2-Ethoxyethanol; CASRN 110-80-5

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 2-Ethoxyethanol

File First On-Line 05/01/1991

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	05/01/1991
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

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

Substance Name — 2-Ethoxyethanol
CASRN — 110-80-5

Not available at this time.

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

Substance Name — 2-Ethoxyethanol
CASRN — 110-80-5
Last Revised — 05/01/1991

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 Effect	Exposures*	UF	MF	RfC
Decreased testis weight, seminiferous tubule degeneration and decreased hemoglobin **New Zealand White Rabbit Subchronic Toxicity Study** **Barbee et al., 1984**	NOAEL: 380 mg/cu.m (103 ppm) NOAEL(ADJ): 68 mg/cu.m NOAEL(HEC): 68 mg/cu.m LOAEL: 1485 mg/cu.m (403 ppm) LOAEL(ADJ): 265 mg/cu.m LOAEL(HEC): 265 mg/cu.m	300	1	2E-1 mg/cu.m

*Conversion Factors: 90.12. Assuming 25C and 760 mm Hg, NOAEL (mg/cu.m) = 103 ppm x 90.12/24.45 = 380 mg/cu.m. NOAEL(ADJ) = 380 x 6 hours/24 hours, 5 days/7 days = 68 mg/cu.m. The NOAEL(HEC) was calculated for a gas:extrarespiratory effect assuming periodicity was attained. Since the b:a lambda values are unknown for the experimental animal species (a) and 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)) = 68 mg/cu.m.

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

Barbee, S.J., J.B. Terrill, D.J. DeSousa and C.C. Conaway. 1984. Subchronic inhalation toxicology of ethylene glycol monoethyl ether in the rat and rabbit. Environ. Health Perspect. 57: 157-163.

Barbee et al. (1984) exposed groups of Sprague-Dawley rats (15/sex/group) to 0, 25, 103 or 403 ppm (0, 92, 380 or 1485 mg/cu.m, assuming 25C and 760 mm Hg) ethylene glycol monoethyl ether, 6 hours/day, 5 days/week for 13 weeks. The duration-adjusted exposure concentrations were 0, 16, 68 and 265 mg/cu.m, respectively. New Zealand white rabbits (10/sex/group) were similarly exposed to 0, 25, 103 or 403 ppm (0, 92, 380 or 1485 mg/cu.m.). Physical examination and body weights measurements were conducted weekly on all animals throughout the study. Hematology, chemical chemistry and histopathological changes (including bone marrow of the sternum) were also assessed. No respiratory effects (nasal turbinates, tracheas and lungs were examined) were observed in either species.

In exposed rats, there was a significant decrease in absolute and relative pituitary weights in males at 403 ppm, a decrease in absolute spleen weight in females at all concentrations and decreased white blood cell count in females at 403 ppm. The decrease in spleen weight was significant only at the low and high concentrations. Histopathologic lesions supportive of organ weight changes for the pituitary or spleen were not observed. No other significant dose-related effects were observed in exposed rats. The NOAEL(HEC) in rats was 265 mg/cu.m, the highest concentration tested.

In both male and female rabbits, body weight was significantly depressed at 403 ppm. The adrenal weight in male rabbits exposed to 25 ppm ethylene glycol monoethyl ether was significantly depressed, but was not found to be related to a concentration response. Significantly decreased testes weight was observed in rabbits exposed to 403 ppm ethylene glycol monoethyl ether. Pathological changes in the testes were characterized as minimal to slight focal degeneration of the seminiferous tubules with loss of epithelium in 3 of 10 rabbits. Spermatogenic activity in the affected males was judged by overall organ morphology and deemed normal. Additionally, both sexes exhibited significantly decreased hemoglobin, hematocrit and erythrocyte count at 403 ppm. Based on the observed testicular and

hematopoietic effects at 403 ppm, the NOAEL(HEC) and LOAEL(HEC) in the rabbit are identified as 68 and 265 mg/cu.m, respectively.

Doe (1984) exposed pregnant Wistar rats (24/group) to 0, 9.9, 50.8 or 249.2 ppm ethylene glycol monoethyl ether (0, 36, 187 or 919 mg/cu.m) 6 hours/day during gestational days 6-15. The dams were killed on day 21 of pregnancy. Body weight, food consumption, hematological parameters, organ weights and uterine examination were factors in assessing maternal toxicity. Parameters used to assess fetal toxicity included body weight and external, visceral and skeletal examinations.

There were decreased hemoglobin and hematocrit levels and mean corpuscular volume in the 249.2 ppm exposure group; however, no other signs of maternal toxicity were observed. There was a significantly elevated preimplantation loss in the dams exposed to 9.9 or 50.8 ppm ethylene glycol monoethyl ether. Since exposure began on gestational day 6, the increased preimplantation loss is probably not treatment related. Increased late intrauterine death, decreased fetal body weight and an increased incidence of delayed ossification were observed in the offspring of rats exposed to 249.2 ppm. Partial ossification of the lumbar vertebrae was observed in rats exposed to 9.9 ppm; however, the incidence was within the historical range for this strain of rats. Based on the qualitative hematological effects, the identified NOAEL(HEC) and LOAEL(HEC) for this maternal study are 47 and 230 mg/cu.m, respectively.

Groups of pregnant Sprague-Dawley rats (n=14-15) were exposed to 0 or 100 ppm ethylene glycol monoethyl ether (369 mg/cu.m., assuming 25C and 760 mm Hg) for 7 hours/24 hours/day on gestational days 7-13 or 14-20. No effect on maternal or fetal body weight was observed. There was a statistically significant increase in gestation length in rats exposed on days 14-20. The mean length of gestation was 22.6 days for exposed rats compared with 21.9 days in the controls. These investigatiors also used six neurobehavioral tests to assess CNS functioning at various stages of development: ascent, rotorod, open field, activity wheel, avoidance conditioning and operant conditioning. In the pups exposed during gestational days 7-13, a decreased rotorod speed and an increased latency period for leaving the central area of an open field were observed. The activity of the offspring of rats exposed during gestational days 14-20 decreased on the activity wheel, and avoidance conditioning, begun on day 60 of age, revealed that these pups received an increased number and duration of shocks. Neurochemical and neurobehavioral changes occurred. Whole brain norepinephrine levels in the newborns of the exposed dams from both exposure groups (7-13 and 14-20 days) decreased. At age 21 days, norepinephrine was increased in the cerebrum, brain stem and midbrian of 7- to 13-day exposed pups only. Increased dopamine levels were found in the cerebrum only of pups from both exposure periods, while serotonin was increased in the 14-20 day exposure group. The midbrains of pups exposed on gestation days 7-13 had protein levels that exceeded the controls. Gross teratogenic anomalies (terata) were not detected due to insufficient numbers of animals or

inadequate procedures. The LOAEL for developmental effects is 369 mg/cu.m (HEC=369 mg/cu.m) (Nelson et al., 1981).

Nelson et al. (1982a,b) exposed Sprague-Dawley rats to 0 or 200 ppm ethylene glycol monoethyl ether (737 mg/cu.m) on gestational days 7-13. Decreased neuromotor ability, assessed by an ascent test and rotorod, and less activity in an open field and shuttle box, were observed in the pups of treated dams, as well as extended pregnancy duration for the dams given 200 ppm ethylene glycol monoethyl ether (Nelson et al., 1982a). Increased dopamine and norepinephrine levels were also observed, especially in the cerebrum, in the 21-day-old pups (Nelson et al., 1982b).

In a range-finding study, Nelson et al. (1981) exposed groups of 3-4 pregnant rats to 300, 600, 900 or 1200 ppm (1106, 2212, 3317 or 4423 mg/cu.m, assuming 25C and 760 mm Hg) 7 hours/day on gestational days 7-13 or 14-20. The dams exposed on gestational days 14-20 were also exposed to 200 ppm ethylene glycol monoethyl ether. These investigators observed increased fetal and pup mortality and increased gestation length at exposure levels greater than or equal to 200 ppm (737 mg/cu.m).

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

UF — An uncertainty factor of 10 was used to account for intraspecies extrapolation, 10 for use of a subchronic study and 3 to account for interspecies extrapolation. The reproductive and developmental studies for ethylene glycol monoethyl ether are considered to be of sufficient number and quality in various species exposed both by oral and inhalation exposure. Thus, an uncertainty factor for an incomplete database is not needed.

MF — None

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

The potential for testicular toxicitiy in a group of workers exposed to ethylene glycol monoethyl ether vapors was assessed by Clapp et al. (1987) and Ratcliffe et al. (1989). Exposure levels ranged from not detectable to 24 ppm (88 mg/cu.m, assuming 25C and 760 mm Hg), with average levels under 6 ppm (22 mg/cu.m) in one building and 11 ppm (41 mg/cu.m) in a second building (Clapp et al., 1987). Exposure occurred by inadvertent skin contact, inhalation or by airborne vapor condensing on the skin. Ratcliffe et al. (1989) obtained semen samples from 37 exposed and 39 unexposed workers. Mean sperm count per ejaculate in exposed workers showed a marginal statistically significant (p=0.047) decrease compared with controls (corrected for abstinence, sample age, caffeine, alcohol and tobacco consumption, urogenital and other medical disorders). No statistically significant differences in semen volume, sperm concentration, semen

pH, viability, motility, velocity and morphology were observed. Sperm counts of both exposed workers and controls were significantly different from historical values, suggesting that controls may also have had some exposure to ethylene glycol monoethyl ether or that both groups may have been exposed to another compound that affects spermatogenesis. Most of the workers in the control and some in the exposed group may have been exposed to metal fumes and dusts, solvents (tetrachloroethylene) or heat and vibration. Analysis of sperm parameters by duration and potential intensity of exposure did not reveal an exposure-related effect. Ethylene glycol monoethyl ether was not identified in the blood of exposed or control workers, although ethoxyacetic acid (primary metabolite of ethylene glycol monoethyl ether) was found in the urine of exposed but not control workers. Ratcliffe et al. (1989) concluded that the results suggest a possible effect of ethylene glycol monoethyl ether exposure on sperm quality in the workers, but noted that the study is limited by the small sample sizes and the large interpersonal variation in the examined parameters.

Doe (1984) exposed groups of pregnant Dutch rabbits (n=24) to 0, 10.1, 51 or 175 ppm ethylene glycol monoethyl ether (0, 37, 188 or 645 mg/cu.m, assuming 25C and 760 mm Hg) 6 hours/day on gestational days 6-18. Maternal toxicity was not observed; hematological parameters were not measured. The offspring of does exposed to 645 mg/cu.m had an increased incidence of skeletal defects and skeletal variants. The NOAEL(HEC) for this study is 188 mg/cu.m.

Andrew et al. (1981) exposed pregnant Wistar rats (n=37) to 0, 202 or 767 ppm (0, 743 or 2821 mg/cu.m, assuming 25C and 760 mm Hg) ethylene glycol monoethyl ether 7 hours/day on gestational days 0-19. In the same study, New Zealand white rabbits (n=29) were exposed to 0, 160 or 617 ppm (0, 588 or 2269 mg/cu.m) ethylene glycol monoethyl ether 4 hours/day on gestational days 0-19. Decreased maternal weight gain was observed in rats exposed to 2827 mg/cu.m; and no fetuses survived (100% litter resorption). In the offspring of rats exposed to 202 ppm, decreased fetal body weight and crown-rump length, increased incidence of cardiovascular defects (transposed and retrotracheal pulmonary artery) and minor skeletal anomalies and common skeletal variants were observed. The LOAEL(HEC) for developmental effects in rats is 743 mg/cu.m. Decreased maternal body weight and food intake were observed in the does; however, no histopathological alterations in the lungs, liver or kidneys were apparent. An increased incidence of resorptions at 160 ppm and in the 617 ppm group (100 resorptions) was observed. An increased incidence of major malformations (ventral wall defects and fusion of aorta with pulmonary artery), minor anomalies (renal changes) and common skeletal variants (supernumerary ribs with associated variations and sternebral defects) were observed in the offspring of the rabbits exposed to 160 ppm. The LOAEL(HEC) is determined to be 588 mg/cu.m.

Female Wistar rats (37/group) were exposed to 1, 150 or 649 ppm ethylene glycol monoethyl ether (36, 552 or 2387 mg/cu.m, assuming 25C and 760 mm Hg) 7 hours/day, 5 days/week for 3

weeks prior to mating with naive males. No reproductive effects were observed (Andrew et al., 1981).

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

Medium confidence is placed in the critical study because of its short duration. Several other studies of rats and rabbits have corroborated the reproductive effects observed in the principal study. Moreover, a subchronic inhalation study in rats and rabbits suggests that reproductive toxicity is the most sensitive endpoint. However, no chronic inhalation studies were located in the available literature. Thus, medium confidence in the database is selected. Reflecting medium confidence in the key study and the 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, 1985

Agency Work Group Review — 09/19/1990, 12/19/1990

Verification Date — 12/19/1990

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 2-Ethoxyethanol conducted in November 2001 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to 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 — 2-Ethoxyethanol
CASRN — 110-80-5

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

VI. Bibliography

Substance Name — 2-Ethoxyethanol
CASRN — 110-80-5

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

Andrew, F.D., R.L. Buschbom, W.C. Cannon, et al. 1981. Teratologic assessment of ethylbenzene and 2-ethoxyethanol. Prepared for the National Institute for Occupational Safety and Health under Contract 210-79-0037, Battelle Pacific Northwest Laboratories, Richland, WA 99352. Microfiche #OTS0513150.

Barbee, S.J., J.B. Terrill, D.J. DeSousa and C.C. Conaway. 1984. Subchronic inhalation toxicology of ethylene glycol monoethyl ether in the rat and rabbit. Environ. Health Perspect. 57: 157-163.

Clapp, D.E., A.W. Smallwood, C. Moseley and K.E. DeBord. 1987. Workplace assessment of exposure to 2-ethoxyethanol. Appl. Ind. Hyg. 2(5): 183-187.

Doe, J.E. 1984. Ethylene glycol monoethyl ether and ethylene glycol monoethyl ether acetate teratology studies. Environ. Health Perspect. 57: 33-41.

Nelson, B.K., W.S. Brightwell, J.V. Setzer, B.J. Taylor, R.W. Hornung and T.L. O'Donohue. 1981. Ethoxyethanol behavioral teratology in rats. Neurotoxicology. 2: 231-249.

Nelson, B.K., W.S. Brightwell and J.V. Setzer. 1982a. Prenatal interactions between ethanol and the industrial solvent 2-ethoxyethanol in rats: Maternal and behavioral teratogenic effects. Neurobehav. Toxicol. Teratol. 4(3): 387-394.

Nelson, B.K., W.S. Brightwell, J.V. Setzer and T.L. O'Donohue. 1982b. Prenatal interactions between ethanol and the industrial solvent 2- ethoxyethanol in rats: Neurochemical effects in the offspring. Neurobehav. Toxicol. Teratol. 4(3): 395-401.

Ratcliffe, J.M., S.M. Schrader, D.E. Clapp, W.E. Halperin, T.W. Turner and R.W. Hornung. 1989. Semen quality in workers exposed to 2-ethoxyethanol. Br. J. Ind. Med. 46(6): 399-406.

U.S. EPA. 1985. Health and Environmental Effects Profile for 2-Ethoxyethanol. 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.

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — 2-Ethoxyethanol
CASRN — 110-80-5

Date	Section	Description
05/01/1991	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 — 2-Ethoxyethanol
CASRN — 110-80-5
Last Revised — 05/01/1991

- 110-80-5
- Ethanol, 2-ethoxy-
- ATHYLENGLYKOL-MONOATHYLATHER [German]
- BETA-ETHOXYETHANOL
- Cellosolve
- CELLOSOLVE SOLVENT
- Celosolv [Czech]
- Dowanol EE
- Ektasolve EE
- Emkanol
- Eter monoetilico del etilenglicol [Spanish]
- Ethanol, 2-Ethoxy-
- ETHER MONOETHYLIQUE DE L'ETHYLENE-GLYCOL [French]
- Ether monoethylique de l'ethyleneglycol [French]
- Ethoxyethanol
- ETHYL CELLOSOLVE
- ETHYL GLYCOL
- ETHYLENE GLYCOL ETHYL ETHER
- Ethylene Glycol Monoethyl Ether
- ETOKSYETYLOWY ALKOHOL [Polish]
- GLYCOL ETHER EE
- GLYCOL MONOETHYL ETHER
- HSDB 54
- Hydroxy ether
- Jeffersol EE
- NCI-C54853
- NSC 8837
- Oxitol
- POLY-SOLV EE
- UN 1171
- 2-ethoxyethanol