Proposition 65 Maximum Allowable Dose Level (MADL) for Reproductive Toxicity for Ethylene Glycol Monomethyl Ether

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Office of Environmental Health Hazard Assessment
Reproductive and Cancer Hazard Assessment Section

Summary

The maximum allowable dose level (MADL) for ethylene glycol monomethyl ether (EGME) is **63 micrograms/day (µg/day)** for the oral route of exposure. This value was derived as described below, based on the male reproductive toxicity of EGME observed in the study reported by Gulati et al. (1990).

Background

This report describes the derivation of a maximum allowable dose level (MADL) for EGME (CAS No. 109-86-4).

EGME is used as a solvent for cellulose acetate and resins. It is also used as a solvent in the semiconductor industry, in dyeing leather, in the manufacture of photographic film, and as an anti-freeze agent in jet fuels (OEHHA, 2001; HSDB, 2004). EGME was listed under Proposition 65 (the Safe Drinking Water and Toxic Enforcement Act of 1986) as known to the State to cause reproductive toxicity (developmental and male reproductive toxicity), effective January 1, 1989. The Proposition 65 listing of EGME was based on a finding by the Scientific Advisory Panel that the chemical had been clearly shown by scientifically valid testing according to generally accepted principles to cause developmental and male reproductive toxicity.

Procedures for the development of Proposition 65 MADLs are provided in regulations (Title 22, California Code of Regulations §12801 and 12803). Exposure at a level 1,000 times greater than the MADL is expected to have no observable effect. As defined in regulations, a MADL is derived from a No Observable Effect Level (NOEL) based on the most sensitive study deemed to be of sufficient quality (Title 22 Cal. Code of Regs. §12803(a)(4)).

Study Selection

Relevant studies and review reports on the male reproductive and developmental toxicity of EGME have been identified through literature searches. These studies and reports, listed in the Bibliography for this document, have been reviewed and considered for the establishment of the MADL.

Male Reproductive Toxicity: The male reproductive toxicity of EGME has been shown in a number of epidemiological studies among occupationally-exposed workers and in numerous studies in laboratory animals. In painters occupationally exposed to mixtures containing EGME and ethylene glycol monoethyl ether (EGEE), the prevalence of oligospermia and azoospermia and the odds ratio for lower sperm counts per ejaculate were increased as compared to those in workers who were not exposed to glycol ethers (Welch et al., 1988). However, exposure to mixtures containing glycol ethers other than EGME and lack of detailed information on exposure levels (e.g., air concentrations) prevented use of the epidemiological studies for establishing a NOEL.

In laboratory animals, EGME causes reduced testis weight, histopathological changes in the testis, decreased sperm count and motility, and increased proportion of epididymal sperm with abnormal morphology. Histopathological changes in the testis of animals treated with EGME are characterized as degeneration of the seminiferous epithelium (germ cell apoptosis), with pachytene spermatocytes as the most sensitive germ cell population (Foster et al., 1983; Chapin and Lamb, 1984; Creasy et al., 1985; Ku et al., 1994). Major findings on the male reproductive toxicity of EGME from several animal studies following oral or inhalation routes of exposure that included repeated treatment with relatively low doses and provided LOELs and/or NOELs are briefly summarized in Table 1.

Developmental Toxicity: The developmental toxicity of EGME has been observed among occupationally-exposed female workers and in EGME-treated pregnant animals. In humans, an association between exposure to ethylene glycol ethers (including EGME or its acetate ester and other glycol ethers) and spontaneous abortion has been observed in several epidemiological studies conducted among fabrication workers in the semiconductor industry (Pastides et al., 1988; Beaumont et al., 1995; Swan et al., 1995; Correa et al., 1996), but not in the prospective study reported by Eskenazi et al. (1995) or in the study reported by Elliott et al. (1999). An increased odds ratio for congenital malformation associated with glycol ether exposure was also found in a case-control study by Cordier et al. (1997). However, exposure to mixtures containing other glycol ethers and lack of detailed information on exposure levels prevent use of the epidemiological studies for MADL calculation.

In animals, decreased fetal weights, increased numbers of fetal deaths or resorptions, increased incidence of visceral and skeletal malformations, and increased incidences of other developmental damages (e.g., cardiovascular malformations, thymic atrophy in the fetuses of exposed dams) have been observed in rats, mice, rabbits, or monkeys following exposure to EGME. Major findings on the developmental toxicity of EGME from several animal studies that included repeated treatment with relatively low doses and provided LOELs and/or NOELs are briefly summarized in Table 2 and Table 3.

Table 1. Brief Summaries of Studies on the Male Reproductive Toxicity of EGME.

Study Reference	Animals	Treatment	General Toxicity	Reproductive Effects & LOEL	NOEL (adjusted)
Gulati et al., 1990 [RACB study by NTP]	Sprague-Dawley rats; NTP-RACB protocol.	**Drinking Water,** 0, 0.01, 0.03, or 0.1%, from breeding to delivery of F2 offspring using **Litter 2** pups as F1 parents.	Decreased body, liver and kidney weights in F0 and F1 parents.	reduced epididymal & prostate weights; reduced epididymal sperm density in F1 males. LOEL: 0.01% (9.07 mg/kg-day; F1males)	Not found.
Foote et al., 1995; Berndtson & Foote, 1997	Male Dutch rabbits, 6/group	**Drinking Water,** 0, 12.5, 25.0, 37.5, 50.0 mg/kg-day, for 12-13 weeks	No general toxicity observed.	Decreased testicular weights; Testicular atrophy; decreased sperm counts. Reduced fertility. LOEL:25.0 mg/kg-day	12.5 mg/kg-day
Scala et al., 1992	Sprague-Dawley rats, male, 10 animals per group	**Gavage**, 0, 25, 50, 100 mg/kg-day, for 49-51 days	Decreased body weights, kidney, liver and thymus weights; abnormal hematological changes.	Decreased testis weights; testicular atrophy. LOEL: 50 mg/kg-day	25 mg/kg-day
Chapin & Sloane, 1997 [RACB study by NTP]	Sprague-Dawley rats; NTP-RACB protocol.	**Drinking Water,** 0, 0.006, 0.012, or 0.024%, from breeding to delivery of F2 pups using **Litter 5** pups as F1 parents.	High postnatal mortality among litter 5 pups. Slightly reduced live weights of F0 females.	No adverse effects on the organ weights of the male reproductive system; no effect on sperm end points.	0.024% (26 mg/kg-day)
Miller et al., 1983a	Male New Zealand White rabbits, 3-5 per group	**Inhalation,** 0, 30, 100, 300 ppm, 6h/d, 5d/wk, 13 wks.	Hematological effect and decreased thymus weight at 300ppm.	Decreased testis weight at 300 ppm. Testicular atrophy. LOEL: 100 ppm (20.11 mg/kg-day)	30 ppm (5.98 mg/kg-day)
Miller et al., 1983a	Sprague-Dawley rats, 6-8 wks of age, 10 of each sex.	**Inhalation,** 0, 30, 100, 300 ppm, 6h/d, 5d/wk, 13 wks.	Decreased body weights, liver and thymus weights; Hematological changes at ≥100ppm.	Decreased testis weight and testicular atrophy. LOEL: 300 ppm (97.50 mg/kg-day)	100 ppm (31.35 mg/kg-day)
Rao et al., 1983	Sprague-Dawley rats, male, 20-30 rats per group	**Inhalation,** 0, 30, 100, 300 ppm, 6 hr/d, 5d/wk, for 13 wks.	Decreased body weights.	Decreased fertility and testis weights; testicular atrophy. LOEL: 300 ppm (99.23 mg/kg-day)	100 ppm (31.87 mg/kg-day)

Notes: NTP: National Toxicology Program; RACB: Reproductive Assessment by Continuous Breeding; Adjusted NOEL: NOELs reported in the original reports were adjusted to mg/kg-day. Inhalation rates were estimated by the allometric method for rabbits (U.S. EPA, 1988) or by the method of Anderson et al. (1983) for rats.

Table 2. Brief Summaries of Studies on the Developmental Toxicity of EGME (Oral Exposure)

Study Reference	Animals	Treatment	Maternal Toxicity	Developmental Effects & LOEL	NOEL (adjusted)
Scott et al., 1989	Female Macaca fascicularis, 8-14 per group	**Gavage**, 0, 12, 24, 36 mg/kg, GD 20-45.	Maternal weight loss at 24 and 36 mg/kg doses.	Increased embryonic death; missing-digit on forelimb in one case at 36 mg/kg. LOEL:12 mg/kg-day	Not found
Nelson et al., 1989	Female SD rats, 10 animals per group	**Feed**, 0, 0.006, 0.012, 0.025, 0.05, 0.1, 0.25% in liquid diet, GD 7-18	Decreased maternal body weight gain at ≥0.05%.	Increased fetal death, reduced fetal weights; cardiovascular malformations. LOEL: 0.006% (16 mg/kg-day)	Not found
Gulati et al., 1990; [RACB study by NTP]	Sprague-Dawley rats; NTP-RACB protocol.	**Drinking Water,** 0, 0.01, 0.03, or 0.1%, from breeding to delivery of F2 offspring; **Litter 2** pups as F1 parents.	Decreased fertility at 0.1%; decreased body weights and water consumption in F1 females.	Increased stillborn and reduced number of live pups per litter. LOEL: 0.03% (30 mg/kg-day)	0.01% (12.65 mg/kg-day)
Chapin & Sloane, 1997 [RACB study by NTP]	Sprague-Dawley rats; NTP-RACB protocol.	**Drinking Water,** 0, 0.006, 0.012, or 0.024%, from breeding to delivery of F2 pups; **Litter 5** as F1 parents.	Slightly reduced live weights of F0 females.	Reduced number of live pups per litter in both generations. LOEL: 0.024% (26.0 mg/kg-day)	0.012% (12.0 mg/kg-day)

Notes: NTP: National Toxicology Program; RACB: Reproductive Assessment by Continuous Breeding; Adjusted NOEL: NOELs reported in the original reports were adjusted to mg/kg-day.

Table 3. Brief Summaries of Studies on the Developmental Toxicity of EGME (Inhalation Exposure)

Study Reference	Animals	Treatment	General Toxicity	Reproductive Effects & LOEL	NOEL (adjusted)
Hanley et al., 1984	New Zealand White rabbits, 29-30 animals per group	**Inhalation,** 0, 3, 10, 50 ppm, 6 hr/d, GD 6-18	Decreased maternal body weights and increased liver weights at 50 ppm.	Decreased fetal weights; increased resorptions; increased visceral and skeletal malformations and variations at 50 ppm. LOEL: 50 ppm (13.97 mg/kg-day)	10 ppm (2.81 mg/kg-day)
Hanley et al., 1984	Fischer 344 rats, 30-31 animals per group	**Inhalation,** 0, 3, 10, 50 ppm, 6 hr/d, GD 6-15	Transient decrease in maternal body weight gains; hematological changes at 50ppm	Increased incidence of minor skeletal variations. LOEL: 50 ppm (39.47 mg/kg-day)	10 ppm (7.89 mg/kg-day)
Nelson et al., 1984	Sprague-Dawley rats, 14-34 animals per group.	**Inhalation,** 0, 50, 100 ppm, 7 hr/d, GD 7-15.	No maternal effects reported. [Body weight data not reported.]	Decreased fetal weights, Increased resorption, visceral and skeletal malformations. LOEL: 50 ppm (45.20 mg/kg-day)	Not found.
Hanley et al., 1984	CF-1 mice, 30-32 animals per group	**Inhalation,** 0, 10, 50 ppm, 6 hr/d, GD 6-15	Slight transient decrease in maternal body weight gain at 50 ppm.	Increased incidences of extra (lumbar) ribs and unilateral testicular hypoplasia. LOEL =50 ppm (66.65 mg/kg-day)	10 ppm (13.33 mg/kg-day)

Notes: Adjusted NOEL: NOELs reported in the original reports were adjusted to mg/kg-day. Inhalation rates were estimated by the allometric method for rabbits (U.S. EPA, 1988) or by the method of Anderson et al. (1983) for rats.

Table 4 LOELs and NOELs for the developmental or male reproductive toxicity of EGME

End-points	Oral				Inhalation			
	Study	**Species**	**LOEL**	**NOEL**	**Study**	**Species**	**LOEL**	**NOEL**
Male Repro-duction	Gulati et al, 1990	Rats	9.07	0.91	Miller et al., 1983	Rabbits	20.11	5.98
	Foote et al., 1995	Rabbits	25.0	12.5	Miller et al., 1983a	Rats	97.50	31.35
Develop-ment	Scott et al., 1989	Primates	12	1.20	Hanley et al., 1984	Rabbits	13.97	2.81
	Nelson et al., 1989	Rats	16	1.60	Hanley et al., 1984	Rats	30.07	6.03
	Chapin & Sloan 1997	Rats	26.0	12.0	Hanley et al., 1984	Mice	48.27	9.65

Note: Underlined NOELs were derived from the respective LOELs divided by 10.

Identification of the Most Sensitive Study: Based on the findings from animal studies reviewed by OEHHA, especially from those presented in Table 1, Table 2, and Table 3, the studies that are deemed to be of sufficient quality (Title 22 Cal. Code of Regs. §12801 and 12803) and which provided relatively low values of LOELs and/or NOELs are listed in Table 4.

The NOEL is based on the most sensitive study deemed to be of sufficient quality and is the highest dose level which results in no observable reproductive effect, expressed in milligrams of chemical per kilogram of bodyweight per day (Title 22 Cal. Code of Regs. §12803(a)). The most sensitive study for the male reproductive toxicity of EGME is the study conducted by the National Toxicology Program (NTP) and reported by Gulati et al. (1990). This study reported the lowest LOEL (9.07 mg/kg-day) for the male reproductive toxicity of EGME among all the studies reviewed by OEHHA for the purpose of Proposition 65. The most sensitive study for the developmental toxicity of EGME is the study in primates by Scott et al. (1989) that provides the lowest LOEL (12 mg/kg-day).

Under the Proposition 65 regulations, when the data from the relevant studies do not allow the determination of a NOEL, the LOEL is converted to a NOEL for purposes of assessment by dividing by 10 (Title 22 Cal. Code of Regs. §12803(a)(7)). Thus, the NOELs for the male reproductive and developmental toxicity of EGME based on the most sensitive studies were 0.907 mg/kg-day and 1.20 mg/kg-day, respectively (9.07 mg/kg-day and 12 mg/kg-day divided by 10, respectively).

The regulation also requires that the reproductive effect for which studies provide the lowest NOEL is utilized for the determination of the NOEL when multiple reproductive effects are listed under Proposition 65 (Title 22 Cal. Code of Regs. §12803(a)(1)). The NOEL for the male reproductive toxicity of EGME (0.91 mg/kg-day) is lower than that for the developmental toxicity (1.20 mg/kg-day). Therefore, the NTP study reported by Gulati et al. (1990) was used as basis for establishing the MADL for EGME. Major findings from this study are summarized in Table 5 and discussed below.

The NTP study reported by Gulati et al. (1990) followed the protocol of Reproductive Assessment by Continuous Breeding (RACB). In this study, groups of male and female Sprague-Dawley rats were treated with EGME in drinking water at concentrations of 0.01, 0.03, and 0.1% (w/v). According to the estimates by the study authors, these levels of EGME in drinking water were approximately equivalent to 8.81, 23.56, and 75.77 mg/kg-day for F0 males. Among the animals of the F0 generation, decreases in the number or proportion of live pups per litter and in weights of male reproductive organs (epididymis, seminal vesicles, and prostate) were observed in the middle-dose group. These changes, in addition to decreased fertility and reduced epididymal sperm density and motility, were also observed in the high-dose group. The NOEL for male reproductive toxicity among F0 males was 0.01% (8.81 mg/kg-day). In the second-generation mating trial (Task 4), F1 animals were treated with EGME in drinking water at concentrations of 0, 0.01%, and 0.03%. The estimated doses (expressed as mg/kg-day) were slightly higher than those for the parents (0, 9.07, and 27.15 mg/kg/d for 0, 0.01%,

and 0.03%, respectively). At the exposure level of 0.03% EGME in drinking water, the body weights of F1 males were decreased by 17%. No treatment-related effects on mating or fertility indices were observed, although the number of live pups was reduced by approximately 17% and the postnatal viability of the pups was reduced by approximately 5%. Organ weights of epididymis and prostate were decreased by 13 and 28%, respectively, but absolute testis weight was unchanged. Epididymal sperm density was also significantly reduced at both the low and middle doses by 17 and 23%, respectively. Histopathological evaluation among ten males randomly selected from each group found seminiferous tubule degeneration in the testes of two animals in the control (minimal severity), seven in the 0.01% group (minimal-mild severity), and five in the 0.03% group (severity not reported). Thus, the low dose (0.01% in drinking water, equivalent to 9.07% mg/kg-day) was considered to be a LOEL. The NOEL derived from the LOEL for the purpose of Proposition 65 is 0.907 mg/kg-day (i.e., the LOEL divided by 10).

Table 5. Major findings on the male reproductive toxicity of EGME from the RACB-L2 study in SD rats conducted by the NTP (Gulati et al., 1990)

Exposure level (% in drinking water)		**0**	**0.01**	**0.03**	**0.10**
F0	Estimated dose (mg/kg/d; male)	0	8.81	23.56	75.77
	Body weights (g, at necropsy)	742.41±10.23	723.41±14.71	719.90±12.25	633.60±11.29*
	Fertility index (%)	36/36 (100%)	20/20 (100%)	16/18 (89%)	1/20 (5%)*
	Live pups per litter (number)	12.82±0.36	11.78±0.54	7.45±0.93*	No statistical analysis
	Testis weights (g, absolute)	1.880±0.024	1.890±0.030	1.806±0.085	1.273±0.093*
	Epididymis weight (mg, adj.)	728.36±16.01	709.28±21.63	674.89±21.59	440.07±25.07
	Seminal vesicles (g, adj.)	3.258±0.065	3.048±0.068	2.985±0.057*	2.643±0.102*
	Prostate (mg, adj.)	806.50±30.05	941.50±40.65	904.64±40.57	650.75±47.13*
	Sperm density (10^6/g epididy.)	492.86±26.45	465.81±18.49	425.04±28.92	186.26±50.27*
	Sperm motility (%)	81.825±1.362	83.685±2.256	84.530±4.634*	40.750±10.38*
F1	Estimated dose (mg/kg/d; male)	0	9.07	27.15	Not included
	Body weights (g)	536.22±13.21	515.08±9.33	467.27±9.24*	
	Fertility index (%)	19/20 (95%)	16/19 (85%)	18/18 (100%)	
	# of live pups per litter	15.37±0.62	15.19±0.67	12.78±0.67*	
	Testis weights (g, absolute)	1.738±0.029	1.701±0.076	1.709±0.115	
	Epididymis weight (mg, adj.)	583.60±8.61	548.32±20.75	483.28±23.90*	
	Sperm density (10^6/g epididy.)	668.56±31.72	532.65±39.06*	496.29±52.62*	
	Sperm motility (%)	86.295±1.335	87.267±1.482	77.870±4.380*	
	Abnormal sperm (proportion)	0.530±0.055	0.686±0.057*	0.941±0.106*	

Note: *: significantly different from the control ($p<0.05$)

MADL Calculation

The NOEL is the highest dose level which results in no observable reproductive effect, expressed in milligrams of chemical per kilogram of bodyweight per day (Title 22 Cal. Code of Regs. §12803 (a)(1)). The NOEL is converted to a milligram per day dose level by multiplying the assumed human body weight by the NOEL (Title 22 Cal. Code of

Regs. §12803 (b)). For male reproductive toxicity, the assumed body weight of men is 70 kg.

For the oral route of exposure, the following calculations were performed to derive the $MADL_{oral}$ for EGME, based on a LOEL of 9.07 mg/kg/d found in the RACB-L2 study sponsored by the NTP, reported by Gulati et al. (1990):

Conversion from a LOEL to NOEL:

9.07 mg/kg-day ÷10 = 0.907 mg/kg-day

Calculation of the NOEL for a 70 kg man:

0.907 mg/kg-day × 70 kg = 63.49 mg/day

The MADL is derived by dividing the NOEL by one thousand (Title 22 Cal. Code of Regs. §12801(b)(1)). Thus, the adjusted NOEL was divided by 1,000 to obtain the MADL.

$MADL_{oral}$ = 63.49 mg/day ÷ 1000 = 63.49 µg/day or **63 µg/day** after rounding.

This MADL represents intake by the oral route of exposure. EGME is almost completely absorbed following oral administration (Miller et al. 1983b; Medinsky et al. 1990). Therefore, the MADL for EGME via oral route of exposure as proposed above should be considered as the absorbed dose.

The MADL of 63 µg/day is applicable to exposure via oral route only. If exposures occur by any non-oral (e.g. inhalation or dermal) or multiple routes, the total exposure to the chemical from a single source or product must be considered. The absorbed dose results from the source or product should be calculated. If the total absorbed dose resulting from any one or multiple routes is less than 63 µg/day, the MADL has not been exceeded.

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