controls. Formulation of diets The caloric value of propylene glycol and dextrose was determined from preliminary feeding studies in rats. Based on this information, the dietary concentration of each was adjusted weekly to approximate the required dose, taking into account the animals' mean body weight and mean food intake. Overall, animals from the high dose group received diet containing approx 20% propylene glycol or approx 25% dextrose. Animals from the low dose group received approx 8% propylene glycol or 10% dextrose admixed with diet. A commercially-available dry dog food, with liver added as a taste-masking agent, was used a the base. General Body weights were determined weekly. Food consumption was also monitored to assist in formulating the diets. (The frequency of these determinations is not stated.) Hematology Total erythrocyte count, total and differential leukocyte count, hemoglobin, hematocrit and erythrocyte fragility (initial and complete hemolysis) were determined after 6, 12

and 23 months on test.

Clinical chemistry
Serum alkaline phosphatase, total bilirubin, bromosulphthalein retention (5 mg/kg, 15 minutes post-dosing), blood glucose concentration, blood propylene glycol concentration, serum glutamic-oxalacetic and glutamic-pyruvic transaminase activities and blood urea nitrogen were assessed at months 6, 12 and 23.

Renal function
Urine volume, specific gravity, pH and microscopic contents were determined after 6, 12 and 23 months on test (no further details given).

Other observations
During the final month of the study, or when the dogs were sacrificed, anisocytosis and poikilocytosis, nucleated-erythrocyte count, reticulocyte count, direct and indirect bilirubin estimations, liver glycogen, metabolic rate of liver slices, total liver lipids, liver triglycerides and water content of liver were determined.

Terminal observations
Liver, kidney and spleen weights were determined at necropsy. A range on internal organs (liver, kidney, lung, heart, diaphragm, spleen, adrenals, thyroid, parathyroid, salivary and maxillary glands, tongue, lymph nodes, gall bladder, oesophagus, stomach, duodenum, pancreas, ileum, jejunum, colon, urinary bladder, testicle, epididymis, prostate, uterus, ovary, skin, eye, brain, pituitary, bone marrow) were subject to macroscopic and microscopic examination.

Statistical methods
Bartlett's test for homogeneity of variance was applied to all samples. The Duncan multiple range test was subsequently applied to homogeneous samples, and Student's t test or the Cochran t test applied to heterogeneous data. The frequency of occurrence of abnormalities was inter-compared by use of 2x2 contingency tables. Non-parametric tests for comparison of sum of ranks were used as appropriate.

Remark : Current guidelines indicate that the concentration of test substance should not exceed 5% of the diet to avoid any concerns about nutritional imbalances.
Dogs given 5000 mg/kg/day propylene glycol (approx. 20% w/w in diet) showed red cell effects (ie hemoglobin, hematocrit and total erythrocyte were lowered slightly, while anisocytosis, poikilocytes and reticulocytes were increased) which were not present in animals given an equicaloric control diet. These changes were indicative of erythrocyte destruction and replacement from bone marrow, although the magnitude and severity of the effect was mild and not associated with any irreversible damage to bone marrow, spleen or any other internal organ or tissue.

Result : General
Findings from animals given dextrose (equicaloric controls) will be discussed only when they are pertinent to interpretation of findings from the propylene glycol groups.

Mortality
One female from the low dextrose group, and one male from the low propylene glycol group, died during weeks 81-85 (ventricular thrombosis and suppurative endocarditis, respectively). There were no deaths in either of the high treatment groups, and these findings were considered co-incidental by the authors.

Body weight, food consumption and water intake
Body weight data and median food consumption did not differ between propylene glycol-treated and control dogs. Mean feed utilization during the first six months of the study was greatest in dogs given 5000 mg propylene glycol/kg/day relative to the low dose and control groups, reflecting the relatively higher caloric content of their rations. Water consumption during the first year was generally lower in animals given propylene glycol relative to controls, but this was not statistically significant.

Hematology
There were no changes in differential leucocyte counts or erythrocyte fragility that were related to chronic ingestion of propylene glycol. Total erythrocyte count, as well as hemoglobin and hematocrit values, were decreased non-significantly in the high dose propylene glycol group after 6 and 12 months treatment, and decreased significantly at the end of the study. Mean reticulocyte count was also significantly decreased at 23 months, while the percentage of nucleated erythrocytes and the degree on anisocytosis and poikilocytosis was greater at the end of the study (sum of ranks). These changes were generally more pronounced in females relative to males. Values from the high dose dextrose group were comparable to controls. Parameters from dogs receiving the equivalent of 2000 mg/kg/day were unaffected by treatment.

Renal function
Urine output was increased intermittently, but inconsistently, in high dose animals, with females affected at months 6 and 12 and males at month 23. Urinary pH was similar to control values, and microscopic examination revealed no abnormal debris.

Clinical chemistry
Serum alkaline phosphatase, bromosulphthalein retention, serum glutamic-oxalacetic and glutamic-pyruvic transminase and blood glucose were comparable in both sexes given propylene glycol and the equicaloric- and diet controls. Total bilirubin was non-significantly increased in high dose males at 6 and 24 months, and significantly increased in high dose females throughout the study. Other parameters were comparable between the groups.

Other findings
The concentration of propylene glycol in serum increased in a dose-related manner, reaching approx. 0.1% v/v (0.2% v/v max.) in animals given 5000 mg/kg/day. Changes in other parameters were generally minor in nature or were

inconsistent between the sexes at the various time-points.

Organ weights and necropsy findings
Kidney and liver weights were comparable to control values at the end of the study. (Spleen weights were not specifically mentioned in the report, and are also presumed to have been unchanged.)

Histopathology
Apart from a slight increase in bone marrow activity in female dogs from the high dose group, histopathological lesions occurred with comparable severity and incidence in the treated, control and equicaloric control groups. The change in bone marrow activity was considered a physiological, rather than a toxicological, response by the study pathologist. Overall, there were no adverse, treatment-related histopathological changes linked to chronic ingestion of propylene glycol.

Source : A.K. Mallett Surrey

Conclusion : The authors conclude that propylene glycol is readily utilized as an energy source, and that no adverse effects were apparent in dogs fed approx. 8% in diet for two years. This was equivalent to a NOAEL of 2000 mg/kg/day over two years. The LOAEL (red cell effects) was 5000 mg/kg/day.

Reliability : (1) valid without restriction
Non-guideline non-GLP study, with adequate and well described methods and detailed results.

Flag : Critical study for SIDS endpoint

29.05.2001 (47)

Species : cat
Sex : male
Strain : no data
Route of admin. : oral feed
Exposure period : 69 - 94 days
Frequency of treatment : daily
Post obs. period : none
Doses : 80, 443, 675, 1763, 4239 mg/kg/d
Contrd group : yes, concurrent vehicle
NOAEL : = 80 mg/kg bw
LOAEL : = 443 mg/kg bw
Method : other: investigative study, predates glp
Year : 1979
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Method : Animals and treatments
This investigation proceeded in two phases. In phase 1 groups of two male cats were fed commercial diet with added propylene glycol designed to deliver 500 or 5000 mg/kg bw/day. In phase 2, groups of two males were fed diets designed to deliver 100 or 1000 mg/kg bw/day. The phase 2 investigation also included 2 cats fed a standard domestic cat diet containing approx 7% propylene glycol as humectant. Water was available ad libitum.

Diet preparation
A pre-determined amount of test substance was mixed directly with 125 g of diet, this being an amount which the animals

were expected to consume within 1 hr. The amount of propylene glycol actually consumed by the animals was calculated based on the amount of diet eaten. Additional (unsupplemented) food was made available as necessary.

Observations
The cats were observed daily for demeanour and clinical signs. Body weights were recorded twice weekly, and used to calculate the amount of propylene glycol to be added to the test diets.

Clinical chemistry
Serum urea nitrogen concentration, alkaline phosphatase, glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, total bilirubin and glucose were determined on blood collected from the jugular vein on 3 occasions before treatment commenced and on 4 - 10 occasions during the study.

Hematology
Packed cell volume, red cell counts, total and differential white blood cell count, hemoglobin concentration, methemoglobin concentration, reticulocyte count, Heinz body count and osmotic fragility were determined on 2 or 3 occasions before treatment commenced and on 5 - 11 occasions during the study.

Urinanalysis
A sample of urine was aspirated from the bladder at necropsy, and examined for specific gravity, pH, glucose, protein, ketones, bilirubin, occult blood and urobilinogen.

Necropsy and histopathological procedures
Animals were fasted overnight and sacrificed by exsanguination following barbiturate anesthesia. A gross pathological examination was performed on the eyes and internal organs. Liver, kidney, heart, brain and testes weights were determined. A comprehensive range of organs, along with any tissue which appeared abnormal, were sampled and processed (H&E staining) for subsequent microscopic evaluation. In addition liver, spleen and vertebral bone with bone marrow were stained with Prussian blue stain (to demonstrate iron), while liver sections were also stained with Periodic Acid Schiff reagent (glycogen). A total of 10 tissues were subject to histopathological examination .

Electron microscopy
Fixed peripheral erythrocytes and sections of liver were stained with toluidine blue (thick sections) or uranyl acetate and lead citrate (thin sections) from one animal from the control and each of the treatment groups.

Statistics
Differences between the groups in final body weight and absolute and relative organ weight values were evaluated using one-way analysis of variance, with differences between the treated and control groups examined using Dunnett's test. No statistical analysis was performed on the other data due to the small group sizes.

Remark : Heinz body formation was the key finding in this investigation. This occurred with no evidence of accompanying hemolytic anemia such as that commonly reported in cats and other species following treatment with aromatic amino or nitro compounds. This indicates a differential mechanism of action for propylene glycol. With the exception of increased hemosiderin deposits in liver and spleen (secondary to Heinz body formation), no other treatment-related systemic toxicity was seen in cats at treatment levels up to 4239 mg/kg bw/d for 94 days.

Result : General
Results from the two investigations have been combined in this summary for ease of presentation and interpretation.

The amount of food consumed by the cats was slightly lower than anticipated, leading to average achieved treatment levels of 80, 443, 675 and 4239 mg/kg bw/day. Animals fed the domestic diet received a calculated average daily dose of 1763 mg/kg bw/day.

There were no adverse changes in demeanour or clinical signs, body weight gain or clinical chemistry parameters in any of the treatment groups.

Pathology
No abnormalities of the eyes or internal organs were reported. Organ weight determinations showed a large degree of variability, presumably reflecting the small group sizes used. Spleen and testis weights were particularly affected but since there was no apparent dose-related trend, and since similar variability was present in the controls, these findings were considered unrelated to propylene glycol treatment.

Histopathology
Treatment-related changes consisted of a slight increase in the amount of hemosiderin in individual Kupffer cells of the liver and in reticuloendothelial cells from the higher treatment groups, particularly those animals given 5000 mg/kg/d. With the exception of hemosiderin deposition, no other treatment-related abnormalities were present in liver from any animals given propylene glycol.

Examination of testis tissue revealed increased numbers of multinucleated giant cells in seminiferous tubules from one of the two animals given 100, 500 and 5000 mg/kg/day or the domestic diet, but not in animals given 1000 mg/kg/d. In one animal from the 5000 mg/kg/d group the testes were hypoplastic. These findings were considered by the investigators to reflect differences in sexual development between the animals rather than any treatment-specific effect.

There were no treatment-related microscopic observations in any of the other tissues examined in this study.

Electron microscopy
The ultrastructural appearance of Heinz bodies from cats given propylene glycol were essentially as expected, and did

not suggest any unusual etiology. Ultrastructural changes in Kupffer cells were consistent with increased hemosiderin deposition. Electron microscopy confirmed an absence of any other changes in the liver of treated animals.

Hematological parameters

General hematology
PCV, RBC, HgB, WBC and differential WBC data showed a large degree of variation during the pretest- and test periods in both the control and treated animals. Against this background, there was no evidence of any propylene glycol-related adverse effects.

Heinz bodies
In contrast to other blood parameters, Heinz body determinations demonstrated a clear response to propylene glycol treatment. The incidence of Heinz bodies increased in cats from the 5000 mg/kg/d after 4 days treatment, and remained elevated until the end of the study. The average incidence in this group was 32% versus a pre-test and control incidence that was generally below 1%. Mean Heinz body incidence in cats fed the commercially-prepared diet (equivalent to ingestion of 1763 mg propylene glycol / kg bw / day) was 13 - 20%.

In cats from the 1000 and 500 mg/kg/d groups the Heinz bodies were smaller in size than observed in the 5000 mg/kg/d group, and were present at an average incidence of 2.5 - 6.4% and 1.5 - 3.5%, respectively. Heinz body appearance, size and incidence (0.4 - 0.7%) in the 100 mg/kg/d group were essentially indistinguishable from the controls or the pre-test values.

Reticulocytes
Detailed examination, and re-examination, of reticulocyte count data for cats ingesting propylene glycol did not reveal a consistent treatment-related increase in the incidence of either punctate or aggregate forms. (Note : an increase in these forms (indicative of an erythrocytic regenerative response) was anticipated by the investigators.)

Methemoglobin
Comparison of control, pre-test and test results indicated there was no induction of methemoglobinaemia in cats consuming propylene glycol.

Osmotic fragility
Red cell osmotic fragility data showed a large degree of variation during the pretest- and test periods in both the control and treated animals. Against this background, there was no evidence of any propylene glycol-related adverse effect.

Source : A.K. Mallett Surrey

Conclusion : Under the conditions of this investigation in cats, the NOAEL for Heinz body formation and associated hemosiderin deposition in liver and spleen was 80 mg/kg bw/d. The NOAEL for other systemic effects was > 4239 mg/kg bw/d.

Reliability	:	(1) valid without restriction Non-guideline non-GLP investigative study, with adequate and well described methods and detailed results.
Flag	:	Critical study for SIDS endpoint
29.05.2001		(38)
Species	:	cat
Sex	:	male/female
Strain	:	
Route of admin.	:	
Exposure period	:	117 days
Frequency of treatment	:	daily
Post obs. period	:	none
Doses	:	6% or 12% in diet (equivalent to 3780 or 10140 mg/cat/d)
Control group	:	yes, concurrent vehicle
NOAEL	:	< 6 %
LOAEL	:	= 6 %
Method	:	other: investigative study
Year	:	1995
GLP	:	no data
Test substance	:	no data
Method	:	Animals and treatments Twenty-one adult cats (7 male, 14 female, bw 2.3-5.1 kg) were acclimatised for two weeks during which time they were fed a standard commercial diet. They were then transferred to an experimental control diet for 30 days (see below), after which they randomly allocated to 3 treatment groups. They were then fed fed diets containing 0%, 6% or 12% propylene glycol for 117 days. Diet preparation The control diet was prepared by mixing 100 parts commercial dried cat food with 25 parts canned commercial cat food and 25 parts water. The test diets were prepared by substituting propylene glycol for an equal volume of water. The concentration and distribution of test article in the diets was analysed by an independent laboratory (method not stated). Observations Food consumption was recorded daily, and body weight weekly. Hematology Blood samples were collected at the start of the test period and every two weeks thereafter. They were collected at the same time each day, but the method used is not stated. PCV, Hb concentration, total WBC, total RBC, mean cell volume, mean cell (MCH), mean cell hemoglobin concentration (MCHC) and RBC distribution width were measured electronically (Coulter S+IV). A differential white cell count (Wright stain), enumeration of punctate and aggregate reticulocytes (methylene blue) and Heinz body count (brilliant cresyl green) were performed microscopically. Bone marrow aspirates were prepared at the end of the study (day 117) and differential counts performed (Wright stain) and myeloid-to-erythroid ratios calculated. Erythrocyte survival

Erythrocyte survival was determined by following the disappearance of 14C -labelled red cells (prepared after incubation of heparinised blood with 14C-cyanate in vitro) from the circulation. Blood was sampled on three consecutive days post-injection with labelled cells, then twice weekly until radioactivity returned to background levels. Radioactivity was determined using liquid scintillation counting.

Necropsy and histopathological procedures
All animals were subject to macroscopic examination of the major internal organs, and tissue samples preserved. Histologic sections were prepared from liver, spleen, bone marrow and any grossly abnormal tissue and exam ined by light microscopy.

Statistics
Differences between control and treated groups was analysed by analysis of variance.

Remark : Current guidelines indicate that the concentration of test substance should not exceed 5% of the diet to avoid any concerns about nutritional imbalances.

Result : Good mixing and distribution of propylene glycol in the diets was achieved, although quantitive results are not reported. There were no significant differences in body weight or food consumption between the groups. Calculated intakes of propylene glycol were 10140 and 3780 mg/cat/d for the 12% and 6% treatment groups, respectively. (Note: based on the body weight range information given in the methods section, this was equivalent to 1900 - 4400 mg/kg bw/day for the high dose group, and 741 - 1600 mg/kg bw/day for the low dose group.)

Only slight non-significant differences in PCV, Hb concentration and RBC counts were noted when individual results for control and treated animals were compared. However, over 117 days of the study, there was a significant 11-13% decrease in red cell counts in treated animals, although this was not clearly dose-related.

Increases in MCV, MCH and MCHC were noted after propylene glycol treatment (significant only in the 12% group), but RBC width was unaffected by treatment.

Initial reticulocyte counts were similar between the groups, but the proportion of punctate forms increased significantly from week 2 in treated animals. Leucocyte counts (total and differential) showed no treatment-related differences.

Heinz body counts were significantly increased in a dose-related manner from two weeks after the start of treatment, and then remained elevated throughout. (By inspection of graphical data presented in the report, it appears values were roughly 3%, 15-25% or 30-45% in the control, 6% or 12% groups, respectively.) Mean erythrocyte survival decreased in the treated animals, from 63.9 d in controls to 44.6 d or 28.7 d in the 6% or 12% groups, respectively.

There was no significant difference in myeloid-to-erythroid ratio or bone marrow cellularity.

At necropsy cats given propylene glycol were found to have grossly nodular spleens (both treatment groups) and mottled livers (12% group only). Microscopic examination revealed enlarged germinal centers in spleen and prominent periportal glycogen deposition in liver.

Source : A.K. Mallett Surrey
Conclusion : Treatment-related increases in Heinz body formation, and decreased mean red cell survival, were the key findings from this study, with a LOAEL of 3780 mg/cat/d. This is equivalent to 741 - 1600 mg/kg bw/day.
Reliability : (1) valid without restriction
Non-guideline non-GLP investigative study, with adequate and well described methods and detailed results.

29.05.2001 (1)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : Salmonella typhimurium TA92, TA94, TA98, TA100, TA1535, TA1537
Concentration : up to 10 mg/plate (concentration range not specified)
Cycotoxic conc. : >10 mg/plate
Metabolic activation : with
Result : negative
Method : other: liquid pre-incubation assay
Year : 1984
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Method : The reaction mixture contained a NADPH-regenerating system, S-9 fraction and tester strain, which were incubated with the test substance (DMSO vehicle) for 20 min at 37 degrees C before plating. Duplicate plates were prepared for each of six (unspecified) concentrations of test substance. The S-9 fraction (also described as a microsomal fraction in the paper) was isolated from the livers of Fischer rats pretreated for 5 days with Kanechlor KC-400 (a PCB, 500 mg/kg in olive oil). The result was considered positive if the number of revertant colonies was double that of the solvent control. No statistical methods were described. Although no positive control substances were included, positive results were obtained with several of the other chemicals included in these investigations.
Result : No increase in revertants was recorded for any of the strains exposed to propylene glycol. Of the other substances tested, 14 gave a positive result in at least one tester strain, validating the responsiveness of the assay.
Source : A.K. Mallett Surrey
Conclusion : Propylene glycol was not mutagenic in Salmonella typhimurium TA92, TA94, TA98, TA100, TA1535 and TA 1537, in the presence of an S-9 fraction, under the conditions of this test.
Reliability : (2) valid with restrictions
Near-guideline study, pre-GLP, methods and results only briefly described but generally acceptable.
Flag : Critical study for SIDS endpoint
24.05.2001 (17)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA98, TA100, TA1535, TA1537
Concentration	:	5 - 300 umol / plate (intermediate concentrations not specified)
Cycotoxic conc.	:	not reported
Metabolic activation	:	without
Result	:	negative
Method	:	other: because this study was conducted before any standardized guidelines were established, the question of guidance methodology and GLP conduct is not applicable.
Year	:	1980
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Only brief details are reported. The direct mutagenic activity of propylene glycol (diluted in sterile distilled water) was assessed using a plate incorporation technique (5 - 300 umol / plate). B-propiolactone and benzopyrene oxide were included as positive controls, and the study also included ethylene oxide and propylene oxide as test substances. Experiments were performed in duplicate, and repeated 6 - 8 times.
Result	:	No increase in revertants was recorded for any of the strains exposed to propylene glycol. An apparently satisfactory response was obtained with the positive control substances. Propylene oxide and ethylene oxide gave a clear, dose-related increase in revertant numbers in TA100 and TA1535, but not in TA98 or TA1537.
Source	:	A.K. Mallett Surrey
Conclusion	:	Propylene glycol was not a direct acting mutagen in Salmonella typhimurium TA98, TA100, TA1535 and TA 1537 under the conditions of this test.
Reliability	:	(2) valid with restrictions Near-guideline study, pre-GLP, methods and results only briefly described but generally acceptable.
Flag	:	Critical study for SIDS endpoint
24.05.2001		(35)

Type	:	Chromosomal aberration test
System of testing	:	human lymphocytes in vitro
Concentration	:	476, 1910, 3810 ug/ml (6.25, 25, 50 mM)
Cycotoxic conc.	:	> 3810 ug/ml
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 473 "Genetic Toxicology: In vitro Mammalian Cytogenetic Test"
Year	:	1990
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Test system Cultured human lymphocytes, stimulated to divide with phytohaemagglutin, were exposed to propylene glycol diluted in sterile distilled water. The test was conducted tw ice, in the presence and absence of a post-mitochondrial fraction from Arochlor 1254-treated SD rats, using a range of test concentrations (7.4 - 3810 ug/ml in the first study, 476 - 3810 ug/ml in the second). Cultures were harvested at 22 hr and 40 hr after treatment, treated with colchicine, and smears prepared for staining (Giemsa) and microscopic examination. Approx. 100 metaphase figures from control,

positive control, and treated cultures were examined.

Positive control substances
Ethylmethane sulphonate (1000 ug/ml) and mitomycin C (0.1 and 0.2 ug/ml) were used as positive control substances in the absence of metabolic activation, and cyclophosphamide (5 - 20 ug/ml) in the presence of S9.

Result : Cytotoxicity
Mitotic indices of all treated cultures, both in the absence and presence of S9, were similar to controls.

Metaphase analysis
Cultures exposed to 476, 1910 and 3810 ug/ml propylene glycol were examined in both studies. No statistically significant increase in the proportion of metaphase figures showing chromosomal aberrations was detected, with the exception of the lowest treatment, in the presence of S9, at the 42 hr harvest in the second study. However, since the value lay within the historical control range and there was no dose-response, it was not considered indicative of a clastogenic response by the laboratory.

Positive controls
All positive control substances resulted in large, highly significant increases in chromosomal damage, confirming the sensitivity of the test system and efficacy of the S9 mix.

Source : A.K. Mallett Surrey
Conclusion : Propylene glycol at concentrations up to 3810 ug/ml (50 mM) showed no evidence of clastogenic activity in human lymphocytes in vitro, under the conditions of this test.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
23.05.2001 (13)

Type : Chromosomal aberration test
System of testing : Chinese hamster fibroblasts (CHL line) in vitro
Concentration : up to 32 mg/ml
Cycotoxic conc. : 32 mg/ml
Metabolic activation : without
Result : ambiguous
Method : other: see methods
Year : 1984
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Method : Test system
Cultured CHL fibroblasts were exposed to three concentrations of propylene glycol (up to 32 mg/ml, lower concentrations not specified) for 24 hr and 48 hr. The highest concentration used was designed to give a 50% reduction in cell growth (based on a pilot study). No external metabolic activation was present in the incubations. Colcemid was added to the incubations 2 hr before the cells were harvested. Smears were prepared on clean glass slides, fixed and stained with Giemsa prior to evaluation. One hundred well-spread metaphases were observed using light microscopy (x600). The incidence of polyploid cells, as well as cells with structural aberrations such as chromatid or chromosome gaps, breaks, exchanges, ring formations, fragmentations etc was recorded. Untreated- and

solvent (saline) treated cells served as negative controls.

Evaluation of results
The results were considered negative if the incidence of aberrations was less than 3.0%. For a quantative evaluation of clastogenic potential, the dose (mg/ml) which induced structural aberrations in 20% of metaphase fields was calculated (defined as D20). No statistical methods were described in this study.

Remark : The apparent clastogenic effect reported in this study at 32 mg/ml appears unreliable. Current testing guidelines recommend that a maximum concentration of no greater than 10 mM is used in mammalian cell assays in order to avoid potentially confounding osmotic effects. The concentration associated with increased chromosomal aberrations in this study was 420 mM, suggesting this result is discounted on technical grounds. Since no information is presented on the other exposure concentrations used in this study, its overall value for hazard identification purposes appears limited.

Result : Thirty eight percent of cells exposed to 32 mg/ml propylene glycol for 48 hr showed structural aberrations, but no increase was seen in any of the other concentration/time combinations. The authors considered this to represent a positive effect at this concentration. The D20 was calculated as 22.3 mg/ml (approx. 300 mM).

Source : A.K. Mallett Surrey

Reliability : (3) invalid
Non-guideline pre-GLP study with poor design that is incompatible with current standards.

Flag : Critical study for SIDS endpoint

24.05.2001 (17)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Cytogenetic assay
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : 6hr, 24hr, 48 hr
Doses : 30, 2500 or 5000 mg/kg
Result : negative
Method : other: because this study was conducted before any standardized guidelines were established, the question of guidance methodology and GLP conduct is not applicable.
Year : 1974
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Method : Animals and treatments
Groups of 15 male SD rats, age 10-12 wk, were given 30, 2500 and 5000 mg/kg propylene glycol by gastric intubation (dosing volume not specified). Groups of 5 animals were sacrificed 6, 24 and 48 hours post-treatment (carbon dioxide), and bone marrow smears prepared as described below. Saline was used as vehicle and also as the negative control (3 rats per time-point). Triethylene melamine (0.3 mg/kg, ip) was used as positive controls (5 rats at 48 hours

post-treatment only).

Preparation and examination of bone marrow smears
Colcemid (4 mg/kg ip) was administered to each animal 2 hr prior to sacrifice. Bone marrow was removed from one femur, cells isolated by centrifugation, fixed with absolute methanol:glacial acetic acid (3:1) and Giemsa-stained smears prepared for subsequent microscopic evaluation. Fifty metaphase spreads from each animal were examined under oil immersion (x40, x63 or x100) and scored for chromatid gaps and breaks, chromosome gaps and breaks, reunions, cells with greater than 10 aberrations, polyploidy, pulverization and any other chromosomal abnormality. Mitotic indices were obtained by counting at least 500 cells, and the ratio of the number of cells in mitosis to the total number of cells observed was expressed as the mitotic index.

Statistical analysis
No statistical analysis was apparently applied to the results of this study.

Result : The mitotic indices for the treated animals (4 - 8%) were lower than those of the negative controls (9- 12%) but this difference did not appear biologically significant. The three treatment groups were within the historical range of negative controls with respect to breaks (0-6%). One dicentric chromosome was noted 24 hr post-treatment with 5000 mg/kg propylene glycol, but this was considered a random event since this type of damage was also observed in the vehicle controls. Furthermore, there was no evidence of chromosomal reunion at the other time-points in this or the lower treatment groups. No other aberrations were present in the treated or vehicle control groups. The positive control group contained 36% cells with aberrations, including severe chromosomal damage (>10 aberrations / cell), breaks and reunions.
Source : A.K. Mallett Surrey
Conclusion : Propylene glycol produced no detectable aberrations in metaphase chromosomes from bone marrow when administered orally to rats as a single treatment at doses up to 5000 mg/kg.
Reliability : (1) valid without restriction
Near-guideline study, pre-GLP, well described methods and detailed results, generally acceptable overall.
Flag : Critical study for SIDS endpoint
24.05.2001 (26)

Type : Cytogenetic assay
Species : rat
Sex :
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : daily treatment on 5 consecutive days
Doses : 30, 2500 or 5000 mg/kg
Result : negative
Method : other: because this study was conducted before any standardized guidelines were established, the question of guidance methodology and GLP conduct is not applicable.
Year : 1974
GLP : no

Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Animals and treatments Groups of 5 male SD rats, age 10-12 wk, were given 30, 2500 and 5000 mg/kg propylene glycol by gastric intubation (dosing volume not specified) on five consecutive days. Six hours after the final dose, the animals were sacrificed by carbon dioxide asphyxiation and bone marrow smears prepared as described below. Saline was used as vehicle and also as the negative control (n = 3 rats). Preparation and examination of bone marrow smears Colcemid (4 mg/kg ip) was administered to each animal 2 hr prior to sacrifice. Bone marrow was rem oved from one femur, cells isolated by centrifugation, fixed with absolute methanol:glacial acetic acid (3:1) and Giemsa-stained smears prepared for subsequent microscopic evaluation. Fifty metaphase spreads from each animal were examined under oil immersion (x40, x63 or x100) and scored for chromatid gaps and breaks, chromosome gaps and breaks, reunions, cells with greater than 10 aberrations, polyploidy, pulverization and any other chromosomal abnormality. Mitotic indices were obtained by counting at least 500 cells, and the ratio of the number of cells in mitosis to the total number of cells observed was expressed as the mitotic index. Statistical analysis No statistical analysis was apparently applied to the results of this study.
Result	:	Mitotic indices for the treated animals (6- 7%) were slightly lower than those of the negative controls (8%) but the difference did not appear to be biologically significant. The negative controls contained 2% of cells with breaks versus 2-3% after administration of propylene glycol. There were no reunions or other aberrations noted in any of the treated animals. Overall there was no difference between control and treated animals in the proportion of cells with aberrations (2-3%).
Source	:	A.K. Mallett Surrey
Conclusion	:	Propylene glycol produced no detectable chromosomal aberrations in bone marrow following repeated oral administration to rats on five consecutive days at doses up to 5000 mg/kg.
Reliability	:	(1) valid without restriction Near-guideline study, pre-GLP, well described methods and detailed results, generally acceptable overall.
Flag	:	Critical study for SIDS endpoint

24.05.2001 (26)

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	male
Strain	:	other: ddY
Route of admin.	:	i.p.
Exposure period	:	18 hr
Doses	:	2500, 5000, 10000 and 15000 mg/kg
Result	:	negative
Method	:	other: no regulatory guideline given
Year	:	1988
GLP	:	no data

Test substance : as prescribed by 1.1 - 1.4

Method : Animals and treatments
Eight week old male ddY mice were used in these investigations. The dose levels were based on published LD50 data.

Preparation and examination of bone marrow smears
Mice were killed by cervical dislocation 18 hr after injection with propylene glycol. Femoral marrow cells were isolated, smeared onto clean glass slides, fixed with methanol and stained with Giemsa. The preparations were coded and analysed blind. One thousand polychromatic erythrocytes (PCEs) per mouse were examined using light microscopy (x100), and the number of micronucleated polychromatic erythrocytes (MNPCEs) was recorded. The proportion of PCEs among the total erythrocytes was also evaluated by observation of 1000 erythrocytes on the same slide.

Positive control substance
No specific positive control substance was included in these tests (but see results).

Statistical analysis
The frequency of MNPCEs in each treatment was compared with the binomial distribution of historical control data. A result was considered positive if the increase in MNPCEs differed from the spontaneous data at $P<0.01$. Any dose-response relationship was tested using the Cochran-Armitage trend test, with $P<0.05$ indicating a positive result.

Result : Three of six mice from the top dose group died during the course of the study. There was no statistically significant increase or trend in MNPCE numbers following ip administration of propylene glycol at doses up to and including 15000 mg/kg. The percentage of PCEs in the top dose group appeared decreased relative to controls (31% versus 54%) suggesting that the test substance had reached the bone marrow. Significant, dose-related increases in MNPCEs were obtained with 5 of 39 chemicals included in these investigations indicating that the test system was capable of detecting a positive response.

Source : A.K. Mallett Surrey

Conclusion : Propylene glycol produced no detectable increase in micronucleated polychromatic erythrocytes when administered by ip injection to mice at doses up to 15000 mg/kg.

Reliability : (2) valid with restrictions
Near-guideline study, no information on GLP status, briefly described methods and results, generally acceptable overall.

Flag : Critical study for SIDS endpoint
24.05.2001 (16)

Type : Dominant lethal assay
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : single dose
Doses : 30, 2500 or 5000 mg/kg

Result : negative
Method : other: because this study was conducted before any standardized guidelines were established, the question of guidance methodology and GLP conduct is not applicable.
Year : 1974
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Method : Animals and treatments
Groups of 10 male SD rats, age 10-12 wk, were given a single treatment of 30, 2500 or 5000 mg/kg propylene glycol by gastric intubation (dosing volume not specified). Each male was subsequently mated with 2 virgin females (age 10 - 12wk) for 5 days (Monday to Friday) on 8 occasions over an 8 wk period. The females were sacrificed (carbon dioxide) 14 d after separating from the males, and the uterine contents examined for corpora lutea, early deaths, late fetal deaths and total implantations. Saline and triethylene melamine were used as negative and positive controls respectively (dose not specified).

Statistical analysis
In addition to comparing each treatment with the concurrent vehicle control, the results were also analysed relative to historical control data in order to clarify the toxicological significance of any effects that were recorded. The following methods were applied :
Fertility index : Chi-square; Armitage trend test
Implantations : T-test; Regression analysis
Corpora lutea : T-test
Preimplantation loss, dead implants : T-test on Freeman-Tukey (arc-sine) transformed data; regression analysis
One or more dead implants : Chi-square; Armitage trend test; probit regression
Dead implants per total implants : T-test on Freeman-Tukey (arc-sine) transformed data
Result : Fertility index
A number of dose levels showed increased fertility compared to the negative control.

Average number of implantations per pregnant female
There were several isolated decreases in average number of implantations but these were minor with no dose-response relationship.

Average corpora lutea per pregnant female
There was a significant decrease in numbers of corpora lutea in the mid- and high dose groups at wk 1 and wk 5, and in all treatments at wk 4 and wk 7. This appeared related to unusually high control values (which were significantly different from the historic controls) rather than any substance-related effect.

Average pre-implantation losses per pregnant female
With the exception of results for the high dose group at wk 2, there was no indication of any substantial, treatment-related effect on pre-implantation losses.

Average dead implantations per female

A significant increase in the number of dead implants was apparent in the low - and intermediate groups, but not the high dose group, at wk 3. This appeared to reflect an unusually low control value (which was significantly different from the historic controls) rather than any treatment-related effect.

Females with one or more dead implants
This analysis indicated that dead implants were more common in the mid-dose groups than in the low- and high-dose groups.

Dead implants per total implants
An increase in dead implants per total implants was apparent when results were compared to the concurrent, but not the historic, controls. This appeared related to a 0% incidence in the negative controls (significantly lower than historic controls) rather than a substance-related effect.

Positive control group
Triethylene melamine treatment lead to a significant decrease in fertility index and number of corpora lutea, and significantly increased preimplantation losses and the number of dead implantations. It also resulted in a major increase in the number of resorptions and the ratio of dead implants to total implants.

Final evaluation
Results for the positive control group demonstrated that the study was capable of detecting dominant lethal events. The apparent effects noted in propylene glycol treated animals at some time-points in the investigation appeared a consequence of unrepresentative concurrent control data rather than any substance-specific effect.

Source : A.K. Mallett Surrey
Conclusion : Propylene glycol produced no increase in dominant lethal (heritable) mutations in male rats following oral administration at doses up to 5000 mg/kg.
Reliability : (1) valid without restriction
Near-guideline study, pre-GLP, well described methods and detailed description and analysis of results, generally acceptable overall.
Flag : Critical study for SIDS endpoint
24.05.2001 (26)

Type : Dominant lethal assay
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : daily treatment on 5 consecutive days
Doses : 30, 2500 or 5000 mg/kg
Result : negative
Method : other: because this study was conducted before any standardized guidelines were established, the question of guidance methodology and GLP conduct is not applicable.
Year : 1974
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Animals and treatments
Groups of 10 male SD rats, age 10-12 wk, were given 30, 2500 and 5000 mg/kg bw propylene glycol by gastric intubation on five consecutive days (dosing volume not specified). Each male was subsequently mated with 2 virgin females (age 10 - 12wk) for 5 days (Monday to Friday) on 7 occasions over a 7 wk period. The females were sacrificed (carbon dioxide) 14 d after separating from the males, and the uterine contents examined for corpora lutea, early deaths, late fetal deaths and total implantations. Saline was used as a negative control substance (dose not specified).

Statistical analysis
In addition to comparing each treatment with the concurrent vehicle control, the results were also analysed relative to historical control data in order to clarify the toxicological significance of any effects that were recorded. The following methods were applied :
Fertility index : Chi-square; Armitage trend test
Implantations : T-test; Regression analysis
Corpora lutea : T-test
Preimplantation loss, dead implants : T-test on Freeman-Tukey (arc-sine) transformed data; regression analysis
One or more dead implants : Chi-square; Armitage trend test; probit regression
Dead implants per total implants : T-test on Freeman-Tukey (arc-sine) transformed data

Result : Fertility index
There were no notable treatment-related findings, although fertility at wk 1 in all groups (including concurrent controls) was unusually low when compared with historic control data.

Average number of implantations per pregnant female
There was no indication of any substance related effects.

Average corpora lutea per pregnant female
There was a significant increase in the number of corpora lutea in treatment groups at wk 4, and a slight decrease in the mid-dose group at wk 1. This effect appeared unrelated to treatment.

Average pre-implantation losses per pregnant female
The incidence of pre-implantation loss in the concurrent controls exceeded that of the historic controls on several weeks. Pre-implantation losses in the low dose group were also increased in weeks 2, 4 and 5, but there was no dose-response relationship discernable.

Average dead implantations per female
An inverse dose-response relationship was apparent at wk 6, which appeared related to an extremely low concurrent control value. Values for the treated animals were highly comparable with historic control data.

Females with one or more dead implants
There were relatively few differences versus controls, although dead implants were more common in the low- and

mid-dose animals than in the high-dose group.

Dead implants per total implants
An increase in dead implants per total implants was apparent at wk 6 when results were compared to the concurrent, but not the historic, controls. This appeared related to a 0.01% incidence in the negative controls (significantly lower than historic controls) rather than a substance-related effect.

Final evaluation
The apparent effects noted at some time-points in propylene glycol treated animals appeared a consequence of unrepresentative concurrent control data rather than any substance-specific effect.

Source : A.K. Mallett Surrey
Conclusion : Propylene glycol produced no increase in dominant lethal (heritable) mutations in male rats following repeated oral administration at doses up to 5000 mg/kg.
Reliability : (1) valid without restriction
Near-guideline study, pre-GLP, well described methods and detailed description and analysis of results, generally acceptable overall.
Flag : Critical study for SIDS endpoint
29.05.2001 (26)

5.7 CARCINOGENITY

Species : rat
Sex : male/female
Strain : other: Charles River, CD strain
Route of admin. : oral feed
Exposure period : 104 wk
Frequency of treatment : daily
Post. obs. period : none
Doses : 6250, 12500, 25000 or 50000 ppm
Result : negative
Control group : yes, concurrent vehicle
Method : other: because this study was conducted before any standardized guidelines were established, the question of guidance methodology and GLP conduct is not applicable.
Year : 1972
GLP : no
Test substance : other TS: British Pharmacopoeia grade
Method : see entry under 'Repeated Dose Toxicity'
Remark : Current guidelines indicate that the concentration of test substance should not exceed 5% of the diet to avoid any concerns about nutritional imbalances.
Result : There was a high incidence of mammary fibroadenomas and pituitary adenomas, affecting mostly female rats, but this did not differ statistically between the treated and control animals and no dose-response relationship was present. There was no evidence of any treatment-related increase in tumors.
Source : A.K. Mallett Surrey
Conclusion : No carcinogenic potential was detected under the conditions of this study following dietary administration up to 50000 ppm (approx 1700 - 2100 mg/kg bw/day).
Reliability : (1) valid without restriction

Non-guideline non-GLP study, with adequate and well described methods and detailed results.

Flag : Critical study for SIDS endpoint
24.05.2001 (15)

Species	:	dog
Sex	:	male/female
Strain	:	Beagle
Route of admin.	:	oral feed
Exposure period	:	104 weeks
Frequency of treatment	:	daily
Post. obs. period	:	none
Doses	:	2000 mg/kg/d (8% in diet), 5000 mg/kg/day (20% in diet)
Result	:	negative
Control group	:	other: diet plus equicaloric controls (dextrose)
Method	:	other: because this study was conducted before any standardized guidelines were established, the question of guidance methodology and GLP conduct is not applicable.
Year	:	1971
GLP	:	no
Test substance	:	other TS: met Food Chemicals Codex and United States Pharmacopoeia XVII standards.
Method	:	see entry under 'Repeated Dose Toxicity'
Remark	:	Current guidelines indicate that the concentration of test substance should not exceed 5% of the diet to avoid any concerns about nutritional imbalances.
Result	:	Apart from a slight increase in bone marrow activity in female dogs from the high dose group, histopathological lesions occurred with comparable severity and incidence in the treated, control and equicaloric control groups. The change in bone marrow activity was considered a physiological, rather than a toxicological, response by the study pathologist. There was no evidence of any effect on tumour incidence.
Source	:	A.K. Mallett Surrey
Conclusion	:	No increase in tumours was apparent in dogs fed approx. 20% propylene glycol in diet for two years. This was equivalent to 5000 mg/kg/day.
Reliability	:	(2) valid with restrictions Non-guideline non-GLP study, with adequate and well described methods and results, but small group sizes limit overall sensitivity of investigation.
Flag	:	Critical study for SIDS endpoint

24.05.2001 (47)

Species	:	mouse
Sex	:	female
Strain	:	Swiss
Route of admin.	:	dermal
Exposure period	:	lifetime
Frequency of treatment	:	twice per week
Post. obs. period	:	none
Doses	:	approx 2, 10 and 21 mg / mouse
Result	:	negative
Control group	:	other: included solvent control (acetone), untreated control and positive control (7,12-dimethylbenzanthracene) groups
Method	:	other: pre-dates regulatory protocols and glp

Year : 1974
GLP : no
Test substance : no data
Method : Methodological details are very briefly described.

Animals and housing
Mice were 7 wk old at the start of treatment. There were 50 treated animals, 135 untreated control animals, 50 solvent controls (acetone) and 50 positive controls. All were group housed (10 per cage), and fed commercial diet and water ad libitum.

Treatment
0.02 ml of undiluted propylene glycol, or a 50% or 10% solution in acetone, was 'dropped' onto a shaved 6.25 cm2 area of the dorsal flank twice weekly. Although not specified by the authors, this is equivalent to approx 21, 10 or 2 mg/mouse/application.

Terminal observations
Animals were allowed to die spontaneously or were killed when moribund. Complete autopsies were performed on all animals. The skin, all grossly observed tumours and other lesions in the lungs kidneys etc from treated and control animals were sampled, preserved and subject to microscopic examination.

Statistical methods
Applied, but specific methods not described.

Result : Results from this study are reported very briefly.

Survival was unaffected by treatment, with the last decedents occurring between weeks 110 and 120 for the control and propylene glycol treated animals, and between weeks 120 and 130 for the untreated controls.

The total number of tumour bearing animals, the percentage of tumour bearing animals and the total number of tumours was statistically indistinguishable from the controls.
There were no skin tumours in animals treated with propylene glycol, while the occurrence of lymphomas, lung adenomas, liver hemangiomas and thymomas was comparable to that of the control groups.

Source : A.K. Mallett Surrey
Conclusion : No carcinogenic potential was detected under the conditions of this study following twice weekly application of up to 21 mg/mouse twice weekly over a lifetime.
Reliability : (4) not assignable
Non-guideline pre-GLP study with brief description of methods and results.
Flag : Critical study for SIDS endpoint
24.05.2001 (42)

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : dermal
Exposure period : 10 - 14 months

Frequency of treatment	:	three times per week
Post. obs. period	:	none
Doses	:	not specified
Result	:	negative
Control group	:	no
Method	:	other: ear painting protocol
Year	:	1973
GLP	:	no
Test substance	:	no data
Method	:	Details of this study are reported very briefly. Propylene glycol was used as a vehicle in this ear painting study. An unspecified amount of undiluted test substance was applied three time per week to the left ear of 15 rats over a period of 10- 14 months. The animals were 45 days old at the start of the study, with a mean bw of 150 g. Two to three rats were sacrificed each month, and the treated ear (and other organs showing macroscopic changes) sampled, fixed and subsequently examined by light microscopy. No other parameters were determined in the investigation.
Result	:	Results for the propylene glycol treated animals are reported very briefly. There were no macroscopic or microscopic changes after 14 months treatment. No tumours were reported.
Source	:	A.K. Mallett Surrey
Conclusion	:	No carcinogenic potential was detected under the conditions of this study following thrice weekly ear painting for periods up to 14 months.
Reliability	:	(4) not assignable Unconventional pre-GLP study with brief description of methods and results.
Flag	:	Critical study for SIDS endpoint

24.05.2001 (45)

5.8 TOXICITY TO REPRODUCTION

Type	:	other: continuous breeding
Species	:	mouse
Sex	:	male/female
Strain	:	CD-1
Route of admin.	:	drinking water
Exposure period	:	continuous (see methods)
Frequency of treatment	:	daily
Premating exposure period		
Male	:	7 days prior to first mating, then continuous exposure
Female	:	7 days prior to first mating, then continuous exposure
Duration of test	:	
Doses	:	1%, 2.5%, 5% in drinking water
Control group	:	yes, concurrent vehicle
NOAEL Parental	:	= 5 %
NOAEL F1 Offspr.	:	= 5 %

NOAEL F2 Offspr. : = 5 %
Method : other: NTP Reproductive Assessment by Continuous Breeding
Year : 1989
GLP : no data
Test substance : no data
Method : Animals
There were 40 controls per sex, along with 20 males and 20 females per treatment group in the F0 generation. The F1 mating groups comprised 20 animals per sex from the control and high dose groups only. Animals were housed in single sex groups during a one week pre-mating period, then in breeding pairs or individually. Deionised filtered water and ground rodent chow were available ad libitum.

Treatment
The mice were exposed during a 7-day premating period, after which they were randomly assigned to mating pairs and cohabited and treated continuously for 98 days. At the end of the cohabitation period, the pairs were separated but treatment continued. Any litters born during this time (F1) were delivered, and kept until weaning on PND21 : treatment of the mothers continued throughout this period. Treatment of high dose animals from the F1 generation continued until mating at around 74 days of age

Parental observations
Body weight and water consumption data were collected at unspecified times during the study.

Pup observations
Data (body weight, proportion of males, number of litters per pair, number of live and dead pups) were collected on all new born animals within 12 hr of birth. Litters were then discarded, with the exception of the final F1 generation which was used for breeding purposes. The F2 litters were examined for litter size, sex and pup weight.

Necropsy observations
No necropsy data were collected on the F0 generation, however the F1 adults were subjected to a detailed examination after delivery of the F2 pups.

Statistical analysis
Methods used included Cochran-Armitage test, Fisher's exact test, Kruskall-Wallis test, Wilcoxon-Mann-Whitney test and two-sided t-test
Remark : The treatment levels used in this study were extremely high : dams from the high dose group received the equivalent of 10 g/kg bw/day.
Result : Results are reported briefly, either as a text summary or in tabulated form in the reference, and no quantitative data were available for evaluation.

Based on data collected during a preliminary dose range finding study, treated animals received the equivalent of 1800, 4800 and 10100 mg/kg bw/day.

Water consumption was consistently higher (6 - 15%) for all groups in the F0 generation, but this was not statistically

significant. Body weight in the F0 generation was unaffected by treatment.

There was no treatment-related effect on pup weight adjusted for litter size in either the F1 or F2 generations. The viability and growth of the F1 litter was unaffected by propylene glycol treatment. There were no treatment-related effects on mating, fertility or on the number, weight or viability of the F2 pups.

Necropsy of the F1 adults revealed no effect on body weight or organ weight in males and females, no change in sperm endpoints and no alteration in estrous cycle parameters.

Source : A.K. Mallett Surrey
Conclusion : Under the conditions of the study, propylene glycol had no effect on fertility or reproduction in F0 or F1 mice, up to a maximum dose of 10000 mg/kg bw/day.
Reliability : (2) valid with restrictions
GLP status unclear, methods and results briefly described but this regulatory study is acceptable overall.
Flag : Critical study for SIDS endpoint
29.05.2001 (24) (29)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : Wistar
Route of admin. : gavage
Exposure period : GD 6 - 15
Frequency of treatment : daily
Duration of test : 20 days
Doses : 16.0, 74.3, 345.0, 1600 mg / kg bw/ day
Control group : other: sham-treated
NOAEL Maternalt. : = 1600 mg/kg bw
NOAEL Teratogen : = 1600 mg/kg bw
Method : other: because this Segment 1 study was conducted before any standardized guidelines were established, the question of guidance methodology and GLP conduct is not applicable.
Year : 1973
GLP : no
Test substance : no data
Method : Animals and treatment
Pregnant female rats were allocated to a sham control group (n = 25), a positive control group (aspirin, 250 mg / kg bw/ day, n = 22) and four treatment groups (16.0, 74.3, 345.0 and 1600 mg/kg bw/day, n = 25, 25, 28 and 25 respectively) at the start of the study. Treatment commenced on GD6 and continued to GD15.

Maternal observations
All animals were observed daily for appearance and behavior. Body weights were recorded on GD0, 6, 11, 15 and 20 but not reported. Food consumption data were collected (periodicity unspecified) but not reported.

Fetal examination

On GD20 all dams were subjected to Caesarean section under anesthesia, and the numbers of implantation sites, resorption sites and live and dead fetuses recorded. The body weights of the live pups were also recorded. All fetuses were examined for congenital abnormalities. One third of the fetuses from each litter were subject to a detailed visceral examination (Wilson technique). The remaining fetuses were cleared (KOH) and stained (alizarin red S) and examined for skeletal defects.

Statistical analysis
There was no reported statistical analysis of the data.

Result : The results were presented in tabular form in the reference, with no further analysis or discussion.

Maternal parameters
All dams pregnant on GD1 survived to the end of the study.

Pregnancy parameters
Treatment with propylene glycol was without effect on the number of live litters, the total or average number of implant sites, total and partial resorptions, the total and average number of live fetuses and their sex ratio, the number of dead fetuses or fetal weight.

Fetal parameters
Alizarin red S staining revealed no propylene glycol-related adverse effects on sternebrae, ribs, vertebrae, skull or extremities, with similar findings occurring in control and treated litters. There were no soft tissue abnormalities in the treated animals.

Positive control group
Aspirin (250 mg/kg bw/day) produced soft tissue abnormalities in 16 pups from 4 dams.

Source : A.K. Mallett Surrey
Conclusion : Under the conditions of the study, there were no adverse effects on pregnancy parameters or maternal or fetal survival after exposure to up to 1600 mg/kg bw/day propylene glycol.
Reliability : (1) valid without restriction
Pre-GLP regulatory study, with adequate description of methods and results and inclusion of positive control substance.
Flag : Critical study for SIDS endpoint
29.05.2001 (14)

Species : rabbit
Sex : female
Strain : other: Dutch-belted
Route of admin. : gavage
Exposure period : GD 6 - 18
Frequency of treatment : daily
Duration of test : 29 days
Doses : 12.3, 57.1, 267.0, 1230 mg / kg bw/ day
Control group : other: sham-treated
NOAEL Maternalt. : = 1230 mg/kg bw
NOAEL Teratogen : = 1230 mg/kg bw

Method : other: because this Segment 1 study was conducted before any standardized guidelines were established, the question of guidance methodology and GLP conduct is not applicable.
Year : 1973
GLP : no
Test substance : no data
Method : Animals and treatment
Pregnant female rabbits rats were allocated to a sham control group (n = 15), a positive control group (6-aminonicotinamide, 2.5 mg/kg bw/day, n = 18) and four treatment groups (12.3, 57.1, 267.0 and 1230.0 mg/kg bw/day, n = 18, 15, 20 and 15 respectively) at the start of the study. Treatment commenced on GD6 and continued to GD18.

Maternal observations
All animals w ere observed daily for appearance and behavior. Body weights were recorded on GD0, 6, 12, 18 and 29 but not reported. Food consumption data were collected (periodicity unspecified) but not reported.

Fetal examination
On GD29 all dams were subjected to Cæsarean section under anesthesia, and the numbers of implantation sites, resorption sites and live and dead fetuses recorded. The body weights of the live pups were also recorded. All fetuses were examined for external congenital abnormalities. The live fe tuses from each litter were then placed in an incubator for 24 hr to determine neonatal survival. All surviving pups were then sacrificed, examined for visceral abnormalities and cleared (KOH), stained (alizarin red S) and examined for skeletal defects.

Statistical analysis
There was no reported statistical analysis of the data.
Result : The results were presented in tabular form in the reference, with no further analysis or discussion.

Maternal parameters
Two dams from the 12.3 mg/kg bw/day group, one from the 57.1 mg/kg bw/day group and two from the 267.0 mg/kg bw/day group died before the end of the study. No details concerning cause of death are presented in the report.

Pregnancy parameters
Treatment with propylene glycol was without effect on the number of live litters, the total or average number of implant sites, total and partial resorptions, the total and average number of live fetuses and their sex ratio, the number of dead fetuses or fetal weight.

Neonatal deaths
There was one neonatal death in one litter from the sham control- and 1230 mg/kg bw/day treatment group. Five to nine deaths occurred in 2 - 3 litters from the intermediate groups, but these appeared unrelated to dose. There were 24 deaths in 8 litters from the positive control group.

Fetal parameters
Alizarin red S staining revealed no difference in the

occurrence of sternebrae effects in fetuses from sham control or propylene glycol-treated dams. Treatment with 6-aminonicotinamide produced skeletal defects in ribs and vertebrae, but these changes were absent in the control and propylene glycol treated groups. There were no soft tissue abnormalities in the treated animals.

Positive control group
6-Aminonicotinamide (2.5 mg/kg bw/day) produced soft tissue abnormalities in 20 pups from 7 dams.

Source : A.K. Mallett Surrey
Conclusion : Under the conditions of the study, there were no adverse effects on pregnancy parameters or maternal or fetal survival after exposure to up to 1230 mg/kg bw/day propylene glycol.
Reliability : (1) valid without restriction
Pre-GLP regulatory study, with adequate description of methods and results and inclusion of positive control substance.
Flag : Critical study for SIDS endpoint
29.05.2001 (14)

Species : mouse
Sex : female
Strain : CD-1
Route of admin. : gavage
Exposure period : GD 6 - 15
Frequency of treatment : daily
Duration of test : 17 days
Doses : 16.0, 74.3, 345.0, 1600 mg / kg bw/ day
Control group : other: sham-treated
NOAEL Maternalt. : = 1600 mg/kg bw
NOAEL Teratogen : = 1600 mg/kg bw
Method : other: because this Segment 1 study was conducted before any standardized guidelines were established, the question of guidance methodology and GLP conduct is not applicable.
Year : 1973
GLP : no
Test substance : no data
Method : Animals and treatment
Pregnant female mice were allocated to a sham control group (n = 25), a positive control group (aspirin, 150 mg/kg bw/day, n = 25) and four treatment groups (16.0, 74.3, 345.0 and 1600 mg/kg bw/day, n = 28, 25, 25 and 25 respectively) at the start of the study. Treatment commenced on GD6 and continued to GD15.

Maternal observations
All animals were observed daily for appearance and behavior. Body weights were recorded on GD0, 6, 11, 15 and 17 but not reported. Food consumption data were collected (periodicity unspecified) but not reported.

Fetal examination
On GD17 all dams were subjected to Caesarean section under anesthesia, and the numbers of implantation sites, resorption sites and live and dead fetuses recorded. The body weights of the live pups were also recorded. All

fetuses were examined for congenital abnormalities. One third of the fetuses from each litter were subject to a detailed visceral examination (Wilson technique). The remaining fetuses were cleared (KOH) and stained (alizarin red S) and examined for skeletal defects.

Statistical analysis
There was no reported statistical analysis of the data.

Result : The results were presented in tabular form in the reference, with no further analysis or discussion.

Maternal parameters
Apart from a single death in the 74.3 mg/kg bw/day group (cause unspecified) all dams pregnant on GD1 survived to the end of the study.

Pregnancy parameters
Treatment with propylene glycol was without effect on the number of live litters, the total or average number of implant sites, total and partial resorptions, the total and average number of live fetuses and their sex ratio, the number of dead fetuses or fetal weight.

Fetal parameters
Alizarin red S staining revealed no propylene glycol-related adverse effects on sternebrae, ribs, vertebrae, skull or extremities, with similar findings occurring in control and treated litters. A single soft tissue abnormality (gastroschisis) occurred in one pup from one dam given 345.0 mg/kg bw/day propylene glycol and in one sham control pup.

Positive control group
Only a single soft tissue abnormality occurred in 1 pup from 1 dam treated with aspirin (150 mg/kg bw/day).

Source : A.K. Mallett Surrey
Conclusion : Under the conditions of the study, there were no adverse effects on pregnancy parameters or maternal or fetal survival after exposure to up to 1600 mg/kg bw/day propylene glycol.
Reliability : (1) valid without restriction
Pre-GLP regulatory study, with adequate description of methods and results and inclusion of positive control substance.
Flag : Critical study for SIDS endpoint
29.05.2001 (14)

Species : other: golden hamster
Sex : female
Strain : other: outbred
Route of admin. : gavage
Exposure period : GD 6 - 10
Frequency of treatment : daily
Duration of test : 14 days
Doses : 15.5, 72.0, 334.5, 1550 mg / kg bw/ day
Control group : other: sham-treated
NOAEL Maternalt. : = 1550 mg/kg bw
NOAEL Teratogen : = 1550 mg/kg bw

Method : other: because this Segment 1 study was conducted before any standardized guidelines were established, the question of guidance methodology and GLP conduct is not applicable.
Year : 1973
GLP : no
Test substance : no data
Method : Animals and treatment
Pregnant female hamsters were allocated to a sham control group (n = 24), a positive control group (aspirin, 150 mg/kg bw/ day, n = 25) and four treatment groups (15.5, 72.0, 334.5 and 1550 mg/kg bw/day, n = 25, 27, 25 and 24 respectively) at the start of the study. Treatment commenced on GD6 and continued to GD10.

Maternal observations
All animals were observed daily for appearance and behavior. Body weights were recorded on GD0, 6, 8, 10 and 14 but not reported. Food consumption data were collected (periodicity unspecified) but not reported.

Fetal examination
On GD14 all dams were subjected to Caesarean section under anesthesia, and the numbers of implantation sites, resorption sites and live and dead fetuses recorded. The body weights of the live pups were also recorded. All fetuses were examined for congenital abnormalities. One third of the fetuses from each litter were subject to a detailed visceral examination (Wilson technique). The remaining fetuses were cleared (KOH) and stained (alizarin red S) and examined for skeletal defects.

Statistical analysis
There was no reported statistical analysis of the data.
Result : The results were presented in tabular form in the reference, with no further analysis or discussion.

Maternal parameters
All dams pregnant on GD1 survived to the end of the study. There were 2 pre-term deaths in the positive control group.

Pregnancy parameters
Treatment with propylene glycol was without effect on the number of live litters, the total or average number of implant sites, total and partial resorptions, the total and average number of live fetuses and their sex ratio, the number of dead fetuses or fetal weight.

Fetal parameters
Alizarin red S staining revealed no propylene glycol-related adverse effects on sternebrae, ribs, vertebrae, skull or extremities, with similar findings occurring in control and treated litters. Soft tissue abnormalities were recorded in 2 pups from 1 dam given 15.5 mg/kg bw/day propylene glycol, and also in 2 pups from 2 dams given 72.0 mg/kg bw/day. This compares with soft tissue abnormalities in 4 pups from 4 dams from the sham control group.

Positive control group
A single soft tissue abnormality (atelcardia) occurred in 1

pup from 1 dam treated with aspirin (250 mg/kg bw/day).

Source : A.K. Mallett Surrey
Conclusion : Under the conditions of the study, there were no adverse effects on pregnancy parameters or maternal or fetal survival after exposure to up to 1550 mg/kg bw/day propylene glycol.
Reliability : (1) valid without restriction
Pre-GLP regulatory study, with adequate description of methods and results and inclusion of positive control substance.
Flag : Critical study for SIDS endpoint
29.05.2001 (14)

5.10 OTHER RELEVANT INFORMATION

Type : Toxicokinetics
Method : Study design
The pharmacokinetics of propylene glycol were determined in cancer patients participating in a Phase I clinical trial involving iv administration of a cytostatic agent. The treatment regime resulted in the administration of 5100 - 7700 mg daily for 5 days (6 trials in 3 subjects), or 13000 - 21000 mg on 1 day every 3 weeks (3 trials in 3 subjects).

The concentration of propylene glycol in blood was determined by gas chromatography using flame ionisation detection, with a limit of detection of 1 ug/ml at a signal:noise ratio of 3:1. The within-run coefficient of variance was 2.4%, and analytical recovery 95% (plus or minus 2.8%).

Venous pH, lactate, serum osmolality, haptoglobin and free hemoglobin were determined before and during infusion, and immediately before the next infusion.

Remark : Propylene glycol was eliminated with apparent first-order kinetics, with an average terminal half life of 2.3 plus or minus 0.7 hr. This varied from 1.4 hr at the lower dose to 3.3 hr at the higher dose. No accumulation was observed following 5 consecutive repeat doses.

There was no significant alteration in lactic acid concentration, venous pH, plasma osmolality, free hemoglobin or haptoglobin either during or after infusion.

Source : A.K. Mallett Surrey
Conclusion : Clearance of propylene glycol after iv administration in humans is rapid, following first-order kinetics with a mean half-life of around 2 hours. No hemolysis or red cell effects were seen after repeat administration of up to 7700 mg per day on 5 consecutive days.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
23.05.2001 (41)

Type : Toxicokinetics
Method : Male Wistar rats (100 - 120 g) were given 4.83 - 77.28 mmole (367 - 5881 mg) aqueous propylene glycol/kg bw by gavage, following an overnight fast. Blood samples (retro-orbital sinus) were collected 0.08 - 24 hr post-treatment, and the

concentration of propylene glycol determined colorimetrically. Other animals were given pyrazole per os (0.025 - 1.0 mmole/kg bw, in saline) 10 min before propylene glycol treatment.

In a separate experiment, rats were pretreated with 0 (saline), 0.2 or 1.0 mmol/kg pyrazole after an overnight fast, followed by 19.32, 38.64 or 77.28 mmol (1470 - 5881 mg) propylene glycol per kg bw. The animals were housed in metabolic cages (2 per cage) and urine collected over 24hr to follow excretion.

Statistical analysis used Student's t test.

Remark : Absorption of propylene glycol from the gut, and disappearance of propylene glycol from blood, were found to be first-order processes both in the absence and presence of pyrazole. The Km and Vmax for elimination were 17.86 mmol/kg and 8.33 mmol/kg/hr, respectively. Pyrazole competitively inhibited metabolism (Ki = 44 umol/kg). Urinary excretion increased linearly with dose, in both the presence and absence of pyrazole pretreatment. Pyrazole treatment enhanced excretion of unchanged propylene glycol.

Source : A.K. Mallett Surrey

Conclusion : Uptake and excretion of propylene glycol in the rat followed first order kinetics, and was inhibited by pyrazole (a competitive inhibitor of alcohol dehydrogenase).

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

23.05.2001 (30)

Type : Toxicokinetics

Method : Adult New Zealand rabbits (2000 - 2500 g, sex not specified) were given 38.66 mmol/kg propylene glycol in water (approx. 2940 mg) by gavage following an overnight fast. The test substance was administered as a 28.4% v/v aqueous solution at 10 mg/kg bw. Controls received an equal volume of saline.

Blood samples were withdrawn from the marginal ear vein 'at fast' (presumably immediately before dosing) and 0.25, 1.0 and 3.0 hr post-treatment and used to determine whole blood pH. The concentration of propylene glycol in blood was determined colorimetrically, while pyruvate, D -lactate and L-lactate were measured using an enyzme-based test kit. Anticoagulant (1% heparin, 1% heparin + 10% NaF, 1% heparin plus 4mM 4-methylpyrazole) was added to the samples used for measurement of blood pH.

Results were evaluated using ANOVA.

Remark : Propylene glycol was rapidly absorbed from the gastrointestinal tract (concentration in blood = 30, 41 and 36 mM at 0.25, 1 and 3 hr post-dose), whereas none was present in blood of control animals. Concentrations of lactate also increased post-treatment, although production of D-form (max 0.15 mM, 3 hr post treatment) was much slower than production of the L-form (2.5, 2.0 and 1.8 mM max at 0.25, 1 and 3 hr post-dose). The concentration of pyruvate was increased, but relatively constant, in blood collected post-treatment (0.07 mM pre-dose, 3 - 4 mM post-dose).

The pH of blood samples collected using heparin alone or heparin + methylpyrazole were constant (range 7.37 - 7.39 and 7.39 - 7.40, respectively) over the timecourse of the study, whereas samples collected using heparin+NaF as anticoagulant were significantly elevated (7.45 - 7.49, P<0.001) relative to the pre-fast values (7.43).

Overll, although pyruvate and lactate levels were increased after oral administration of a large bolus dose of propylene glycol to fasted rabbits, changes in blood pH were minimal. Anticoagulant-type was shown to influence blood pH from propylene glycol-treated animals, an observation the authors ascribe to an artefact or to an interaction between the anticoagulant and free propylene glycol.

Source : A.K. Mallett Surrey
Conclusion : Oral administration of Propylene glycol leads to increased concentrations of pyruvate and lactate in blood without no change in blood pH.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
29.05.2001 (31)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

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