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16. ABSTRACT

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with specific chemicals or compounds. The Office of Emergency and Remedial Response (Superfund) uses these documents in preparing cost-benefit analyses under Executive Order 12991 for decision-making under CERCLA. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data are available. The interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed. Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval. The RfD is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan. For compounds for which there is sufficient evidence of carcinogenicity, q_1^*s have been computed, if appropriate, based on oral and inhalation data if available.

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HEALTH EFFECTS ASSESSMENT FOR ETHYLENE GLYCOL

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with ethylene glycol. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to May, 1986. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review.

The intent in these assessments is to suggest acceptable exposure levels for noncarcinogens and risk cancer potency estimates for carcinogens whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard or risk associated with exposure to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, RfD_S (formerly AIS) or subchronic reference dose, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used, or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for RFD_S estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure. These values are developed for both inhalation (RfD_{SI}) and oral (RfD_{SO}) exposures.

The RfD (formerly AIC) is similar in concept and addresses chronic exposure. It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The RfD is route-specific and estimates acceptable exposure for either oral (RfD_O) or inhalation (RfD_I) with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for identifying reportable quantities and the methodology for their development is explained in U.S. EPA (1984).

For compounds for which there is sufficient evidence of carcinogenicity RfD_S and RfD values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. For carcinogens, q_1*s have been computed, if appropriate, based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Orally administered ethylene glycol at high doses produces severe effects on the kidneys and results in increased mortality. In addition, high doses of ethylene glycol produce fetotoxicity which appears to be the critical effect for short-term exposure. A NOEL for fetotoxicity in the rat of 200 mg/kg/day was established by Maronpot et al. (1983). From these data an RfD_{SO} of 140 mg/day was derived. An RfD_{O} of 140 mg/day was derived from a NOAEL of 200 mg/kg/day in rats (DePass, 1986a). A CS of 10 was associated with increased mortality at 1% in the diet in the same 2-year study in rats. However, higher CSs are suggested based on occular effects following inhalation exposure. However, these effects at low exposure levels are only supported by one study.

The critical effect of inhalation exposure to ethylene glycol appears to be inflammation in the lungs, which was observed in several species of laboratory animals (Coon et al., 1970). Deficiencies in this study combined with lack of supporting data precluded calculation of an RfD_{SI} or an RfD_{I}.

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
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Office of Air Quality Planning and Standards
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Office of Drinking Water

Editorial review for the document series was provided by the following:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by the following:

Bette Zwayer, Jacky Bohanon and Kim Davidson
Environmental Criteria and Assessment Office
Cincinnati, OH

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LIST OF ABBREVIATIONS

bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
EEG	Electroencephalogram
EKG	Electrocardiogram
FEL	Frank effect level
K_{oc}	Soil sorption coefficient standardized with respect to organic carbon
LD_{10}	Dose lethal to 10% of recipients (and all other subscripted dose levels)
LD_{20}	Dose lethal to 20% of recipients
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RBC	Red blood cells
RfD	Reference dose
RfD_I	Inhalation reference dose
RfD_O	Oral reference dose
RfD_S	Subchronic reference dose
RfD_{SI}	Subchronic inhalation reference dose
RfD_{SO}	Subchronic oral reference dose
RV_d	Dose-rating value
RV_e	Effect-rating value
w/v	Weight per volume

1. ENVIRONMENTAL CHEMISTRY AND FATE

Selected chemical and physical properties and environmental fate of ethylene glycol are presented in Table 1-1.

In the atmosphere, ethylene glycol should exist mostly in the vapor phase and is expected to react with photochemically generated HO radical. Based on an estimated rate constant of 6.252×10^{-2} cm^3/molecule-sec at 25°C and an ambient HO radical concentration of 8.0×10^5 molecules/cm^3, the hydroxyl reaction half-life has been estimated to be 1.60 days (U.S. EPA, 1986a). Considering the complete solubility of ethylene glycol in water, removal from the atmosphere by dissolution into clouds and wet deposition may also be significant (NLM, 1986). In water, ethylene glycol will readily biodegrade under aerobic and anaerobic conditions (NLM, 1986). River die-away tests with four river waters indicated 100% degradation in 3 to >14 days (Evans and David, 1974). Adsorption to suspended solids and sediments and bioaccumulation in aquatic organisms should not be significant (NLM, 1986). The half-life of ethylene glycol in soil could not be located in the available literature, although the fact that it is highly biodegradable in water suggests that it will biodegrade in soil. Based on an estimated K_{oc} value of 4, this compound should be highly mobile in soil (Swann et al., (1983); however, rapid degradation would limit the extent of leaching. In groundwater, rapid biodegradation is expected (NLM, 1986).

TABLE 1-1

Selected Chemical and Physical Properties and
Environmental Fate of Ethylene Glycol

Property	Value	Reference
CAS number:	107-21-1	
Chemical class:	aliphatic diol	
Molecular weight:	62.07	
Vapor pressure at 20°C:	0.06 mm Hg	NLM, 1986
Water solubility:	completely miscible	NLM, 1986
Log octanol/water partition coefficient:	-1.36	Hansch and Leo, 1985
Bioconcentration factor:	0.05 (estimated)	Lyman et al., 1982
Soil adsorption coefficient:	4 (estimated)	Lyman et al., 1982
Half-lives in		
Air:	1.60 days (estimated)	Lyman et al., 1982
Water:	several days	Evans and David, 1974
Soil:	NA	

NA = Not available

2. ABSORPTION FACTORS IN HUMAN AND EXPERIMENTAL ANIMALS

2.1. ORAL

NLM (1986) briefly reported an excerpt from the foreign literature in which an investigator drank 100 mℓ of water containing an unspecified amount of ethylene glycol and collected his urine. Within 24 hours of ingestion, 24-31% of the ethylene glycol was excreted in an unchanged form in the urine. Urinary oxalic acid was elevated above background levels for 8-12 days. These data suggest that humans absorb a minimum of 24-31% of an unspecified oral dose of ethylene glycol in drinking water and that absorption from the gastrointestinal tract is rapid. Regardless of route, following absorption ethylene glycol is metabolized primarily as follows:

ethylene glycol → glycoladehyde → glycolic acid → glycoxylic acid

Glycoxylic acid is metabolized through a number of pathways, but predominantly to CO_2 and water via formic acid (Rowe and Wolf, 1982).

2.2. INHALATION

Wills et al. (1974) exposed 20 male volunteers to aerosolized ethylene glycol at a wide range of atmospheric concentrations averaging ~30 mg/m³, 20-22 hours/day for 30 days. Ten unexposed male volunteers were maintained as controls. Droplet size was monitored at unspecified intervals during the exposure period and was determined with a calibrated microscope to be 1-5 μ in diameter, larger than that usually associated with penetration past the bronchial and bronchiolar passages to the alveoli (Menzel and McClellan, 1980). Serum and urinary levels of unchanged ethylene glycol were monitored as indicators of absorption. Concentrations of ethylene glycol in serum and urine varied widely in both control and exposed groups,

but there appeared to be no readily discernible differences between values from the two groups. The investigators concluded that there was "little evidence of the absorption of important quantities of ethylene glycol."

Marshall and Cheng (1983) exposed rats by nose only to ^{14}C-ethylene glycol vapor at 32 mg/m^3 for 30 minutes or to an aerosol formed by condensation on inert particles at 184 mg/m^3 for 17 minutes. The investigators estimated that ~60% of the inhaled material was deposited, primarily in the nasal cavity; the data substantiating this estimate were not provided in the abstract. Absorption and distribution from the site of deposition appeared to be rapid, since 75-80% of the initial body burden was distributed throughout the body on sacrifice immediately after exposure.

3. TOXICITY IN HUMAN AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

Rowe and Wolf (1982) have summarized the clinical symptoms of ethylene glycol toxicity following acute exposure. They separate clinical signs into three stages: central nervous system effects occurring from 30 minutes to 12 hours following exposure; cardiopulmonary effects stage lasting from 12-36 hours following exposure; and the final stage of renal failure occurring if the patient survives the first two stages. Included within the central nervous system stage are ocular signs including optic atrophy. Acute ethylene glycol toxicity has been effectively treated in animals with ethanol or alcohol dehydrogenase inhibitors.

3.1.1. Oral. Groups of 10 male and 10 female Fischer 344/N rats and 10 male and 10 female B6C3F1 mice were fed diets containing 0, 0.32, 0.63, 1.25, 2.5 or 5.0% (0, 3200, 6300, 12,500, 25,000 or 50,000 ppm) of ethylene glycol for 13 weeks (Melnick, 1984). The endpoints evaluated included mortality, body and organ weights, serum and urine analyses and histopathological effects. In rats, the mortality rate was 40% in males ingesting 5.0%. Decreased body weight gain, increased kidney-to-body weight ratios, increased serum urea nitrogen levels and renal histopathology were observed in the male rats ingesting 2.5 or 5.0%. High-dose males also had crystal deposits in the brain. Increased kidney-to-body weight ratio was observed in female rats ingesting 2.5 or 5.0%, but was accompanied by adverse histological changes only in females ingesting 5.0%. Among groups of mice, only the males at 2.5 and 5.0% had adverse effects, which consisted of renal cytoplasmic vacuolization and centrilobular hepatic degeneration. No adverse effects were observed in males at $\leq$1.25% or in females at any dietary concentration. Melnick (1984) concluded that the NOEL for renal

toxicity in male rats is 1.25% of dietary ethylene glycol, which corresponded to a dose of 0.6-1.0 g/kg/day. The dietary level of 1.25% was also a NOAEL for male mice.

3.1.2. Inhalation. Twenty mice and 10 rats were exposed to an average concentration of 398 mg/m³ of ethylene glycol for 8 hours/day, 5 days/week for up to 16 weeks (Wiley et al., 1936). Selected animals were sacrificed at intervals starting with week 7 of exposure. Endpoints evaluated included mortality rate, body weight and histology of liver, kidney, testes, brain, lung, pancreas, spleen, adrenals, stomach, intestines and lymph nodes. Although three mice and one rat died during the experiment, cause of death was not reported and no pathological changes that could be attributed to ethylene glycol treatment were reported. Mice gained weight during the experiment, but rats did not. Controls were not evaluated in this experiment.

Groups of male and female Sprague-Dawley and Long-Evans rats (n=15), male and female Princeton-derived guinea pigs (n=15), male New Zealand albino rabbits (n=3), male squirrel monkeys (n=3) and male beagle dogs (n=2) were exposed continuously to 12 mg/m³ ethylene glycol for 90 days (Coon et al., 1970). Unexposed control groups were maintained. The endpoints evaluated included mortality rate, hematology, histology of heart, lung, liver, kidney and spleen and enzyme levels in the blood, liver and kidneys. In addition, the histology of brain, spinal cord and adrenals in monkeys and dogs and of the thyroid in dogs was evaluated. Deaths occurred in 1/15 rats, 3/15 guinea pigs and 1/3 rabbits; cause of death was not reported. Pulmonary inflammation was observed in treated groups of all species to a greater degree than in controls. Ocular irritation and edema, resulting in eye closure, was observed in the rabbits. Corneal opacity, which resulted

in blindness, developed in two of the rats. In both species, the ocular lesions developed within 8 days of the start of treatment. No other effects were reported by Coon et al. (1970).

In another experiment, similar groups of rats, guinea pigs, rabbits, dogs and monkeys were exposed to 10 or 57 mg/m³ for 8 hours/day, 5 days/week for 6 weeks (Coon et al., 1970). Unexposed controls were maintained. Death did not occur at either exposure level. Two rabbits at 10 mg/m³ had mild, unilateral conjunctivitis, but these signs were not observed at 57 mg/m³ and were attributed to accidental trauma rather than to the chemical. On histopathological examination, mild splenic congestion was observed in dogs at 10 but not 57 mg/m³. Mild liver changes were observed in some rats and guinea pigs at both levels of exposure and in monkeys at 57 mg/m³, but these changes were not attributed to exposure to ethylene glycol. Nonspecific inflammatory changes in the lungs and hearts of all species were reported at 57 but not 10 mg/m³. These changes may have been associated with treatment.

3.2. CHRONIC

3.2.1. Oral. Groups of 16 male and 16 female Sprague-Dawley rats were fed diets containing 0, 0.1, 0.2, 0.5, 1.0 or 4.0% (0, 1000, 2000, 5000, 10,000 or 40,000 ppm) of ethylene glycol for 2 years (Blood, 1965). The endpoints evaluated included mortality, food and water consumption, body and organ weights, hematology and histology. Accelerated mortality was observed in the male rats ingesting 1.0 or 4.0% and in the female rats ingesting 4.0% ethylene glycol. In addition, the rats in these three groups had decreased growth rates, increased water consumption, proteinuria before death and renal calculi in $\geq$68% of the males and $\geq$93% of the females. An increased incidence of cytoplasmic crystal deposition in renal tubular epithelium occurred in 4/10 males evaluated at the 0.5% dose level and in 5/15 female

rats evaluated at the 1.0% dose level. No other adverse effects were reported and Blood (1965) concluded that the NOEL in rats is 0.2% of dietary ethylene glycol.

Groups of 130 male and 130 female Fischer 344 rats and groups of 80 male and 80 female CD-1 mice were fed diets containing ethylene glycol in amounts such that the rats and mice ingested 0, 0.04, 0.2 or 1.0 g of ethylene glycol/kg of body weight each day for 2 years (DePass et al., 1986a). The endpoints evaluated included mortality rate, body and organ weights, food and water consumption, clinical chemistry, hematology, urine analysis and histology of major organs. The high-dose male rats had statistically significant increases in mortality rate, neutrophil count, water intake, kidney weight, urine volume and blood urea nitrogen levels and a statistically significant decrease in body weight, RBC count and hematocrit and hemoglobin levels. Also observed in the high-dose male rats were chronic nephritis including tubular dilation and proteinosis, glomerular shrinkage, tubular cell hyperplasia and interstitial nephritis. Increased kidney weights unaccompanied by any other renal changes were observed in the high-dose female rats. Mild fatty changes in the liver were reported in female rats ingesting 1.0 or 0.2 g of ethylene glycol/kg bw/day. Adverse effects were not observed at any other dose level in the rats or at any dose level in the mice.

Blood et al. (1962) fed a diet containing ethylene glycol at 0.2% to two male rhesus monkeys and a diet containing 0.5% to one female rhesus monkey for 3 years. Radiographic examinations of the urinary tract at 3-month intervals revealed no evidence of calcification or calculi formation. Histopathological examinations of major organs and tissues revealed no lesions in one male or the female monkey. The other male monkey had become obese, weighing twice as much as his companion, and mild lesions in the

kidney tubules and scattered foci of sclerotic Bowman's capsules. The investigators did not associate these findings with exposure to ethylene glycol and concluded that no toxic effects were seen in this experiment.

3.2.2. Inhalation. Pertinent data regarding the toxicity of chronic inhalation of ethylene glycol could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. The teratogenic and reproductive effects of orally administered ethylene glycol in rats and mice have been evaluated using five different experimental designs (Maronpot et al., 1983; Schuler et al., 1984; Lamb et al., 1985; Price et al., 1985; DePass et al., 1986b). In the Maronpot et al. (1983) study, groups of 20 pregnant Fisher 344 rats were exposed to dietary ethylene glycol at "concentrations based upon established food consumption and body weight gain data to produce dosage goals of 1.0, 0.2 and 0.04 g/kg." The rats received treated food on days 6-15 of gestation. The dams were killed on day 21 of gestation, and the pups were examined. The endpoints evaluated included maternal body weight, fetal length and body weight, number of implantations, litter size and incidence of major malformations. The only effects were increased preimplantation loss and increased incidence of poorly ossified and unossified vertebral centra in the high-dose group. Only the skeletal changes were statistically significant.

In the Schuler et al. (1984) study that was designed to screen chemicals for their potential to cause reproductive toxicity in pregnant females, 50 pregnant CD-1 mice were treated by gavage on days 7-14 of gestation with 11,090 mg/kg/day of ethylene glycol, approximately the LD_{10} for mice.

Fifty pregnant CD-1 mice constituted the control group. The endpoints evaluated included pup survival in utero measured by the ratio of live litters/pregnant survivors, pup perinatal and postnatal survival measured by the ratio of the number of live pups/litter and the number of dead pups/litter and the percent of pups surviving 2.5 days postpartum, and pup body weight measured at birth and at 2.5 days of age. Compound-related deaths occurred in five treated mice. Statistically significant adverse effects were observed in each of the six parameters measured in this study. Schuler et al. (1984) concluded that ethylene glycol belongs in the group of chemicals given a high priority for further testing because of the drastic reduction in viable litters observed at dose levels equal to or below the maternal LD_{20}.

In the Lamb et al. (1985) experiment, which followed the Continuous Breeding Protocol designed by the NTP to assess fertility, groups of 20 male and 20 female 6-week-old COBS Crl:CD1, (ICR)BR outbred albino mice were provided drinking water containing 0, 0.25, 0.5 or 1.0% ethylene glycol (w/v) for 14 weeks. The Gulati et al. (1984) report summarizes the same study. The mice in each group were housed in pairs and allowed to breed continuously for 14 weeks, during which time litters were evaluated and discarded. After 14 weeks, the males and females in the F_0 generation were separated and the litters born to the control group and the high-dose group during the next 3 weeks were allowed to survive as the F_1 generation. Exposure of the F_1 generation to 0 or 1.0% ethylene glycol in the drinking water continued uninterrupted for 70±10 days after birth, at which time the F_1 generation was mated and the reproductive performance evaluated by examining the F_2 pups. The endpoints evaluated included maternal and fetal body weight, water consumption, number of litters/fertile pair, number of live pups/litter, proportion of pups born alive and skeletal

changes in the offspring. A statistically significant decrease in the number of litters/fertile pair, in the mean number of live pups/litter and in the mean live pup weight was observed in the offspring of the F_0 generation of high-dose mice. Although the fertility of the F_1 generation and the number of live pups/litter and the live pup weight of the F_2 generation were decreased, the decrease was not statistically significant. Gross, but not histological, alterations were observed in the cranial and axial skeletons of F_2 pups treated with 1% ethylene glycol in the drinking water. Skeletal changes were not present in F_2 control pups. Lamb et al. (1985) reported that cleft lip occurred in "at least six pups from three treated litters" of the F_2 generation and concluded that exposure to drinking water contaminated with 1.0% ethylene glycol, equivalent to >1600 mg/kg/day, resulted in adverse effects on reproduction.

In a 3-generation reproductive study (DePass et al., 1986b), groups of 20 female and 10 male Fischer 344 rats were treated with ~1000, 200 or 40 mg/kg/day of dietary ethylene glycol. Two untreated diet control groups were included to estimate the variation between two groups handled in like manner. The litter size of each dam was culled to 10, if necessary, on postpartum day 4. Twenty females and 10 males were randomly selected for mating from the F_1 and the F_2 generations in each treatment group at ~100 days of age. The endpoints evaluated included adult and pup body weights, food consumption, male and female fertility indices, gestation index, gestation survival index, days from first mating to litter, and survival indices at 0, 4, 14 and 21 days.

Histopathological evaluation of liver, kidneys, lungs, heart, adrenal thyroids, trachea, accessory sex glands, adipose tissue, lymph nodes, pituitary, thymus, testes and epididymis or uterus and ovaries were performed on

five males and five females randomly selected from each dosage level of the F_2 parents and the F_3 weanlings.

In addition, males from the F_2 generation were removed from diets containing ethylene glycol at 155 days of age and mated with groups of 15 untreated female rats each week for 3 weeks in a study of dominant lethal effects. On day 12 of gestation, the females were killed, the uteri and ovaries examined and the number of live and dead fetuses tabulated. A group of 15 male rats that had been maintained on the control diets was injected intraperitoneally with triethylenemelamine (0.5 g/kg) and served as a positive control group. No statistically significant effects were observed at any dose level in the 3-generation reproductive study.

Slight increases in the dominant lethal mutation index were observed in high-dose rats for the week-2 mating and in low-dose rats for the week-3 mating. The investigators concluded that these elevations were probably random occurrences rather than effects of treatment because they did not occur in a dose-related manner. Positive controls responded appropriately.

In the Price et al. (1985) study designed to evaluate teratogenicity, groups of at least 20 pregnant CD rats and 20 pregnant CD-1 mice were treated by gavage on days 6-15 of gestation with 0, 1250, 2500 or 5000 mg/kg/day of ethylene glycol (rats) or 0, 750, 1500 or 3000 mg/kg/day (mice). Endpoints evaluated included maternal toxicity, the number of implantation sites/litter, the number of live fetuses/litter, percentages of postimplantation (resorbed + dead fetuses) losses/litter, the number of litters with postimplantation losses at one or more sites, the number of males/litter, live fetuses malformed/litter and litters with one or more malformed live fetuses. The percentage of litters with one or more malformed live fetuses was significantly increased in a dose-related manner ($p \leq 0.01$; Fisher Exact

Probability Test) in both rats and mice at all dose levels tested. In addition, there was a dose-related increase in the postimplantation losses/litter in both species, reaching statistical significance only in high-dose rats. Maternal body weight gain during treatment was significantly decreased in a dose-related manner at all dose levels in the rats and at the two higher dose levels in the mice.

3.3.2. Inhalation. Groups of 25 timed pregnant CD rats and CD-1 mice were exposed to a respirable aerosol of ethylene glycol at concentrations of 0, 60, 400 or 1000 ppm (0, 150, 1000, 2500 mg/m^3) for 6 hours/day on days 6-15 of gestation (Tyl, 1985). The rats and mice were killed on day 21 and day 18 of gestation, respectively. The endpoints evaluated included maternal body, liver, kidney and gravid uterine weights; the number of corpora lutea, resorptions, dead fetuses and live fetuses/litter; and the fetal weight, sex and number of visceral and skeletal malformations. In the rats, ethylene glycol exposure was associated with a significant increase in maternal liver weight at 1000 ppm and delayed ossification in the zygomatic arch, metatarsals and proximal phalanges in the hindlimb of pups at 400 ppm and 1000 ppm. No effect on pre- or postimplanation loss, the number of live fetuses/litter, sex ratio, fetal body weight or the incidence of fetal malformations was observed in the rats exposed to ethylene glycol. In the mice, decreased maternal and fetal body weight was observed at the two highest dose levels tested. Ethylene glycol exposure was associated with a significant decrease in the number of viable implants/litter and a significant increase in the number of late resorptions and dead fetuses at 1000 ppm. A significant increase in the number of late resorptions was observed in the mice exposed to 400 ppm. A significant increase in the incidence of external, visceral and skeletal malformations was observed in mice exposed

to 1000 and 400 ppm. The malformations observed included cleft palate, exencephaly, destruction of normal brain architecture, axial skeletal defects and facial deformities. An increased incidence of adverse effects was not observed in the mice exposed to 60 ppm.

Although the study of Tyl (1985) was designed to evaluate the developmental toxicity of inhaled ethylene glycol in rats and mice, nearly continuous grooming by the rats and mice both in and out of the inhalation chamber was observed. The investigator concluded that a substantial amount of ethylene glycol was ingested from the fur. Based on experimentally determined amounts of ethylene glycol present on the hair coats after 1 exposure, 5 exposures, 10 exposures and at the time of sacrifice of similarly exposed sentinal animals of both species, Tyl (1985) determined that rats ingested 263.43 and 620.1 mg/kg/day and that mice ingested 385.89 and 909.1 mg/kg/day at the middle- and high-exposure levels, respectively. The investigator did not estimate the ingested dose at 60 ppm, which was not associated with adverse effects in either species, but did conclude that in this experiment the ingested dose was substantially larger than the inhaled dose.

3.4. TOXIC INTERACTIONS

Metabolism of ethylene glycol, with the subsequent precipitation of oxalate crystals, can be blocked or slowed down by concurrent ingestion or infusion of ethyl alcohol (Balazs et al., 1982). Pyrazole and 4-methylpyrazole, which are inhibitors of alcohol dehydrogenase activity, were effective in reducing the mortality of rats treated by gavage with ethylene glycol from 100 to 0%. The protective effect was observed when the dehydrogenase inhibitors were administered intraperitoneally either 4 hours before or concurrently with the ethylene glycol, but not when administered more than 4 hours after gavage treatment with ethylene glycol (Chou and Richardson, 1978).

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenicity of ingested or inhaled ethylene glycol in humans could not be located in the available literature.

4.2. BIOASSAYS

4.2.1. Oral. In the DePass et al. (1986a) study described in more detail in Section 3.2.1., groups of 130 male and 130 female Fischer 344 rats and groups of 80 male and 80 female CD-1 mice were exposed to food containing ethylene glycol in amounts such that the rats and mice ingested 0, 0.04, 0.2 or 1.0 g ethylene glycol/kg body weight daily for 2 years. Ethylene glycol exposure was not associated with an increased incidence of tumors in the rats or the mice. In the Blood (1965) study, also discussed in greater detail in Section 3.2.1., an increased incidence of cancer was not reported in any of the groups of 16 male and 16 female Sprague-Dawley rats treated with diets containing 0, 0.1, 0.2, 0.5, 1.0 or 4.0% ethylene glycol for 2 years. However, these studies were not designed primarily as cancer bioassays and hence did not report control tumor incidence and other appropriate details.

The NTP (1986) management status report indicates that histopathological examinations of mice chronically fed ethylene glycol in the diet is currently in progress.

4.2.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled ethylene glycol in animals were not located in the available data.

4.3. OTHER RELEVANT DATA

Ethylene glycol was not mutagenic in Salmonella typhimurium strains TA98, TA100, TA1535 or TA1537 with or without metabolic activation (McCann et al., 1975).

An increased incidence of polychromatic erythrocytes with Howell-Jolly bodies, which may indicate chromosome breakage, were reported in mice treated orally or intraperitoneally with ethylene glycol (Conan et al., 1970). In the same study, an increased incidence of chromosome anomalies in bone marrow cells of mice treated with ethylene glycol was not observed.

4.4. WEIGHT OF EVIDENCE

IARC has not evaluated the carcinogenic potential of ethylene glycol. Applying the criteria described in the EPA's proposed guidelines for assessment of carcinogenic risk (U.S. EPA, 1986b), ethylene glycol may be classified in Group D: not classifiable as to human carcinogenicity. This category is for chemicals that show inadequate evidence of carcinogenicity for both humans and animals. This classification may be modified pending the outcome of the NTP (1986) dietary study using mice currently in progress. Ethylene glycol may also be classified in IARC Group 3: cannot be classified.

5. REGULATORY STANDARDS AND CRITERIA

Based on the study of Wills et al. (1974), the ACGIH (1986a,b) has recommended a ceiling limit of 50 ppm (~125 mg/m^3) for ethylene glycol vapor and mist to minimize irritation of the respiratory passages. In the study by Wills et al. (1974), one group of 20 human males were exposed to a mean concentration of ~30 mg/m^3 of ethylene glycol for 20-22 hours/day for 30 days. A group of 14 human males served as controls. The endpoints evaluated included hematology, clinical chemistry, urinalysis, EKG and EEG and psychological testing of reaction time with and without discrimination, visual-motor coordination, perception and mental ability. No adverse effects were associated with exposure to the mean concentration of 30 mg/m^3 (11.8 ppm) of ethylene glycol. Sporadic increases in the concentration of atmospheric ethylene glycol indicated that the respiratory system became irritated at 140 mg/m^3 of ethylene glycol and that the irritation became intolerable at 200 mg/m^3 of ethylene glycol.

6. RISK ASSESSMENT

6.1. SUBCHRONIC REFERENCE DOSE (RfD_S)

6.1.1. Oral (RfD_{SO}). Based on the subchronic oral study by Melnick (1984), a NOEL was identified in rats and mice ingesting diets containing 1.25% ethylene glycol. At 2.5% of the diet, the next higher concentration tested, male rats had lesions in the kidney and male mice had lesions in the liver and kidney. In both species, the male appears to be more sensitive than the female to the toxicity of ethylene glycol. Female rats had lesions at 5.0 but not 2.5% of the diet, and female mice had no adverse effects on diets containing $\leq$5.0%. The dietary NOEL of 1.25% in male rats is equivalent to 625 mg/kg/day, assuming rats eat food equivalent to 5% of their body weight/day.

Developmental toxicity may be a more sensitive endpoint than subchronic toxicity for ethylene glycol. Maronpot et al. (1983) observed fetotoxicity manifested as increased preimplantation embryo loss and retarded vertebral ossification in rats fed a diet that provided 1000 mg/kg/day. No effects were observed at 200 mg/kg/day, the next lower dose. In mice, reduced fecundity and evidence of fetotoxicity were observed with exposure to drinking water containing 1% ethylene glycol (Lamb et al., 1985; Gulati et al., 1984). No such effects were observed at 0.5%. The investigators estimated that ethylene glycol intake at the 1% level exceeded 1600 mg/kg/day, but did not estimate compound intake at the lower dose level. Assuming that mice weigh 0.03 kg and drink 0.0057 ℓ/day, the 0.5% level corresponds to an intake of 950 mg/kg/day.

In a teratogenicity study using rats and mice, Price et al. (1985) observed a dose-related increase in the incidence of litters with

malformations in both species at all doses tested. Rats were treated with 1250, 2500 and 5000 mg/kg/day and mice were treated at 750, 1500 and 3000 mg/kg/day.

Tyl (1985) exposed rats and mice to aerosols of ethylene glycol at concentrations of 0, 60, 400 or 1000 ppm (0, 150, 1000 or 2500 mg/m^3) 6 hours/day on days 6-15 of gestation. Although the study was designed to evaluate developmental toxicity of inhaled ethylene glycol, the investigators noted nearly continuous grooming during and after exposure and concluded that a substantial amount of ethylene glycol was ingested. By measuring the amounts of ethylene glycol that adhered to the haircoats of similarly exposed sentinel rats and mice at 400 and 1000 ppm, Tyl (1985) estimated that rats ingested 263.43 and 620.1 mg/kg/day and mice ingested 385.89 and 909.1 mg/kg/day at 400 and 1000 ppm, respectively. These atmospheric concentrations were associated with fetotoxicity manifested as delayed ossification in the rats and an increased incidence of fetal malformations in the mice. Adverse effects were not observed in either species at 60 ppm, but Tyl (1985) did not estimate the dose of ethylene glycol ingested by rats and mice at this exposure. Tyl (1985) concluded that the ingested doses were substantially greater than the inhaled doses in this experiment.

Assuming that the ventilatory volume of a rat is 0.223 m^3/24 hours (U.S. EPA, 1980), that 50% of the ethylene glycol inhaled was absorbed and that the rat body weight was 0.35 kg, rough estimates of the inhaled component of the dose can be estimated as 79.6 mg/kg for the mid-concentration group rats (1000 mg/m^3). Assuming that the ventilatory volume of a mouse is 0.039 m^3/24 hours (U.S. EPA, 1980), that 50% of the dose was absorbed and that the mouse body weight was 0.03 kg, the inhaled component of the dose for the 1000 mg/m^3 exposure group of mice can be estimated as 162.5

mg/kg/day. The total doses then for the 1000 mg/m³ groups would be 263 mg/kg/day + 80 mg/kg/day = 343 mg/kg for rats and analagously 549 mg/kg/day for mice. These doses were associated with both fetotoxicity and maternal toxicity in both species. The finding of maternal toxicity at these dose levels when compared with the other subchronic and reproductive studies strongly suggests that the dose may have been underestimated.

Arraying the data to compare NOELs and LOAELs results in the following summary:

Subchronic toxicity

Rat			
male	NOEL	625 mg/kg/day	Melnick, 1984
	LOAEL	1250 mg/kg/day	
female	NOAEL	1250 mg/kg/day	
	LOAEL	2500 mg/kg/day	
Mouse			
male	NOEL	625 mg/kg/day	Melnick, 1984
	LOAEL	1250 mg/kg/day	
female	NOEL	2500 mg/kg/day	
	None established		

Reproductive and Teratology Studies

Rat teratology			
fetotoxicity	NOEL	200 mg/kg	Maronpot et al., 1983
	LOAEL	1000 mg/kg	Maronpot et al., 1983
	LOAEL	1250 mg/kg	Price et al., 1985
Mouse teratology			
fetotoxicity	LOAEL	750 mg/kg	Price et al., 1985
Mouse 3-generation			
	NOEL	950 mg/kg	Lamb et al., 1985
	LOAEL	1650 mg/kg	
Rat 3-generation			
	NOEL	1000 mg/kg	DePass et al., 1986b
	LOAEL	None	

The teratology studies appear to show effects at lower doses than the 3-generation studies. The study showing a NOEL for fetal effects at a dose below the LOAELs is the Maronpot et al. (1983) teratology study in rats which defined a NOEL of 200 mg/kg/day.

An RfD_{SO} of 2 mg/kg/day or 140 mg/day for a 70 kg human can be derived by dividing the NOEL of 200 mg/kg/day by an uncertainty factor of 100 to account for interspecies extrapolation uncertainty and intraspecies variability.

6.1.2. Inhalation (RfD_{SI}). Three subchronic animal inhalation studies are available for consideration in the derivation of an RfD_{SI}. Wiley et al. (1936) observed deaths in rats and mice exposed 8 hours/day, 5 days/week to 398 mg/m³ for 16 weeks, but this experiment did not define a NOAEL. Coon et al. (1970) observed deaths and ocular lesions in guinea pigs, rats and rabbits, and pulmonary inflammation in these species and in dogs and monkeys continuously exposed to 12 mg/m³ for 90 days. Inflammation in the heart and lungs was also observed in all the species mentioned above when exposed to 57 but not 10 mg/m³, 8 hours/day, 5 days/week for 6 weeks (Coon et al., 1970).

The Coon et al. (1970) study is limited in scope and reporting detail. It was designed to be a preliminary investigation. Animal group sizes were small, no mention was made of evaluations of organ or body weights which frequently provide the first indication of adverse effects of a chemical. Although the authors state in the abstract that there were no chemically-induced changes following exposure to 10 and 57 mg/m³ ethylene glycol, this conclusion is not clearly supported by the discussion of the results.

For example, the 10 mg/m³ group was described as follows:

> "Histopathologic examination revealed mild congestion in the spleens of both dogs, hepatic fatty changes in 2/8 guinea pigs and 1/8 rats (sex not specified); and focal necrosis in the liver of 1/8 guinea pigs and 1/8 rats. Focal necrosis of the liver was also seen in 1/3 control guinea pigs."

For the 57 mg/m³ group the following summary was provided:

> "Histopathologic examinations revealed nonspecific inflammatory changes in the lungs and occasionally the hearts of all species. The livers of 2 of the 3 monkeys and 1 of the 8 guinea pigs revealed areas of focal necrosis; these were considered not to be chemically induced."

In addition, continuous exposure to 12 mg/m³ ethylene glycol resulted in moderate to severe eye irritation in rabbits and rats. Two rats "appeared" to be blind after 8 days of exposure. Histopathologic examination showed inflammatory changes in the lungs of all species. "Occasional" foci of inflammatory cells were seen in kidneys from "several" guinea pigs. "These, however, were not interpreted as being specific chemically induced changes."

In addition to the animal studies mentioned above, Wills et al. (1974) exposed humans almost continuously to ~30 mg/m³ for 30 days and observed no adverse effects. Although this level appears to be a NOAEL in humans, the most sensitive indication of toxicity, nonspecific inflammation of the thoracic viscera, was of necessity not evaluated, and the experimental period is too short for this study to be useful for risk assessment. In conclusion, the data are deemed inadequate for quantitative risk assessment.

6.2. REFERENCE DOSE (RfD)

6.2.1. Oral (RfD_0). Two chronic experiments, the DePass et al. (1986a) study and the Blood (1965) study, can be used to derive an RfD_0 for ethylene glycol. Based on the Blood (1965) study, a NOEL of 100 mg/kg/day

of ethylene glycol was identified in rats. The next highest dose tested, 250 mg/kg/day, was identified as a LOAEL in male rats associated with increased incidences of renal calcification and calculi. An increased mortality rate as well as renal toxicity was observed in male rats ingesting 500 mg/kg/day and in female rats ingesting 1000 mg/kg/day. The DePass et al. (1986a) study using rats and mice defined a NOAEL at 200 mg/kg/day, a dose resulting in increased incidence of fatty changes in the liver in female rats. The incidence of fatty liver changes increased at the highest dose tested, 1000 mg/kg/day, which was identified as a FEL because of the increased mortality observed in male rats. An RfD_0 of 2.0 mg/kg/day, or 140 mg/day for a 70 kg human, for ethylene glycol is derived by dividing the NOAEL of 200 mg/kg/day by an uncertainty factor of 100 to account for inter-species extrapolation and the range of sensitivity to xenobiotics within the human population.

CS values, summarized in Table 6-1, are based on the adverse liver and kidney effects and the increased mortality rate observed in rats after chronic ingestion of food contaminated with ethylene glycol (DePass et al., 1986a; Blood, 1965). In addition, the lowest oral dose of ethylene glycol, 750 mg/kg/day, administered to pregnant mice was associated with an increased incidence of malformations and was used as the basis for a CS for teratogenicity (Price et al., 1985). Because the teratogenic effects of oral exposure cannot be clearly separated from the effects due to inhalation, this study is not used in the derivation of a CS. The highest CS is 10, based on the increased mortality observed in male rats ingesting food contaminated with ethylene glycol for 2 years (Blood, 1965).

TABLE 6-1

Composite Scores for the Toxicity of Ethylene Glycol by Oral Exposure

Species/Strain	Sex	Exposure Dosage	Human MED[a] (mg/day)	RV_d	Effect	RV_e	CS	Reference
Rat/F344	F	200 mg/kg/day from food	2394	1	fatty changes in in the liver	5	5	DePass et al., 1986a
Rat/Sprague-Dawley	M	0.5% dietary for 2 years (250 mg/kg/day)[b]	2993	1	renal calculi and/or calcification with necrosis	6	6	Blood, 1965
Rat/Sprague-Dawley	M	1% dietary for 2 years (500 mg/kg/day)[b]	5986	1	increased mortality rate	10	10	Blood, 1965
Mouse/CD-1	F	750 mg/kg/day	3958	1	teratogenicity and maternal toxicity	9	9	Price et al., 1985

[a]The human MED in mg/day is derived by multiplying the LOAEL in mg/kg/day by the cube root of the reference animal (rat = 0.35 kg, mouse = 0.03 kg) to human body weight ratio and by the reference human body weight (70 kg).

[b]The dose in mg/kg/day was obtained by multiplying the dietary concentration by 0.05 which assumes that a rat consumes the equivalent of 5% of its body weight as food each day (U.S. EPA, 1985).

6.2.2. Inhalation (RfD_I). There are no available inhalation data on the chronic toxicity of ethylene glycol. Subchronic data are summarized in Section 6.1.2. Data are deemed inadequate for quantitative risk assessment.

The effect of concern for short duration continuous inhalation exposure appears to be ocular irritation. This effect was not seen in any of the reports utilizing intermittent exposure protocols. In addition, Coon et al. (1970) cited a personal communication from another laboratory which failed to confirm severe ocular effects at a similar exposure level. Consequently, it is uncertain whether this report of severe ocular irritation is an experimental anomaly or represents a reproducible effect. Coon et al. (1970) also cite unpublished data suggesting that higher exposure concentrations than those associated with severe eye irritation in rats and rabbits in their study were tolerated by humans with no ill effects. These potential ocular effects would be of concern if an accidental release of ethylene glycol occurred in a confined space. Inhalation composite scores are summarized in Table 6-2.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. No evidence of carcinogenicity was observed in male or female Fischer 344 rats or CD-1 mice ingesting 40, 200 or 1000 mg/kg/day of ethylene glycol for 2 years (DePass et al., 1986a) or in male or female Sprague-Dawley rats ingesting up to 4% dietary ethylene glycol (2000 mg/kg/day) for up to 2 years (Blood, 1965).

6.3.2. Inhalation. Pertinent data regarding the carcinogenicity of inhaled ethylene glycol could not be located in the available literature.

TABLE 6-2

Composite Scores for the Toxicity of Ethylene Glycol by Inhalation Exposure[a]

Species	Sex	Exposure	Human MED[b]	RV_d	Effect	RV_e	CS
Rat	M,F	12 mg/m³ continuous 90 days	9.2	4.1	corneal opacity	8	32.5
Rabbit	M	12 mg/m³ continuous 90 days	16.7	3.7	ocular irritation	7	25.7
Rat	M,F	57 mg/m³ 8 hours/day 5 days/week	10.4	4.0	lung and heart inflammation	6	23.9
Guinea pig	M,F	57 mg/m³ 8 hours/day 5 days/week	10.4	4.0	lung and heart inflammation	6	23.9
Rabbit	M	57 mg/m³ 8 hours/day 5 days/week	18.9	2.1	lung and heart inflammation	6	12.5

[a]Source: Coon et al., 1970

[b]Divided by a factor of 10 to approximate chronic exposure

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APPENDIX

Summary Table for Ethylene Glycol Using the Rat

	Experimental Exposure/Dose (mg/kg/day)	Effect	Reference Dose (RfD) (mg/day)	Reference
Inhalation				
RfD_{SI} (formerly AIS)		Data Inadequate		
RfD_I (formerly AIC)		Data Inadequate		
Oral				
RfD_{SO}	200 mg/kg/day	none; fetotoxicity at 1000 mg/kg/day	140	Maronpot et al., 1983
RfD_O	200 mg/kg/day	fatty liver changes	140	DePass, 1986a
Maximum*				
CS	1% in food for 2 years (500 mg/kg/day) (RV_d=1)	increased mortality rate (RV_e=10)	CS=10	Blood, 1965

*Limited data suggest the potential for severe ocular effects following continuous exposure to relatively low concentrations.