Propylene glycol monomethyl ether (PGME); CASRN 107-98-2

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR PGME

File First On-Line 07/01/1991

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	07/01/1991
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Propylene glycol monomethyl ether (PGME)
CASRN — 107-98-2

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Propylene glycol monomethyl ether (PGME)
CASRN — 107-98-2
Last Revised — 07/01/1991

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Concentration — 658 mg/cu.m {1Nh}
UF — 300
MF — 1
RfC — 2E+0 mg/cu.m

Critical Study 1

Critical Effect — Mild reversible sedation

Study Type — Rat/Rabbit Subchronic Inhalation Study

Reference — Landry et al., 1983

NOAEL — 3678 mg/cu.m (1000 ppm)
NOAEL(ADJ) — 658 mg/cu.m
NOAEL(HEC) —- 658 mg/cu.m

LOAEL — 11060 (3000 ppm)
LOAEL(ADJ) — 1975 mg/cu.m
LOAEL(HEC) — 1975 mg/cu.m

Conversion Factors and Assumptions — MW = 90.14. Assuming 25C and 760 mm Hg, NOAEL (mg/cu.m) = 1000 ppm x 90.14/24.45 = 3687. NOAEL(ADJ) = 3687 mg/cu.m x 6 hours/24 hours x 5 days/7 days = 658 mg/cu.m.

Scenario — The NOAEL(HEC) was calculated for a gas:extrarespiratory effect assuming periodicity was attained. b:a lambda(a) = 403 (Stott and McKenna, 1984). Since the b:a lambda value is unknown for humans (h), a default value of 1.0 is used for this ratio. NOAEL(HEC) = NOAEL(ADJ) x (b:a lambda(a)/b:a lambda(h)) = 658 mg/cu.m. {GE}

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Landry, T.D., T.S. Gushow and B.L. Yano. 1983. Propylene glycol monomethyl ether: A 13-week inhalation toxicity study in rats and rabbits. Fund. Appl. Toxicol. 3: 627-630.

Fischer 344 rats (10/sex/group) and New Zealand White rabbits (7/sex/group) were exposed to 0, 300, 1000, or 3000 ppm propylene glycol monomethyl ether (PGME) (1106, 3686, or 11,060 mg/cu.m) 6 hours/day, 5 days/week for 13 weeks. The duration-adjusted values are 0, 1106, 3686, or 11,060 mg/cu.m, respectively. The criteria studied included daily observations for signs of toxicity, changes in body and organ weights, hematology, clinical chemistry, urinalyses (rats), and gross and histopathologic examinations (nasal turbinates, trachea, lungs, liver, kidneys, brain, etc.). There were no mortalities recorded due to PGME exposure. During the first 2 weeks of exposure, rats and rabbits exposed to 3000 ppm appeared to be sedated during the first several days of exposure. After approximately 2 weeks, the sedative effects were no longer apparent. No other effects were observed in rabbits. The only additional effects observed in rats at 3000 ppm were small significant increases (6-8%) in liver weights, and increased hepatocyte size and cytoplasmic eosinophilia indicating hepatocellular hypertrophy, but there was no evidence of degenerative changes in the livers of female rats. Leukocyte counts were higher in the 300-ppm group and lower in the 3000-ppm group compared with controls. In the absence of a concentration-response relationship, these differences are apparently due to unrelated, sporadic occurrences. Only liver weights in the 3000 ppm group (female rats only) were higher than controls. Histopathologic examination showed hepatocellular swelling, but no degenerative changes were found in the affected group. It was concluded that the hepatocellular swelling and increased liver weights appeared to be the result of a physiologic adaptation rather than a manifestation of toxicity.

The narcosis observed during the first 2 weeks of exposure to PGME is considered to be an adverse effect. The concomitant changes in the liver are considered to be an adaptive response to PGME exposure which after 2 weeks alleviates the sedative effects of this chemical. Therefore, the 1000 ppm concentration is the NOAEL in rats and rabbits (HEC=658 mg/cu.m). The LOAEL for neurotoxicity (mild CNS depression) for rats and rabbits is 3000 ppm (HEC=1975 mg/cu.m).

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — An uncertainty factor of 10 is used to protect sensitive individuals and another factor of 10 for use of a subchronic study for a chronic RfC derivation. An additional factor of 3 is used for interspecies extrapolation given the dosimetric adjustment and the zero-order pharmacokinetic rate of elimination of PGME that is suggestive of an adaptive metabolic response (Morgott and Nolan, 1987). An additional factor to account for lack of a complete database (in this case, the lack of a reproductive study) is not thought to be needed since the available pharmacokinetic data suggests that the reproductive system will not be a target.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

PGME is similar in structure to a larger group of related chemicals collectively known as the glycol ethers. Other glycol ethers have been shown to cause developmental and reproductive effects, especially testicular changes, at much lower effect levels than that identified for CNS depression by PGME. The reason for this apparent discrepancy of type and level of critical effect has been reported and is discussed below.

A comparison of PGME and ethylene glycol monomethyl ether (EGME) metabolism was conducted in male rats (Miller et al., 1983, 1984a). The observed difference in toxicity between these two glycol ethers is apparently the result of the biotransformation of EGME and PGME via different metabolic routes. Male Fischer 344 rats were given a single oral dose of 14-C labeled EGME or PGME. Following administration of the dose, expired air, excreta and tissues were analyzed for labeled metabolites and, when applicable, isolated and identified. After 48 hours, 50-60% of the EGME dose was excreted in urine and 10-20% eliminated as labeled CO2 in expired air. Methoxyacetic acid was identified as the primary urinary metabolite of EGME in urine. PGME administration resulted in only 10-20% of the administered (14-C) label excreted in urine primarily as sulfate and glucuronide conjugates and 50-60% eliminated in expired air. Ethylene glycols like EGME are primary alcohols and are possibly metabolized in the same manner as ethanol. The adverse effects of EGME are plausibly due to its primary metabolite, methoxyacetic acid, which has been shown to have the same spectrum of toxicity as EGME in male rats (Miller et al., 1983). Propylene series glycol ethers are predominantly secondary

alcohols and are biotransformed via microsomal enzymes to metabolites that are relatively innocuous. The increased liver weight changes noted in 3000 ppm PGME-treated rats may be a result of compensatory changes from PGME induction of hepatic microsomal enzyme activity. Fischer 344 rats given daily 6-hour inhalation exposures of PGME for 1 or 10 days failed to develop blood level plateaus following exposure. Blood levels of propylene glycol indicated that PGME demethylation reached saturation levels at exposure concentrations exceeding 1500 ppm. Furthermore it was noted that following multiple exposures to 3000 ppm of PGME, levels of cytochrome P-450 and mixed function oxidase activity were higher (Morgott and Nolan, 1987).

The pharmacokinetics of PGME and propylene glycol monomethyl ether acetate (PGMEAc) in the upper respiratory tract (URT) of rats was studied by Stott and McKenna (1984) as part of a comparative study. Both glycol ethers were found to be completely absorbed (near 100%) by the URT in an isolated ventilated URT of anesthetized Fischer 344 rats at a ventilation rate of one and two times the respiratory minute volume. Given the route and extent of absorption in the URT of PGME and PGMEAc, one would expect morphologic changes to occur in the URT if effects were to be found in the respiratory tract. Such effects were not reported in any of the studies reviewed here at exposures of PGME up to 3000 ppm. However, exposure to 3000 ppm of PGMEAc, which has similar systemic toxicity as PGME, showed morphologic changes in the olfactory nasal mucosa (Miller et al., 1984b). Since PGME and PGMEAc are metabolized in a similar fashion, the histopathological changes were attributed to hydrolysis to acetic acid in the nasal epithelium. It should also be noted that the NOAEL for PGME occurs below and the LOAEL above the reported saturation concentration of 1500 ppm (Morgott and Nolan, 1987).

Groups of one to six male volunteers were exposed to 50, 100, or 250 ppm PGME (184, 369 or 922 mg/cu.m) in an exposure chamber for 1-7 hours (Stewart et al., 1970). The single person exposed to 184 mg/cu.m detected the odor of propylene glycol monomethyl ether but did not find the exposure irritating. At 100 ppm the subjects felt that the odor was too strong to be tolerated, but odor tolerance developed within 25 minutes. During a 3.5-hour exposure at 100 ppm, mild eye irritation was noted in three of the six individuals. At 250 ppm, the majority of the 23 subjects exposed for 1-7 hours complained of eye, nose or throat irritation; several subjects developed headaches, and one was nauseated. None of the exposures resulted in changes in visual, coordination, neurological or brake-reaction tests. Clinical studies (e.g., blood cell count, SGOT, SGPT, BUN and complete urinalysis) completed before and after exposure showed no effects. Exposure of an unspecified number of men in a truck cab indicated that the odor of propylene glycol monomethyl ether was detectable at 10 ppm (37 mg/cu.m).

Rats (10 or 20/sex) and guinea pigs (five or eight/sex) were exposed to 1500, 3000, or 6000 ppm PGME (5530, 11,060, or 22,120 mg/cu.m); rabbits (1 or 2/sex) and monkeys (species not specified, 1 or 2/group; a total of four females and one male was used) were exposed to 800, 1500, or 3000 ppm propylene glycol monomethyl ether (2949, 5530, or 11,060 mg/cu.m) (Rowe

et al., 1954). In addition, one female rabbit was exposed at 6000 ppm (22,120 mg/cu.m). All exposures were for 7 hours/day, 5 days/week for 80-147 exposures. At 6000 ppm, narcosis was observed in rats, guinea pigs and the rabbit, and 4/10 male and 7/10 female rats died (HEC=4608 mg/cu.m). At 3000 ppm (HEC=2304 mg/cu.m), rats exhibited mild CNS depression at the end of each exposure. Increased liver and kidney weights were also observed. The guinea pig LOAEL is 6000 ppm (HEC=4608 mg/cu.m) for CNS depression, growth depression, increases in liver and kidney weights and slight typical microscopic changes in the liver. Slightly increased liver weights and slight microscopic changes in the lungs and livers of female, but not male, rabbits were observed. Slight microscopic changes in the lungs were observed in monkeys at 1500 ppm. This study is limited by the small number of rabbits and monkeys used, lack of statistical analysis of the data, only limited control data for rats and guinea pigs, and limited discussion of observed microscopic changes.

F344 rats (5/sex/group) and B6C3F1 mice (5/sex/group) were exposed to 0, 300, 1000, or 3000 ppm (1106, 3687, or 11,060 mg/cu.m) PGME 6 hours/day for 9 days during an 11-day period (Miller et al., 1981). Increased liver weights were observed in male rats exposed to 11,060 mg/cu.m. The LOAEL for neurotoxicity (CNS depression) in rats and mice is 3000 ppm (HEC=11,060 mg/cu.m).

Pregnant Wistar Alderley Park rats (20/group) at 0, 200, or 600 ppm PGME (737 or 2212 mg/cu.m). Pregnant rats were exposed on gestation days 6-17 for 6 hours/day. The rats were allowed to deliver, and the litters were observed for 3 days. In a second study, male rats (10/group) were exposed for 10 days, sacrificed and examined for testicular and hematological effects. No effects were observed in either study. The NOEL identified is 600 ppm (HEC=2212 mg/cu.m) (Doe et al., 1983).

Pregnant F344 rats and New Zealand White rabbits (29-32/group) were exposed to 0, 500, 1500, or 3000 ppm PGME (1843, 5530, or 11,060 mg/cu.m) 6 hours/day on gestation days 6-15 (rats) and 6-18 (rabbits). The rabbit LOAEL is 3000 ppm for decreased reduction in maternal weight gain and mild transient CNS depression (HEC=11,060 mg/cu.m). Significant fetotoxic effects were not observed in rabbits. The rat LOAEL is 3000 ppm for maternal toxicity (decreased food intake and body weight gain, transient CNS depression) and slight fetal toxicity (delayed ossification of sternebrae) (HEC=11,060 mg/cu.m) (Hanley et al., 1984).

Pregnant female rats (20-23/group) were exposed to 0, 500, 1980, or 4160 ppm propylene glycol monomethyl ether acetate (PGMEAc, M.W. = 132.18) (0, 2703, 10,704, or 22,490 mg/cu.m) 6 hours/day on gestation days 6-15. On day 20 of gestation, each dam was euthanized and the dams and fetuses morphologically examined. The dams were examined grossly for structural abnormalities or pathological changes. Only the liver and brain were weighed in the dams; no other tissues were examined or saved. PGMEAc caused transient CNS effects, decreased food

consumption and decreased weight gain in the dams. Total weight gain was the only effect in dams which was significant at the end of the study. No other maternal effects were found. Fetuses exposed up to the highest concentration (4160 ppm) of PGMEAc did not exhibit any teratological or other developmental effects. A NOAEL of 4160 ppm (HEC=22,490 mg/cu.m) for PGMEAc is identified (U.S. Army, 1989).

As described by Stott and McKenna (1984), the systemic toxicity of PGME and PGMEAc is similar. Therefore, the developmental toxicity for PGMEAc described above can be validly applied for assessing developmental toxicity of PGME. Furthermore, the reproductive effects of the propylene monomethyl glycol ethers is not expected to be of concern, since as previously described (Miller et al., 1983, 1984a; Morgott and Nolan, 1987), the metabolism of PGME is substantially different than that of EGME. EGME causes testicular degeneration in a number of animal species. Although structurally similar to EGME, PGME and PGMEAc are metabolized to innocuous conjugates and not to active testicular degenerative metabolites.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

Confidence in the principal study is medium. The study examined the toxicity of propylene glycol monomethyl ether in two species at three concentrations and a sufficient number of relevant biological endpoints were examined. Confidence in the database is medium. A human exposure study (Stewart et al., 1970) indicates that the RfC should prevent irritation. Chronic studies were not identified, nor were multi-generation reproductive studies. However, since the metabolic fate of PGME has been characterized and has been shown to result in innocuous conjugates, lack of these studies does not significantly diminish the database confidence. Reflecting the confidence in the study and database, confidence in the inhalation RfC is medium.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1986

Agency Work Group Review — 06/15/1989, 04/25/1991

Verification Date — 04/25/1991

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Propylene glycol monomethyl ether conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Propylene glycol monomethyl ether (PGME)
CASRN — 107-98-2

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Propylene glycol monomethyl ether (PGME)
CASRN — 107-98-2

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

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Stewart, R.D., E.D. Baretta, H.C. Dodd and T.R. Torkelson. 1970. Experimental human exposure to vapor of propylene glycol monomethyl ether: Experimental human exposure. Arch. Environ. Health. 20: 218-223.

Stott, W.T. and M.J. McKenna. 1984. The comparative absorption and excretion of chemical vapors by the upper, lower, and intact respiratory tract of rats. Fund. Appl. Toxicol. 4: 594-602.

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U.S. EPA. 1986. Health and Environmental Effects Profile for Glycol Ethers. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EPA/540/1-86/052.

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Propylene glycol monomethyl ether (PGME)
CASRN — 107-98-2

Date	Section	Description
07/01/1991	I.B.	Inhalation RfC summary on-line
12/03/2002	I.B.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Propylene glycol monomethyl ether (PGME)
CASRN — 107-98-2
Last Revised — 07/01/1991

- 107-98-2
- 2-Propanol, 1-methoxy-
- alpha-PROPYLENE GLYCOL MONOMETHYL ETHER
- DOWANOL-33B
- Dowtherm 209
- HSDB 1016
- METHOXY ETHER of PROPYLENE GLYCOL
- Methoxypropanol
- NSC 2409
- PROPASOL SOLVENT M
- Propylene Glycol Monomethyl Ether
- PROPYLENGLYKOL-MONOMETHYLAETHER [German]
- 1-METHOXY-2-HYDROXYPROPANE
- 1-Methoxy-2-Propanol
- 2-METHOXY-1-METHYLETHANOL
- 2-Propanol, 1-Methoxy-