0500
Ethylene glycol monobutyl ether (EGBE) (2-Butoxyethanol) (CASRN 111-76-2)

Human health assessment information on a chemical substance is included in IRIS only after a comprehensive review of toxicity data by U.S. EPA health scientists from several program offices, regional offices, and the Office of Research and Development. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the positions that were reached during the review 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 at http://www.epa.gov/iris/backgr-d.htm.

STATUS OF DATA FOR ETHYLENE GLYCOL MONOBUTYL ETHER (EGBE)

File First On-Line 12/30/1999

Category (section)	Status	Last Revised
Chronic Oral RfD Assessment (I.A.)	on-line	00/00/0000
Chronic Inhalation RfC Assessment (I.B.)	on-line	00/00/0000
Carcinogenicity Assessment (II.)	on-line	00/00/0000

_I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Substance Name -- Ethylene glycol monobutyl ether (EGBE)
CASRN -- 111-76-2
Section I.A. Last Revised -- 00/00/0000

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgr-d.htm for an elaboration of these

concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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.

The previous oral RfD for EGBE (posted on the IRIS database in 1999) was 0.5 mg/kg-day, based on a National Toxicology Program (NTP, 1993) subchronic drinking water study in rats and mice using changes in mean corpuscular volume as the critical effect. C_{max} (peak blood concentrations) for 2-butoxyacetic acid (BAA) in arterial blood of female rats following oral exposure was estimated using the physiologically based pharmacokinetic (PBPK) model of Corley et al. (1994) as modified by Corley et al. (1997). The benchmark dose $(BMD)_{05}$ was determined to be 64 µM, using the 95% lower confidence limit of the dose-response curve expressed in terms of the C_{max} for BAA in blood. The PBPK model of Corley was used to "back-calculate" " to a human equivalent dose (HED) of 5.1 mg/kg-day, assuming that rats and humans receive their entire dose of EGBE from drinking water over a 12-hour period each day. The RfD was calculated by applying a uncertainty factor (UF) of 10 for intrahuman variability to the benchmark dose, 95% lower bound (BMDL) HED of 5.1 mg/kg-day.

___I.A.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD
Hemosiderin deposition in the liver	BMDL(HED): 1.4 mg/kg-day (PBPK and BMD_{10})	10	0.1 mg/kg-day
Chronic (rat and mouse) inhalation study			
NTP 2000			

*Conversion Factors and Assumptions -- The database of oral studies for EGBE is more limited than the database of inhalation studies. For this reason, a PBPK model for EGBE has been applied to the inhalation data for derivation of an RfD. As with the animal-to-human extrapolation used in the development of the reference concentration (RfC), the dose metric used for animal-to-human and route-to-route (inhalation-to-oral) extrapolation for the derivation of the RfD is the area under the curve (AUC) of BAA at 12 months in arterial blood. This dose metric was used for dose-response modeling of chronic inhalation data to derive the point of departure (POD) of 133 µmol-hour/L, expressed as a BMDL. The BMDL was then back-calculated using the human PBPK model (Corley et al., 1997, 1994) to obtain an equivalent human oral drinking water dose ($BMDL_{HED}$) of 1.4 mg/kg-day. A simplifying assumption was used that the entire dose of drinking water EGBE was consumed over a 12-hour period each day.

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES

NTP (National Toxicology Program). (2000) NTP technical report on the toxicology and carcinogenesis studies of 2-butoxyethanol (CAS No. 111-76-2) in F344/N rats and $B6C3F_1$ mice (inhalation studies). Public Health Service, U.S. Department of Health and Human Services;

NTP TR 484; NIH Publ. No. 00-3974. Available from the National Institute of Environmental Health Sciences, Research Triangle Park, NC and online at http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr484.pdf.

NTP (2000) completed a two-species, 2-year inhalation study on EGBE in both genders of rats and mice. In this chronic study, animals were exposed to EGBE 6 hours/day, 5 days/week at concentrations of 0, 31, 62.5, and 125 ppm (0, 150, 302, and 604 mg/m^3) for groups of 50 F344/N rats and 0, 62.5, 125, and 250 ppm (0, 302, 604, and 1,208 mg/m^3) for groups of 50 B6C3F_1 mice. The researchers stated that the highest exposure was selected to produce a 10–15% depression in hematologic indices. They reported that no effect on survival was observed in rats, but survival was statistically significantly decreased in male mice exposed to 125 or 250 ppm, compared with chamber controls (54, 52, and 78% respectively). Although statistics were not reported for mean body weights, the rats exposed to 31 and 62.5 ppm had similar mean body weights to the control rats. Mean body weights of the exposed mice were generally less than for controls, with females experiencing greater and earlier reductions. From week 17 to the end of the study, the mean body weights of 125 ppm female rats were generally less than those of controls. Non-neoplastic effects in rats included hyaline degeneration of the olfactory epithelium in males (13/48, 21/49, 23/49, 40/50) and females (13/50, 18/48, 28/50, 40/49) and Kupffer cell pigmentation in the livers of males (23/50, 30/50, 34/50, 42/50) and females (15/50, 19/50, 36/50, 47/50). The severity of the olfactory lesion was not affected by exposure. The Kupffer cell pigmentation is a result of hemosiderin accumulation and is a recognized secondary effect of the hemolytic activity of EGBE.

Non-neoplastic, statistically significant effects in mice included forestomach ulcers and epithelial hyperplasia, hematopoietic cell proliferation and hemosiderin pigmentation in the spleen, Kupffer cell pigmentation in the livers, and bone marrow hyperplasia (males only). Hyaline degeneration of the olfactory epithelium (females only) was increased relative to chamber controls but was not statistically significant. As in the rats, the Kupffer cell pigmentation was considered a secondary effect of the hemolytic activity of EGBE. Bone marrow hyperplasia, hematopoietic cell proliferation, and hemosiderin pigmentation in the spleen were also attributed to the primary hemolytic effect; it was followed by regenerative hyperplasia of the hematopoietic tissue. The forestomach lesions did not appear to be related to the hemolytic effect of EGBE. Incidences of ulcer were significantly increased in all exposed female groups, as well as males exposed to 125 ppm. Incidences of epithelial hyperplasia, usually focal, were significantly increased in all exposed groups of males and females. The hyperplasia was often associated with ulceration, particularly in the females, and consisted of thickness of the stratified squamous epithelium and sometimes the keratinized layer of the forestomach. Ulceration consisted of a defect in the forestomach wall that penetrated the full thickness of the epithelium and frequently contained accumulations of inflammatory cells and debris.

Using the same exposure levels described above, additional groups of rats (27/gender/exposure group) and mice (30/gender/exposure group) in the 2-year study were examined at 3, 6, and 12 months (8–10 animals/time point) for hematologic effects. Nine male and nine female rats were exposed to 31 ppm EGBE, specifically to evaluate hematology at 3 months and to receive a total evaluation at 6 months. Animals were continuously exposed, as described above, until their sacrifice at 3, 6, or 12 months. As in the 14-week study, inhalation of EGBE by both species resulted in the development of exposure-related hemolytic effects, inducing a responsive anemia. In rats, the anemia was persistent and did not progress or ameliorate in severity from

3 months to the final blood collection at 12 months. Statistically significant ($p < 0.05$) decreases in automated and manual hematocrit (Hct) values, hemoglobin (Hb) concentrations, and red blood cell (RBC) counts occurred at 3, 6, and 12 months in the 125 ppm female mice and the 250 ppm male and female mice. Statistically significant decreases in these same endpoints were also observed in 62.5 ppm females at 6 months and in 125 ppm males at 6 and 12 months (decreases in Hct were observed only at 3 and 6 months). Mean cell volume (MCV) was increased in female mice at the highest duration (12 months) and exposure (250 ppm) levels. Reticulocyte counts were increased significantly in the 125 ppm females at 3 and 6 months and in the 125 ppm males at 6 months of exposure.

In the subchronic portion of the inhalation NTP (2000) study, F344 rats and $B6C3F_1$ mice (10/gender) were exposed to EGBE concentrations of 0, 31, 62.5, 125, 250, and 500 ppm (0, 150, 302, 604, 1,208, and 2,416 mg/m^3) 6 hours/day, 5 days/week for 14 weeks. Hematologic and hemosiderin staining results are indicative of the various degrees of hemolysis caused by exposure to increasing concentrations of EGBE. Both rat genders exhibited clinical signs at the three highest doses, consistent with the hemolytic effects of EGBE, including: (1) deficits in RBCs as a result of lysis manifestation through the clear dose-related decrease in Hct, a finding consistent with decreases noted for both RBC count and Hb concentrations; and (2) increases in both reticulocytes and nucleated erythrocytes at higher doses, homeostatic responses that would be anticipated to occur as the lysed blood cells are being replaced. Female rats may be somewhat more sensitive: several statistically significant effects occurred at the 31 ppm level in females, as opposed to a single parameter for males. In addition, the degree to which these various measures are affected is somewhat greater in females than males, indicated as percent control, particularly at the three highest concentrations. Hematologic evaluation showed mild-to-moderate regenerative anemia at all concentrations in females and at the three highest concentrations in males. Exposure-related trends were noted for reticulocyte count, RBC count, MCV, Hb concentration, and Hct. Liver-to-body-weight ratios increased significantly in males at the two highest concentrations and in females at the highest concentration. Histopathologic effects at concentrations in excess of 62.5 ppm for male rats and 31 ppm for females consisted of excessive splenic congestion in the form of extramedullary hematopoiesis, hemosiderin accumulation in Kupffer cells, liver necrosis, centrilobular hepatocellular degeneration, renal tubular degeneration, intracytoplasmic Hb and hemosiderin deposition, and bone marrow hyperplasia. In addition, five moribund female rats were sacrificed from the highest concentrations, and one from the 250 ppm group. The lowest-observed-adverse-effect level (LOAEL) for hematological alterations was 31 ppm for female rats and 62.5 ppm for male rats. The 31 ppm exposure level was considered a no-observed-adverse-effect level (NOAEL) for male rats.

The mice exposed via the inhalation route exhibited clinical signs consistent with the hemolytic effects of EGBE at the two highest concentrations for both genders. Hematologic evaluation indicated a moderate regenerative anemia (marked by decreased RBC counts, increased reticulocyte counts, and increased MCV) with an increase in platelets at the three highest concentrations in both genders. Histopathological effects consisted of excessive extramedullary splenic hematopoiesis, renal tubular degeneration, hemosiderin deposition in the spleen and kidney and accumulation in Kupffer cells, and testicular degeneration. Forestomach necrosis, ulceration, inflammation, and epithelial hyperplasia were observed at concentrations >31 ppm for females and 62.5 ppm for males. In addition, four females and four males either died or were sacrificed moribund at the highest concentration. The NOAEL for male and female

mice was 31 ppm and the LOAEL in mice was 62.5 ppm, based on histopathological changes in the forestomach.

___I.A.3. UNCERTAINTY FACTORS

UF = 10

A factor of 10 was selected to account for the uncertainty associated with the variability of the human response (UF_H) to the effects of EGBE. Potentially susceptible subpopulations include individuals with enhanced metabolism or decreased excretion of BAA and individuals whose RBC membranes are more susceptible to the lysis caused by BAA, the precursor step to developing hemosiderin staining in the liver. Human in vitro studies suggest that the elderly and patients with fragile RBCs would not be more sensitive to the hemolytic effects of EGBE than normal adults. Laboratory animal studies suggest that older animals are more sensitive than neonates and that females are more sensitive than males. While developmental studies do not reveal increased susceptibility in infants, none of the developmental studies examined fetal or infant blood for signs of effects from prenatal exposure to EGBE. Additionally, human responses to EGBE have not been observed under a broad range of exposure conditions (e.g., repeated or long-term exposures) and potentially sensitive subjects (e.g., individuals predisposed to hemolytic anemia or infants).

A factor of 1 was selected to account for the uncertainty associated with interspecies variability resulting from toxicodynamic and toxicokinetic differences between animals and humans (UF_A). Traditionally, these components (toxicodynamic and toxicokinetic) are individually represented by partial UFs of 3 for a total UF of 10 in the absence of chemical-specific information; thus, application of a full UF of 10 would depend on two areas of uncertainty (i.e., toxicokinetic and toxicodynamic uncertainties). In this assessment, the toxicokinetic uncertainty is addressed by the determination of an HED, using a combination of measured internal blood levels in the test animals and PBPK modeling. A value of 1 was selected for the toxicokinetic portion of the UF_A. Regarding toxicodynamics, in vivo (Carpenter et al., 1956) and in vitro (Udden, 2002; Udden and Patton, 1994; Ghanayem and Sullivan, 1993) studies indicate that humans may be significantly less sensitive than rats to the hematological effects of EGBE. A value of 1 was selected for the toxicodynamic portion of the UF_A.

A factor to account for extrapolation from subchronic to chronic exposure (UF_S) was not needed because the RfD was derived from a chronic inhalation study.

A factor for LOAEL to NOAEL (UF_L) was not applied because the current approach is to address this extrapolation as one of the considerations in selecting a benchmark response (BMR) for BMD modeling. In this case, EPA concluded a 10% increase in hemosiderin staining, indicating a precursor to an adverse effect, is appropriate for use in deriving the RfD under the assumption that it represents a minimal biologically significant change.

A factor of 1 was selected to account for deficiencies in the database (UF_D). While no chronic oral studies or adequate human data are available for EGBE, PBPK models allow for deriving a BMDL from the chronic inhalation study using measured internal dose metrics and then extrapolating it back to an equivalent human oral dose. The database for inhalation exposure includes chronic and subchronic studies in two species (rats and mice), and several reproductive and developmental studies, including a two-generation reproductive toxicity study.

___I.A.4. ADDITIONAL STUDIES/COMMENTS

Carpenter et al. (1956) conducted three controlled inhalation studies. In the first study, a group of two men and six rats were exposed simultaneously for 4 hours to an EGBE concentration of 113 ppm in a 1,250 cubic foot room. Effects observed in humans included nasal and ocular irritation, a metallic taste, and belching. Erythrocyte osmotic fragility did not change for the men, yet rose appreciably for the rats. In a second study, a group of two men, one woman, and three rats were exposed to 195 ppm EGBE for two 4-hour periods, separated by a 30-minute recess, in a 6.5 cubic foot room. There was no change in the subjects' blood pressure, erythrocyte fragility, or pulse rate. They experienced nose and throat irritation, followed by ocular irritation and disturbed taste; one subject reported a headache. In the rats, an increase in erythrocyte fragility values was noted. In the third study, two men and two women were exposed for 8 hours to a 100 ppm EGBE concentration. No changes in blood pressure, erythrocyte fragility, or pulse rate were observed. Again, nasal and throat irritation followed by ocular irritation and a disturbing metallic taste were experienced. Two subjects reported headaches.

There are a number of case reports of acute ingestion of EGBE, consisting primarily of accidental or intentional ingestion. Bauer et al. (1992) reported the effects of acute ingestion of 500 mL of window cleaner containing 9.1% EGBE and 2.5% ethanol by a 53-year-old alcoholic male. He was comatose with metabolic acidosis, shock and noncardiogenic pulmonary edema when brought to a hospital, approximately 10 hours after ingestion. He had increased heart rate, decreased blood pressure, and transient polyuria and hypoxemia. Hypochromic anemia was evident with an Hb concentration of 9.1 g/100 mL, a Hct of 25%, and thrombocytopenia. The patient recovered and was discharged after 15 days.

Gijsenbergh et al. (1989) reported that a 23-year-old woman weighing 64 kg ingested approximately 25–30 g of EGBE (~400–500 mg/kg) and ethanol (~4:1 ratio) as a window cleaner in an apparent suicide attempt. She was comatose when admitted to the hospital, exhibiting dilated pupils, obstructive respiration, and metabolic acidosis, including depression of blood Hb concentration and hematuria. The presence of EGBE in the blood and dialysis fluid was confirmed. Treatment consisted of supportive therapy, forced diuresis, bicarbonate administration, and hemodialysis. Her Hb concentration fell from 11.9 g Hb/100 mL upon admission to 8.9 g Hb/100 mL. She was discharged after 8 days.

Gualtieri et al. (2003, 1995) reported a case of a suicide attempt with an industrial-strength window cleaner. The 18-year-old male weighed 71 kg; he consumed between 360 and 480 mL of a concentrated glass cleaner that contained 22% EGBE, a dose equivalent to 1,131–1,509 mg/kg. He was admitted to the hospital with no abnormalities other than epigastric discomfort within 3 hours postingestion. Approximately 10 hours postadmission, the patient was noticeably lethargic, weak, and hyperventilating, symptoms consistent with the onset of metabolic acidosis. BAA was measured; the highest serum concentration found was 4.86 mmol/L, collected approximately 16 hours postingestion. The patient was transferred to a tertiary care hospital where hemodialysis was initiated at approximately 24 hours postingestion. Ethanol therapy was started 30 minutes later. Treatment also consisted of intravenousdoses of 100 mg thiamine and 50 mg folic acid every 12 hours and 50 mg pyridoxine every 6 hours. Following 4 hours of dialysis, the patient was alert and remained hemodynamically stable. Ten days after discharge, the patient was readmitted following a second ingestion of 480 mL of the

same cleaner, an EGBE dose equivalent to 1,509 mg/kg. Treatment included ethanol therapy and hemodialysis, and was initiated within a few hours of ingestion to control the metabolic acidosis. Due to this early treatment, ethanol therapy had an impact on the disposition of EGBE and BAA. As with the first episode, metabolic acidosis was manifest. This high-dose oral ingestion was nearly 1.1–1.5 g EGBE/kg body weight. The highest serum BAA concentration was 2.07 mmol/L, collected 22 hours postingestion. No evidence of hemolysis or renal abnormalities was detected.

A 50-year-old woman ingested approximately 250–500 mL of a window cleaner containing 12% EGBE, representing ~30–60 mL, in an apparent suicide attempt (Rambourg-Schepens et al., 1988). She was diagnosed with metabolic acidosis, hypokalemia, a rise in serum creatinine level, and a marked increase in urinary excretion of oxalate crystals. Moderate hemoglobinuria appeared on the third day postexposure, and a progressive erythropenia was noted. In the absence of more complete hematologic details from this and other similar case studies, it is not possible to determine whether these effects were due to hemolysis or other factors related to the profound blood chemistry changes observed. The clinical status improved gradually and the patient was discharged on the 10th day.

Burkhart and Donovan (1998) summarized the case of a 19-year-old male who ingested 20–30 ounces, or ~590–885 mL, of a product that contained 25–35% EGBE (an exposure equivalent to ~177–265 mL, estimated at >3,000 mg/kg) along with 15–25% propylene glycol, 5–10% monoethanolamine, and 1–3% potassium hydroxide. On his arrival at the hospital 3.5 hours after ingestion, the patient was deeply comatose with severe hypotension. Hematuria developed on the second day, with no evidence of renal or hepatic toxicity; however, pulmonary toxicity consisting of severe aspiration pneumonia was present. The patient had a significant recovery, despite severe neurologic deficits that were slow to resolve.

Osterhoudt (2002) reported on a 16-month-old girl who ingested an unknown amount of cleaning solution containing EGBE (10–30%), monoethanolamine (5–10%), alkoxylated linear alcohols (1–5%), ethylenediaminetetraacetic acid (1–5%), and potassium hydroxide (1–5%). Metabolic acidosis was manifest, and a single dose (15 mg/kg) of the aldehyde dehydrogenase (ALDH) inhibitor fomepizole was administered. Within 2 hours, the metabolic acidosis was completely resolved, and there was no evidence of alkaline mucosal injury, hepatic or renal dysfunction, or hemolysis.

Dean and Krenzelok (1991) reported that 24 children, aged 7 months to 9 years, were observed subsequent to oral ingestion of at least 5 mL of glass window cleaner containing EGBE in the 0.5–9.9% range. Two children drank more than 15 mL and were treated by gastric lavage. No symptoms of EGBE poisoning, such as metabolic acidosis, and no hemolysis were observed in any of the children.

Raymond et al. (1998) reported on seven clerical workers who were evaluated 8 months after they entered a file room where the supervisor believed that EGBE had been applied overnight to strip the floor. Exact details of the product used were unknown, but based on containers found and exposure symptoms of noted intense eye and respiratory irritation, marked dyspnea, nausea, and faintness, the authors suggested that they were exposed to EGBE concentrations of 200–300 ppm. Of major concern were skin spots—cherry angiomas—that appeared between 4 and 22 weeks after exposure in six of the seven workers. All workers continued to experience recurrent eye and tracheobronchial irritation; four had a dry cough.

Workplace air sampling conducted by a certified industrial hygienist 1 week after the floor stripping found no detectable EGBE, although traces (0.1–0.2 ppm) of formaldehyde were identified. Five years after the exposure, four of the workers who could be contacted reported that they continued to have outbreaks of new cherry angiomas. It should be noted that no other studies linking EGBE exposure to outbreaks of cherry angiomas are available in the literature. The authors included the observation that, since this report, they had seen three patients who they believe were also exposed to EGBE vapor in an unrelated incident, and who did not develop any skin spots. Cherry angiomas are the most common cutaneous vascular lesion; they are benign and formed by a proliferation of dilated venules. The spots occur more frequently with increasing age but can appear in younger individuals. There are reports in the literature of cherry angiomas appearing following individual exposure to other chemicals, such as bromides (Cohen et al., 2001), glutaraldehyde (Raymond et al., 1998), and sulfur mustard gas (Firooz et al., 1999).

A cross section of 31 male workers, aged 22–45, employed for 1–6 years, who were exposed to low levels of EGBE in a beverage packing production plant were monitored by Haufroid et al. (1997). The effect of external EGBE exposure and internal BAA levels on erythrocyte lineage were investigated by monitoring: RBC count, Hb, Hct, MCV, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), haptoglobin (Hp), reticulocyte count, and osmotic resistance (OR), a measure of osmotic fragility. Also studied were serum glutamic-oxaloacetic and glutamic-pyruvic transaminases and renal creatinine and urinary retinol binding protein parameters. The average airborne concentration of EGBE was 2.91 mg/m^3, or 0.6 ppm (standard deviation [SD] of ±1.30 mg/m^3 or 0.27 ppm). In addition, there was coexposure to methyl ethyl ketone. Single determinations of BAA in postshift urine samples were used to assess exposure to low levels of EGBE. No differences were observed for RBC counts, Hb, MCV, MCH, Hp, reticulocyte count, or OR between exposed and control workers. The only statistically significant change observed in exposed workers when compared with a matched control group (n = 21) was a 3.3% decrease in Hct (p = 0.03) and a 2.1% increase in MCHC (p = 0.02). The implications of these small erythroid effects are unclear. Both values are within their corresponding normal clinical ranges and, given that no statistically significant changes were observed in other erythroid parameters, they do not appear to be related to the more severe adverse effects observed in laboratory animals. Furthermore, no correlation was found between any of the nine erythroid parameters measured and the parameters of internal exposure. No significant differences were observed in hepatic and renal biomarkers.

Several human studies investigated the dermal absorption of EGBE. Jakasa et al. (2004) dermally exposed six male research subjects, ages 22–55, to 50%, 90%, or neat EGBE for 4 hours on the forearm over an area of 40 cm^2. The dermal absorption of EGBE from aqueous solutions was markedly higher than from neat EGBE. In Jones et al. (2003), four research subjects were exposed via inhalation of 50 ppm EGBE for 2 hours on nine separate occasions, with each occasion separated by 3 weeks, at varying temperatures and humidity levels. Results show that "baseline" dermal contribution to total body absorption of EGBE vapor in appropriately dressed workers was, on average, 11%. Higher temperature (30°C, mean 14%, p = 0.03) and greater humidity (65% relative humidity, mean 13%, p = 0.1) both increased dermal absorption. The wearing of whole-body overalls did not attenuate absorption (mean 10%). By combining several factors together in the industrial scenario, dermal absorption of vapors was reported to be as high as 39% of the total absorbed dose.

___I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Study -- High
Data Base -- Medium to high
RfD -- Medium to high

The overall confidence in the RfD is medium to high because theRfD has been calculated using a route-to-route extrapolation from the PBPK/benchmark concentration (BMC) method used to derive the RfC. This method accounts for pharmacokinetic differences between rats and humans using a validated PBPK model (Corley et al., 1997, 1994). There is high confidence in the NTP (2000) study because it was a chronic study, employed both male and female rats and mice, had a wide range of exposure levels, and animals were observed twice daily. There is medium-to-high confidence in the database, because data are available for a variety of animal species, including humans. Confidence in the database is not high, because the potential for effects in humans from repeat, long-term exposures has not been investigated.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document -- U.S. EPA (2009) Toxicological review of ethylene glycol monobutyl ether.

This document was provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Ethylene Glycol Monobutyl Ether* (U.S. EPA, 2009).

___I.A.7. EPA CONTACTS

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 (email address).

__I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Substance Name -- Ethylene glycol monobutyl ether (EGBE)
CASRN -- 111-76-2
Section I.B. Last Revised -- 00/00/0000

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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.

The previous RfC for EGBE (posted on the IRIS database in 1999) was 13 mg/m^3, based on an NTP (1998) subchronic inhalation study in rats using changes in mean RBC count as the critical effect. C_{max} (peak blood concentrations) for BAA in arterial blood of female rats following inhalation exposure was estimated using the PBPK model of Lee et al. (1998). The BMD_{05} was calculated to be 225 µM, using the 95% lower confidence limit of the dose-response curve expressed in terms of the C_{max} for BAA in blood. The PBPK model of Corley et al. (1997, 1994) was used to "back-calculate" to a human equivalent concentration (HEC) of 78 ppm (380 mg/m^3) assuming continuous exposure (24 hours/day). The RfC was calculated by applying a UF of 30 (10 for intrahuman variability and 3 for extrapolation from a LOAEL) to the benchmark concentration, 95% lower bound (BMCL) HEC of 380 mg/m^3.

___I.B.1. CHRONIC INHALATION RfC SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfC
Hemosiderin deposition in the liver Chronic (rat and mouse) inhalation study NTP 2000	BMCL(HEC): 16 mg/m^3 (PBPK and $BMCL_{10}$)	10	1.6 mg/m^3

*Conversion Factors and Assumptions -- For the purposes of deriving an RfC for EGBE, hemosiderin staining data were evaluated in male and female rats from the 2-year chronic study by NTP (2000). A 10% extra risk was used as a BMR level for quantal data as this is at or near the limit of sensitivity in most cancer bioassays and in some noncancer bioassays as well. Because the hemosiderin staining endpoint was observed in control animals and a 10% increase in incidence was within the observable range of the data, 10% extra risk was considered an appropriate BMR and a $BMCL_{10}$ an appropriate POD for derivation of the RfC (U.S. EPA, 2000, 1995).

The AUC was selected as the appropriate dose metric due to the nature of the endpoint, hemosiderin deposition. This endpoint increased in severity with increased duration (subchronic to chronic) and is believed to be the result of the cumulative exposure to EGBE as opposed to a peak event. A $BMCL_{10}$ of 133-µmol hour/L for hemosiderin staining in liver of male rats chronically exposed to EGBE (NTP, 2000) was used as the POD to calculate the RfC. A human PBPK model (Corley et al., 1997) was used to back-calculate to an HEC of 16 mg/m^3 (3.4 ppm) for the $BMCL_{HEC}$.

___I.B.2. PRINCIPAL AND SUPPORTING STUDIES

NTP (National Toxicology Program). (2000) NTP technical report on the toxicology and carcinogenesis studies of 2-butoxyethanol (CAS No. 111-76-2) in F344/N rats and B6C3F$_1$ mice (inhalation studies). Public Health Service, U.S. Department of Health and Human Services; NTP TR 484; NIH Publ. No. 00-3974. Available from the National Institute of Environmental Health Sciences, Research Triangle Park, NC and online at http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr484.pdf.

See Section 1.A.2 for a complete description.

___I.B.3. UNCERTAINTY FACTORS

UF = 10

A factor of 10 was selected to account for the uncertainty associated with the variability of the human response (UF_H) to the effects of EGBE. Potentially susceptible subpopulations include individuals with enhanced metabolism or decreased excretion of BAA and individuals whose RBC membranes are more susceptible to the lysis caused by BAA, the precursor step to developing hemosiderin staining in the liver. Human in vitro studies suggest that the elderly and patients with fragile RBCs would not be more sensitive to the hemolytic effects of EGBE than normal adults. Laboratory animal studies suggest that older animals are more sensitive than neonates and that females are more sensitive than males. While developmental studies do not reveal increased susceptibility in infants, none of the developmental studies examined fetal or infant blood for signs of effects from prenatal exposure to EGBE. Additionally, human responses to EGBE have not been observed under a broad range of exposure conditions (e.g., repeated or long-term exposures) and potentially sensitive subjects (e.g., individuals predisposed to hemolytic anemia or infants).

A factor of 1 was selected to account for the uncertainty associated with interspecies variability resulting from toxicodynamic and toxicokinetic differences between animals and humans (UF_A). Traditionally, these components (toxicodynamic and toxicokinetic) are individually represented by partial UFs of 3 for a total UF of 10 in the absence of chemical-specific information; thus, application of a full UF of 10 would depend on two areas of uncertainty (i.e., toxicokinetic and toxicodynamic uncertainties). In this assessment, the toxicokinetic uncertainty is addressed by the determination of an HEC, using a combination of measured internal blood levels in the test animals and PBPK modeling. A value of 1 was selected for the toxicokinetic portion of the UF_A. Regarding toxicodynamics, in vivo (Carpenter et al., 1956) and in vitro (Udden, 2002; Udden and Patton, 1994; Ghanayem and Sullivan, 1993) studies indicate that humans may be significantly less sensitive than rats to the hematological effects of EGBE. A value of 1 was selected for the toxicodynamic portion of the UF_A.

A factor to account for extrapolation from subchronic to chronic exposure (UF_S) was not needed because the RfC was derived from a chronic inhalation study.

A factor to account for the extrapolation from a LOAEL to a NOAEL (UF_L) was not applied because the current approach is to address this extrapolation as one of the considerations in selecting a benchmark response (BMR) for BMD modeling. In this case, EPA concluded a 10% increase in hemosiderin staining, indicating a precursor to an adverse effect, is appropriate for

use in deriving the RfC under the assumption that it represents a minimal biologically significant change.

A factor of 1 was selected to account for deficiencies in the database (UF_D). Chronic and subchronic studies are available for two species (rats and mice), and several reproductive and developmental studies, including a two-generation reproductive toxicity study. There are also limited human studies available following short-term inhalation exposure.

___I.B.4. ADDITIONAL STUDIES/COMMENTS

See Section 1.A.4. for additional information.

___I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Study -- High
Data Base -- Medium to high
RfC -- Medium to high

The overall confidence in the RfC is medium to high because the RfC was derived from internal dose measures (PBPK method and combined PBPK/BMC method) which account for pharmacokinetic differences between rats and humans using PBPK models (Corley et al., 2005, 1997; Lee et al., 1998) and actual measurements of internal blood concentrations in test animals of interest were used (Dill et al., 1998). There is high confidence in the NTP (2000) study because it was a chronic study, employed both male and female rats and mice, had a wide range of exposure levels, and animals were observed twice daily. There is medium-to-high confidence in the database, because data are available for a variety of animal species, including humans. Confidence is not high, because the potential for effects in humans from repeat, long-term exposures has not been investigated.

___I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC

Source Document -- U.S. EPA (2009) Toxicological review of ethylene glycol monobutyl ether.

This document was provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Ethylene Glycol Monobutyl Ether* (U.S. EPA, 2009).

___I.B.7. EPA CONTACTS

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 (email address).

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Ethylene glycol monobutyl ether (EGBE)
CASRN -- 111-76-2
Section II. Last Revised -- 00/00/0000

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per μg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

This assessment revises the current carcinogenicity assessment of 1999 in which the human carcinogen potential could not be determined at that time

__II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), EGBE is deemed "not likely to be carcinogenic to humans" at environmental concentrations at or below the RfD and RfC, based on laboratory animal evidence, mode-of-action information, and limited human study information. The available data indicate that carcinogenic effects from EGBE are not likely to occur in humans in the absence of the critical noncancer effects, including hepatic hemosiderin staining and irritant effects at the portal of entry, and are not likely to be carcinogenic to humans exposed at levels at or below the RfC and RfD values established in this assessment. Carpenter et al. (1956) reported that no changes in erythrocyte osmotic fragility were found in human subjects exposed to up to 195 ppm (942 mg/m^3; ~600 times the RfC) for two 4-hour periods separated by a 30-minute break. At oral doses of 400–500 mg/kg with a one-time bolus dose, hematuria has been noted in two human case reports. This dose is 3,000–3,500 times the RfD and would need to be sustained for a significant period of time to produce hemosiderin deposition. This is unlikely to occur because the primary response of humans to high oral doses of EGBE, as shown in the case studies, is metabolic acidosis, which, if not treated, can lead to shock and eventually death. No information is available on the carcinogenic effects of EGBE via the oral or inhalation route in humans. A 2-year inhalation bioassay with mice and rats (NTP, 2000) reported tumors of the liver in male mice, forestomach tumors in female mice, and tumors of the adrenal medulla in female rats. Non-neoplastic effects in rats included hyaline degeneration of the olfactory epithelium and Kupffer cell pigmentation. Non-

neoplastic effects in mice included forestomach ulcers and epithelial hyperplasia, hematopoietic cell proliferation, Kupffer cell pigmentation, hyaline degeneration of the olfactory epithelium (females only), and bone marrow hyperplasia (males only).

EGBE has been tested in conventional genotoxicity tests for its potential to induce gene mutations in vitro and for cytogenicity in both in vitro and in vivo assays. The available data do not support a mutagenic or clastogenic mechanism for EGBE. Two laboratories (Elias et al., 1996; Hoflack et al., 1995) reported weak genotoxicity responses in vitro at high treatment concentrations, but results were not replicated in five other labs reporting negative results. The hypothesized MOA for the tumors observed following EGBE treatment involves exposure to high doses for prolonged periods of time. The weight of evidence indicates that EGBE is not likely to be carcinogenic to humans at expected environmental concentrations.

___II.A.2. HUMAN CARCINOGENICITY DATA

There are currently no human studies addressing the potential carcinogenicity of EGBE.

___II.A.3. ANIMAL CARCINOGENICITY DATA

NTP (2000) conducted a 2-year inhalation study on EGBE in both genders of F344/N rats and $B6C3F_1$ mice. Rats (50/gender/group) were exposed to concentrations of 0, 31, 62.5, and 125 ppm (0, 150, 302, and 604 mg/m^3) and mice (50/gender/group) were exposed to concentrations of 0, 62.5, 125, and 250 pm (0, 302, 604, and 1,208 mg/m^3). The NTP report stated that the highest exposure was selected to produce a 10–15% depression in hematologic indices and survival was significantly decreased in male mice at 125 and 250 ppm (54.0 and 53.1%, respectively). While the NTP researchers report that no effect on survival was observed in rats, the female rats appeared to show a trend toward decreased survival that may have been attributable to the hematological effects. Mean body weights of rats exposed to 31 and 62.5 ppm were similar to those of control animals. Mean body weights of the exposed mice were generally less than for controls, with females experiencing greater and earlier reductions. From week 17 to the end of the study, the mean body weights of 125 ppm female rats were generally less than those of controls.

At the end of the 2-year chronic bioassay (NTP, 2000), neoplastic effects were observed in female rats and in male and female mice. In female rats, the combined incidence of benign and/or malignant pheochromocytoma of the adrenal medulla was 3/50, 4/50, 1/49, and 8/49. The incidence in the high-dose group (16%) did not represent a statistically significant increase over the chamber control group (6%), but it exceeded the historical control (6.4 ± 3.5%; range 2–13%) for this effect.

The low survival rate in male mice exposed to 125 and 250 ppm EGBE may have been due to carcinogenic effects in the liver. A high rate of hepatocellular carcinomas was found in these exposure groups (10/50 [control], 11/50, 16/50, 21/50); the increase at the high-exposure level was statistically significant ($p < 0.01$). However, when hepatocellular adenomas and carcinomas were combined, no significant increase was observed in any exposure group. The incidence of hemangiosarcomas in males exposed to 250 ppm (8%) was also significantly increased ($p = 0.046$) relative to chamber controls (0/50, 1/50, 2/49, 4/49) and exceeded the range of historical controls (14/968; 1.5 ± 1.5%; range 0–4%). No significant increases in benign or malignant hepatocellular tumors or hemangiosarcomas were noted in the female mice,

and the incidence of hepatocellular adenomas actually decreased significantly ($p < 0.05$) in relation to the control chamber group (16/50, 8/50, 7/49, 8/49). It should be noted that in light of the high survival rate of the exposed female mice relative to controls (29/50, 31/50, 33/50, 36/50), the high exposure of 250 ppm may not have provided the maximum tolerated dose.

Forestomach squamous cell papillomas and carcinomas, combined, were significantly increased (trend test = 0.003) in female mice relative to the chamber control group (0/50, 1/50, 2/50, 6/50). The incidence of these tumor types (12%) at the highest exposure level was also statistically significant and exceeded the range for the occurrence of these tumors in historical controls (0.9 ± 1.1%; range 0–3%). The first incidence of these tumors appeared in the group exposed to 250 ppm at 582 days, as compared to 731 days at 62.5 and 125 ppm, indicating a decreased latency period in the highest exposure group. While the incidence of these types of forestomach tumors was not significantly increased over controls in male mice (1/50, 1/50, 2/50, 2/50), the incidence of squamous cell papillomas (4%) in the two highest exposure groups exceeded the range for historical controls (0.5 ± 0.9%; range 0–2%). The increased incidence of forestomach neoplasms in males, as in females, occurred in groups with ulceration and hyperplasia.

The NTP (2000) study concluded that there was no evidence showing carcinogenic activity in male F344/N rats and equivocal evidence of carcinogenic activity in female F344/N rats, based on increased combined incidences of benign (mainly) and malignant pheochromocytoma of the adrenal medulla. The researchers reported some evidence of carcinogenic activity in male $B6C3F_1$ mice based on increased incidences of hemangiosarcoma of the liver and an increase in the incidence of hepatocellular carcinoma, as well as some evidence of carcinogenic activity in female $B6C3F_1$ mice based on increased incidence of forestomach squamous cell papilloma (mainly) or carcinoma.

With respect to the pheochromocytomas reported in female rats, while the data showed a positive trend ($p = 0.044$) and the high-dose tumor frequencies (16%) were above the upper range of historical controls (13%), the tumor incidence data were not statistically significant. Further, the NTP (2000) report noted that pheochromocytomas can be difficult to distinguish from non-neoplastic adrenal medullary hyperplasia. The presence of mild-to-moderate compression of the adjacent tissue is a primary criterion used to distinguish pheochromocytomas from medullary hyperplasia; most tumors observed were small and not substantially larger than the more severe grades of adrenal medullary hyperplasia. Interpretation of these tumors should be done cautiously. Given the marginal dose response, lack of tumor evidence in any other organ system of the rats, and reported difficulties in distinguishing pheochromocytomas from non-neoplastic adrenal medullary hyperplasia, this tumor type was not given significant weight in the qualitative or quantitative assessment of EGBE cancer potential.

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Although weakly genotoxic responses have been obtained in two laboratories (Elias et al., 1996; Hoflack et al., 1995), EGBE is not expected to be mutagenic or clastogenic based on the available data. The NTP reported negative responses for mutagenicity when EGBE was tested in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 at up to 10 mg/plate with and without metabolic activation (Zeiger et al., 1992). However, Hoflack et al. (1995) reported that at 38 µmol/plate (4.5 mg/plate), EGBE induced a weak mutagenic response in salmonella tester strain TA97a in the absence of S9 mix (Hoflack et al., 1995). The work of Hoflack and colleagues was repeated by Gollapudi et al. (1996), and EGBE was found to be

negative in these tester strains when evaluated at 0.5, 1.0, 2.5, 5.0, 8.5, and 10 mg/plate in the presence and absence of Aroclor-induced rat liver S9 mix. Thus, the weak positive result reported in salmonella TA97a by Hoflack et al. (1995) is unconfirmed. A plausible explanation put forth by Gollapudi et al. (1996) is that, given the sensitivity of the Ames test, perhaps the weak positive result reported by Hoflack et al. (1995) is attributed to an impurity in their test material.

Elias et al. (1996) reported that EGBE did not induce chromosomal aberrations in Chinese hamster V79 fibroblast cells but that EGBE, at treatment concentrations of ≥8.5 mM, weakly induced sister chromatid exchanges (SCEs) and micronuclei (MN) and potentiated the clastogenicity induced by methyl methanesulfonate. Elias et al. (1996) also reported that EGBE weakly induced aneuploidy (numerical chromosomal anomalies) in V79 cells; however, this response was found at very high concentrations (16.8 mM EGBE).

When tested at doses nearing toxicity, EGBE and its metabolite butoxyacetaldehyde (BAL) were not mutagenic in an in vitro gene mutation assay using Chinese hamster ovary (CHO) cells (CHO-AS52) (Chiewchanwit and Au, 1995). In contrast, Elias et al. (1996) reported that both EGBE and BAL weakly induced gene mutations in Chinese hamster V79 cells only at high treatment concentrations (≥7.5 mg/mL). It should be noted that Chiewchanwit and Au (1995) reported high cytotoxicity at 38.1 mM EGBE (4.5 mg/mL). The gene mutation data presented by Elias et al. (1996) is in graphic form only with mean values and no SDs presented. The presence or absence of cytotoxicity was not reported. BAL was also tested for induction of deoxyribonucleic acid (DNA) damage in the mouse endothelial cell line, SVEC4-10, using the comet assay. BAL failed to produce a statistically significant increase in DNA strand breaks at any of the concentrations or time points examined (Klaunig and Kamendulis, 2005, 2004; Reed et al., 2003). Other lines of evidence indicate that direct interaction of BAL with the DNA molecules does not play a significant role in the carcinogenic activity of EGBE. First, BAL causes cytotoxicity at levels associated with chromosome effects, and cytotoxicity itself can have effects that result in chromosome damage, such as reduction in the repair of SCEs. Second, acetaldehyde is recognized as "weakly mutagenic" and structural comparisons of the aldehyde metabolites of glycol ethers shows that longer-chain aldehydes such as BAL are less mutagenic (Chiewchanwit and Au, 1995). Third, if BAL were a stable mutagenic metabolite in any of the in vitro assays exposed to EGBE, one would expect them to give positive results; however, the results were generally negative. Elias et al. (1996) suggested that the V79 cells possess neither ALDH nor alcohol dehydrogenase. The relevance of these studies, or of any systems that lack these enzymes, is of limited value in elucidating the MOA of toxicity in biological systems that possess these enzymes. BAA has been found negative for reverse mutations in *S. typhimurium* his^- with and without metabolic activation (Hoflack et al., 1995). Concentrations of up to 8 µmol/plate were tested, and dose was limited by toxicity. BAA (up to 10 mM) was also found negative for induction of DNA damage in SVEC4-10 mouse endothelial cells (Klaunig and Kamendulis, 2005) and in an SCE assay in V79 cells (Elias et al., 1996). BAA was weakly positive for aneuploidy in V79 cells at 0.38 mM and positive for MN induction in the same cell line at 10 mM, as reported by Elias et al. (1996). As noted above, the data means are presented in graphic form without SDs and cannot be critically evaluated; no cytotoxicity data are reported.

EGBE did not increase the incidence of MN in the bone marrow cells of male mice or rats (NTP, 1996). Animals were given three intraperitoneal injections of EGBE 24 hours apart and sacrificed 24 hours after the last injection; rats were dosed at 0, 7, 14, 28, 56, 112.5, 225, or 450 mg/kg and mice were dosed at 0, 17, 34, 69, 137.5, 275, or 550 mg/kg (NTP, 1996). There

was high mortality (2/5 mice survived) in mice injected with 1,000 mg/kg doses of EGBE. Keith et al. (1996) treated Sprague-Dawley rats and transgenic FVB/N mice carrying the v-Ha-ras oncogene with a single oral dose of 120 mg/kg EGBE; there was no increase in DNA adducts in the brain, liver, kidney, testes, or spleen of the rats, and no changes in DNA methylation patterns in either species.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

No reliable human epidemiological studies or chronic oral animal studies are available that address the potential carcinogenicity of EGBE. However, the NTP (2000) performed a 2-year inhalation bioassay with rats and mice and found no evidence of carcinogenic activity in male F344/N rats and equivocal evidence of carcinogenic activity in female F344/N rats, based on increased combined incidences of benign and malignant pheochromocytoma (mainly benign) of the adrenal medulla. The researchers reported some evidence of carcinogenic activity in male $B6C3F_1$ mice, based on an increased incidence of hemangiosarcoma of the liver and an increase in the incidence of hepatocellular carcinoma that may have been exposure related. They also reported some evidence of carcinogenic activity in female $B6C3F_1$ mice, based on an increased incidence of forestomach squamous cell papilloma or carcinoma (mainly papilloma).

The MOAs presented for the animal tumors indicate that both high doses and sustained periods of exposure are necessary for the carcinogenic response. The available human exposure/response information indicates that these conditions are unlikely to occur because the primary response of humans to high oral doses of EGBE, as shown in the case studies, is metabolic acidosis, which, if not treated, can lead to shock and eventually death. Further, based on simulations from PBPK modeling, the maximum blood concentrations of BAA that could be produced in humans following exposure to a saturated atmosphere of EGBE would be below those needed to produce hemolysis (Corley et al., 2005a).

The available data indicate that carcinogenic effects from EGBE are not likely to occur in humans in the absence of the critical noncancer effects, including hepatic hemosiderin staining and irritant effects at the portal of entry, and are not likely to be carcinogenic to humans exposed at levels at or below the RfD values established in this assessment. Based on its physical-chemical properties, toxicokinetic and dynamic factors, and MOA information, under existing EPA guidelines (U.S. EPA, 2005a), EGBE is judged not likely to be carcinogenic to humans at expected environmental concentrations.

Following the U.S. EPA (2005a) Guidelines for Carcinogen Risk Assessment, a nonlinear approach to dose-response assessment is taken for agents, such as EGBE, for which the most plausible mode of action at low doses is consistent with nonlinearity. The RfD of 0.1 mg/kg-day derived in Section 5.2 of the Toxicological Review represents the outcome of nonlinear assessment based on hemolytic effects (i.e., hemosiderin deposition) associated with oral and exposure to EGBE. Doses (or concentrations) of EGBE below the RfD would not be expected to produce hemolytic effects (i.e., hemosiderin depostition) and is therefore not expected to produce any increase in cancer risk.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

No reliable human epidemiological studies are available that address the potential carcinogenicity of EGBE. The NTP (2000) performed a 2-year inhalation bioassay with rats and mice and found no evidence of carcinogenic activity in male F344/N rats and equivocal evidence of carcinogenic activity in female F344/N rats, based on increased combined incidences of benign and malignant pheochromocytoma (mainly benign) of the adrenal medulla. The researchers reported some evidence of carcinogenic activity in male $B6C3F_1$ mice, based on an increased incidence of hemangiosarcoma of the liver and an increase in the incidence of hepatocellular carcinoma that may have been exposure related. They also reported some evidence of carcinogenic activity in female $B6C3F_1$ mice, based on an increased incidence of forestomach squamous cell papilloma or carcinoma (mainly papilloma).

The MOAs presented for the animal tumors indicate that both high doses and sustained periods of exposure are necessary for the carcinogenic response. The available human exposure/response information indicates that these conditions are unlikely to occur because the primary response of humans to high oral doses of EGBE, as shown in the case studies, is metabolic acidosis, which, if not treated, can lead to shock and eventually death. Further, based on simulations from PBPK modeling, the maximum blood concentrations of BAA that could be produced in humans following exposure to a saturated atmosphere of EGBE would be below those needed to produce hemolysis (Corley et al., 2005a).

The available data indicate that carcinogenic effects from EGBE are not likely to occur in humans in the absence of the critical noncancer effects, including hepatic hemosiderin staining and irritant effects at the portal of entry, and are not likely to be carcinogenic to humans exposed at levels at or below the RfC values established in this assessment. Based on its physical-chemical properties, toxicokinetic and dynamic factors, and MOA information, under existing EPA guidelines (U.S. EPA, 2005a), EGBE is judged not likely to be carcinogenic to humans at expected environmental concentrations.

Following the U.S. EPA (2005a) Guidelines for Carcinogen Risk Assessment, a nonlinear approach to dose-response assessment is taken for agents, such as EGBE, for which the most plausible mode of action at low doses is consistent with nonlinearity. The RfC of 1.6 mg/m^3 derived in Section 5.1 of the Toxicological Review represents the outcome of a nonlinear assessment based on hemolytic effects (i.e., hemosiderin deposition) associated with inhalation exposures to EGBE. Doses (or concentrations) of EGBE below the RfC would not be expected to produce hemolytic effects (i.e., hemosiderin depostition) and is therefore not expected to produce any increase in cancer risk.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA (2009) Toxicological review of ethylene glycol monobutyl ether.

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Ethylene glycol monobutyl ether* (U.S. EPA, 2009).

___II.D.2. EPA REVIEW

___II.D.3. EPA CONTACTS

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 (email address).

_III. [reserved]
_IV. [reserved]
_V. [reserved]

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CASRN -- 111-76-2
Section VI. Last Revised -- 00/00/0000

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__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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_VII. REVISION HISTORY

Ethylene glycol monobutyl ether (EGBE)
CASRN -- 111-76-2
File First On-Line -- 00/00/0000

Date	Section	Description
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.
12/30/1999	I...VI	RfD, RfC, and carcinogenicity assessment first on line
12/03/2002	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.
02/09/2004	I., II.	This chemical is being reassessed under the IRIS Program.

_VIII. SYNONYMS

Ethylene glycol monobutyl ether (EGBE)
CASRN -- 111-76-2
Section VII. Last Revised -- 00/00/0000

Bucs, Butoxyethanol, N-Butoxyethanol, 2-Butoxyethanol, 2-Butoxy-1-Ethanol, Butyl Cellosolve, O-Butyl Ethylene Glycol, Butyl Glycol, Butyl Oxitol, Dowanol EB, Ektasolve EB, Ethylene Glycol N-Butyl, Gafcol EB, Glycol Butyl Ether, Glycol Ether EB, Glycol Ether EB Acetate, Glycol Monobutyl Ether, Jeffersol EB, Monobutyl Ether Of Ethylene Glycol, Monobutyl Glycol Ether, 3-Oxa-1-Heptanol, Poly-Solv EB