7 ASSESSMENT OF EFFECTS

The principal health effects documented in humans exposed to EGEE, EGME, and their acetates involve the blood, central nervous and hematopoietic systems, liver, and kidneys. These effects include headache, drowsiness, dizziness, forgetfulness, personality change, loss of appetite, tremors, hearing loss, slurred speech, hematuria, hemoglobinuria, anemia, and leukopenia.

Only limited direct evidence indicates that exposure to EGEE, EGME, or their acetates causes adverse reproductive effects in humans. However, experimental studies in animals provide strong evidence of adverse reproductive and developmental effects related to these exposures. Summaries of the developmental and reproductive toxicity of EGEE, EGEEA, and EGME are presented in Tables 7-1 through 7-3. Because humans and the animal species studied metabolize these glycol ethers in the same way, the animal data are considered to be highly predictive of the hazard for humans.

7.1 CORRELATION OF EXPOSURE AND EFFECTS

7.1.1 EGEE

7.1.1.1 Studies in Humans

No epidemiologic studies describe the effects of EGEE in humans, and only one case report exists. A 44-year-old woman who mistakenly drank 40 ml of EGEE (Section 4.1.1) experienced chest pains and vertigo, and lost consciousness shortly after the ingestion [Fucik 1969]. Upon hospitalization, the following signs and symptoms were observed: restlessness, cyanosis, tachycardia, swelling of the lungs, tonoclonic spasms, and breath smelling of acetone. The urine tested positive for protein, acetone, and RBCs; the liver became enlarged and jaundice developed. After 44 days, the woman's condition improved, but insomnia, fatigue, and paresthesia of the extremities persisted for 1 year.

Several cases of anemia were reported in shipyard workers exposed to EGEE and EGME, and all cases were suspected to have been caused by the exposure [Welch and Cullen 1988]. A detailed description of this study is provided in Chapter 4.

Few data are available on the reproductive effects of EGEE in humans. Ratcliffe et al. [1986] concluded that EGEE may have affected the semen quality by lowering the sperm counts of male workers exposed to this chemical during the preparation of ceramic shells for casting

Table 7-1.—Reproductive and developmental toxicity of EGEE

Study type and reference	Sex and species	Route of administration and dose	Male		Maternal		Developmental		Observed effects
			LOAEL*	NOAEL*	LOAEL	NOAEL	LOAEL	NOAEL	
Reproductive, Nagano et al. [1979]	Male mice	Oral; 500, 1,000, 2,000, or 4,000 mg/kg per day, 5 days/wk for 5 wk	1,000 mg/kg per day	500 mg/kg per day	—	—	—	—	Testicular atrophy
Reproductive, Foster et al. [1983]	Male rats	Oral; 250, 500, or 1,000 mg/kg per day for 11 days	500 mg/kg per day	250 mg/kg per day	—	—	—	—	Decreased testis weight and spermatocyte depletion and degeneration
Reproductive, Creasy and Foster [1984]	Male rats	Oral; 250, 500, or 1,000 mg/kg per day for 11 days	500 mg/kg per day	250 mg/kg per day	—	—	—	—	Microscopic testicular lesions
Reproductive, Oudiz et al. [1984]	Male rats	Oral; 936, 1,872, or 2,808 mg/kg per day for 5 days	936 mg/kg per day	—	—	—	—	—	Decreased sperm count, increased abnormal sperm forms, and decreased epididymal weights

(Continued)

*Abbreviations: g.d. = gestation day; LOAEL = lowest observable adverse effect level; NOAEL = no observable adverse effect level.

Table 7-1 (Continued).—Reproductive and developmental toxicity of EGEE

Study type and reference	Sex and species	Route of administration and dose	Male		Maternal		Developmental		Observed effects
			LOAEL	NOAEL	LOAEL	NOAEL	LOAEL	NOAEL	
Reproductive; Barbee et al. [1984], Terrill and Daly [1983a,b]	Male rabbits	Inhalation; 25, 100, or 400 ppm, 6 hr/day, 5 days/wk for 13 wk	400 ppm	—	—	—	—	—	Decreased testis weight and microscopic testicular lesions
	Male rats	Inhalation; 25, 100, or 400 ppm, 6 hr/day, 5 days/wk for 13 wk	—	—	—	—	—	—	No biologically significant effects
Developmental and reproductive, Stenger et al. [1971]	Female rats	Oral; 11.5, 23, 46.5, 93, 186, or 372 mg/kg per day on g.d.* 1–21	—	—	—	—	93 mg/kg per day	46.5 mg/kg per day	Skeletal defects
	Male rats	Oral; 46.5, 93, or 186 mg/kg per day for 13 wk	186 mg/kg per day	—	—	—	—	—	Microscopic testicular lesions

Developmental, Andrew et al. [1981], Hardin et al. [1981]	Female rabbits	Inhalation; 160 or 615 ppm, 7 hr/day on g.d. 1-18	—	—	160 ppm	—	160 ppm	—	Decreased maternal food consumption; 22% fetolethality and renal, cardiovascular, and ventral body wall defects
	Female rats	Inhalation; 150 or 650 ppm, 7 hr/day, 5 days/wk for 3 wk before breeding; then 200 or 765 ppm, 7 hr/day on g.d. 1-19	—	—	765 ppm	—	200 ppm	—	Slight maternal toxicity; retarded fetal growth and fetal cardiovascular and skeletal defects
Developmental, Doe [1984a]	Female rats	Inhalation; 10, 50, or 250 ppm, 6 hr/day on g.d. 6-15	—	—	—	—	250 ppm	50 ppm	Retarded fetal growth, decreased ossification, and increased skeletal variations
	Female rabbits	Inhalation; 10, 50, or 175 ppm, 6 hr/day on g.d. 6-18	—	—	—	—	175 ppm	50 ppm	Fetal skeletal variations
Developmental, Nelson et al. [1981]	Female rats	Inhalation; 100 ppm on g.d. 7-13 and 14-20	—	—	100 ppm	—	—	—	Extended gestation time (0.7 day)
							100 ppm	—	Altered behavioral tests and brain neurochemical concentrations in offspring

(Continued)

Table 7-1 (Continued).—Reproductive and developmental toxicity of EGEE

Study type and reference	Sex and species	Route of administration and dose	Male		Maternal		Developmental		Observed effects
			LOAEL	NOAEL	LOAEL	NOAEL	LOAEL	NOAEL	
Developmental, Hardin et al. [1982]	Female rats	Dermal; 4 applications of 0.25 or 0.5 ml on g.d. 7-16	—	—	4×0.5 ml	—	—	—	Decreased maternal body weight gain and ataxia
			—	—	—	—	4×0.25 ml	—	Fetotoxicity, 75% fetolethality and malformations

Table 7-2.—Reproductive and developmental toxicity of EGEEA

Study type and reference	Sex and species	Route of administration and dose	Male		Maternal		Developmental		Observed effects
			LOAEL*	NOAEL*	LOAEL	NOAEL	LOAEL	NOAEL	
Reproductive, Nagano et al. [1979]	Male mice	Oral; 500, 1,000, 2,000, or 4,000 mg/kg per day, 5 days/wk for 5 wk	1,000 mg/kg per day	500 mg/kg per day	—	—	—	—	Testicular atrophy
Reproductive, Foster et al. [1984]	Male rats	Oral; 726 mg/kg per day for 11 days	726 mg/kg per day	—	—	—	—	—	Testicular atrophy and spermatocyte depletion
Developmental, Nelson et al. [1984b]	Female rabbits	Inhalation; 130, 390, or 600 ppm, 6 hr/day on g.d.* 7-15	—	—	—	—	130 ppm	—	Decreased fetal weights and visceral malformations
Developmental, Doe [1984a]	Female rabbits	Inhalation; 25, 100, or 400 ppm, 6 hr/day on g.d. 6-18	—	—	—	—	100 ppm	—	Reduced fetal body weight and retarded fetal ossification
			—	—	400 ppm	100 ppm	—	—	Decreased maternal body weight gain and food consumption

(Continued)

*Abbreviations: g.d. = gestation day; LOAEL = lowest observable adverse effect level; NOAEL = no observable adverse effect level.

Table 7-2 (Continued).—Reproductive and developmental toxicity of EGEEA

Study type and reference	Sex and species	Route of administration and dose	Male		Maternal		Developmental		Observed effects
			LOAEL	NOAEL	LOAEL	NOAEL	LOAEL	NOAEL	
Developmental, Tyl et al. [1988]	Female rabbits	Inhalation; 50, 100, 200, or 300 ppm, 6 hr/day on g.d. 6-18	—	—	100 ppm	50 ppm	—	—	Maternal toxicity (increased liver weight, decreased gravid uterine weight)
			—	—	—	—	100 ppm	50 ppm	Fetotoxicity
Developmental, Tyl et al. [1988]	Female rats	Inhalation; 50, 100, 200, or 300 ppm, 6 hr/day on g.d. 6-15	—	—	100 ppm	50 ppm	—	—	Maternal toxicity (reduced weight gain and food consumption)
			—	—	—	—	100 ppm	50 ppm	Fetotoxicity
Developmental, Hardin et al. [1984]	Female rats	Dermal; 1.4 ml/day on g.d. 7-16	—	—	—	—	1.4 ml/day	—	Visceral malformations and skeletal variations

Table 7-3.—Reproductive and developmental toxicity of EGME

Study type and reference	Sex and species	Route of administration and dose	Male		Maternal		Developmental		Observed effects
			LOAEL*	NOAEL*	LOAEL	NOAEL	LOAEL	NOAEL	
Reproductive, Nagano et al. [1979]	Male mice	Oral; 62.5, 125, 250, 500, 1,000, or 2,000 mg/kg per day, 5 days/wk for 5 wk	250 mg/kg per day	125 mg/kg per day	—	—	—	—	Testicular atrophy
Reproductive, Foster et al. [1983]	Male rats	Oral; 50, 100, 250, or 500 mg/kg per day for 11 days	100 mg/kg per day	50 mg/kg per day	—	—	—	—	Lesions in primary spermatocytes and partial depletion and degeneration of spermatids and spermatocytes
Reproductive, Chapin et al. [1985a]	Male rats	Oral; 50, 100, or 200 mg/kg per day for 5 days	50 mg/kg per day	—	—	—	—	—	Decreased sperm counts

(Continued)

*Abbreviations: g.d. = gestation day; LOAEL = lowest observable adverse effect level; NOAEL = no observable adverse effect level.

Table 7-3 (Continued).—Reproductive and developmental toxicity of EGME

Study type and reference	Sex and species	Route of administration and dose	Male		Maternal		Developmental		Observed effects
			LOAEL	NOAEL	LOAEL	NOAEL	LOAEL	NOAEL	
Reproductive, Chapin et al. [1985b]	Male rats	Oral; 50, 100, or 200 mg/kg per day for 5 days	50 mg/kg per day	—	—	—	—	—	Abnormal sperm morphology at week 4
Reproductive, Rao et al. [1983]	Male and female rats	Inhalation; 30, 100, or 300 ppm, 6 hr/day, 5 days/wk for 13 wk	300 ppm	100 ppm	—	—	—	—	Decreased male fertility No effect on reproductive performance
Reproductive and developmental, Doe et al. [1983]	Female rats	Inhalation; 100 or 300 ppm, 6 hr/day on g.d. 6-17	—	—	100 ppm	—	—	—	Increased gestation time
			—	—	—	—	100 ppm	—	Decreased numbers of live pups
	Male rats	Inhalation; 100 or 300 ppm, 6 hr/day for 10 days	300 ppm	100 ppm	—	—	—	—	Testicular atrophy

Reproductive, Miller et al. [1983a]	Male rats	Inhalation; 30, 100, or 300 ppm, 6 hr/day, 5 days/wk for 13 wk	300 ppm	100 ppm	—	—	—	—	Microscopic testicular lesions and decreased testis weights
	Male rabbits	Inhalation; 30, 100, or 300 ppm, 6 hr/day, 5 days/wk for 13 wk	100 ppm	—	—	—	—	—	Slight microscopic changes in testicular tissue in 1 of 5 rabbits
			—	30 ppm	—	—	—	—	Microscopic testicular lesions and decreased testis weights
Reproductive, McGregor et al. [1983]	Male rats	Inhalation; 25 or 500 ppm, 7 hr/day for 5 days	500 ppm	25 ppm	—	—	—	—	Decreased fertility during weeks 3-8
Developmental, Nagano et al. [1981]	Female mice	Oral; 31.25, 62.5, 125 250, 500, or 1,000 mg/kg per day on g.d. 7-14	—	—	—	—	31.25 mg/kg per day	—	Bifurcated or split cervical vertebrae
Developmental, Toraason et al. [1985]	Female rats	Oral (gavage); 25 or 50 mg in 10 ml water/kg per day for 11 days	—	—	—	—	25 mg	—	Increased number of fetuses with abnormal QRS complexes

(Continued)

Table 7-3 (Continued).—Reproductive and developmental toxicity of EGME

Study type and reference	Sex and species	Route of administration and dose	Male		Maternal		Developmental		Observed effects
			LOAEL	NOAEL	LOAEL	NOAEL	LOAEL	NOAEL	
Developmental, Scott et al. [1989]	Female monkeys	Oral; 12, 24, or 36 mg/kg on g.d. 20–45	—	—	—	—	12 mg	—	23% embryonic death (3 of 13 pregnancies ended in death)
Developmental, Hanley et al. [1984a]	Female rats	Inhalation; 3, 10, or 50 ppm, 6 hr/day on g.d. 6–15	—	—	50 ppm	10 ppm	—	—	Decreased maternal body weight gain
			—	—	—	—	50 ppm	10 ppm	Increased incidence of lumbar spurs and delayed ossification
	Female rabbits	Inhalation; 3, 10, or 50 ppm, 6 hr/day on g.d. 6–18	—	—	50 ppm	10 ppm	—	—	Decreased maternal body weight gain
			—	—	—	—	50 ppm	10 ppm	Increased resorption rate, decreased mean fetal body weights, and increased incidence of malformations of all organ systems

	Female mice	Inhalation; 10 or 50 ppm, 6 hr/day on g.d. 6–15	—	—	50 ppm	10 ppm	—	—	Minimally decreased maternal body weight gains
			—	—	—	—	50 ppm	10 ppm	Increased incidence of extra lumbar ribs and unilateral testicular hypoplasia
Developmental, Nelson et al. [1984a]	Male rats	Inhalation; 25 ppm, 7 hr/day, 7 days/wk for 6 wk	—	—	—	—	25 ppm	—	Neurochemical deviations in offspring
	Female rats	Inhalation; 25 ppm, 7 hr/day on g.d. 7–13 or 14–20	—	—	—	—	25 ppm	—	Significant differences in avoidance conditioning of offspring from mothers exposed on g.d. 7-13; neurochemical deviations in offspring
Developmental, Wickramaratne [1986]	Female rats	Dermal; 3%, 10%, 30%, or 100% solutions	—	—	100%	—	—	—	100% maternal death
			—	—	—	—	10%	—	Reduced litter sizes
Developmental, Feuston et al. [1990]	Female rats	Dermal; 250, 500, 1,000, or 2,000 mg/kg on g.d. 12, or	—	—	500 mg/kg	250 mg/kg	—	—	Decrease in mean body weight gain
		2,000 mg/kg on g.d. 10, 11, 12, 13, or 14	—	—	—	—	500 mg/kg	250 mg/kg	Increases in external, visceral, and skeletal malformations

metal parts. Lowered sperm counts were also demonstrated in shipyard painters exposed to airborne EGEE ranging from nondetectable concentrations to 22 ppm [Welch et al. 1988]. The potential also existed for skin absorption. In addition, the shipyard painters had been exposed to EGME, lead, and epichlorohydrin, all of which have been reported to affect semen quality. Airborne concentrations of lead were well below those known to depress sperm count. Most blood lead concentrations were below 20 μg%, with the highest single concentration being 40 μg%. Epichlorohydrin was not detected in the air sampling during the study [Sparer et al. 1988].

7.1.1.2 Studies in Animals

Studies in animals have provided evidence of adverse reproductive and developmental effects from EGEE exposure (see Appendix B). The LOAELs and the NOAELs of the following studies were used in determining the REL for EGEE.

Testicular atrophy occurred in mice given oral doses of EGEE (1,000 mg/kg of body weight per day or more), for 5 days/wk during a 5-wk period. The NOAEL noted in this study was 500 mg EGEE/kg per day [Nagano et al. 1979]. Decreased testis weight, spermatocyte depletion and degeneration, and microscopic testicular lesions were observed in rats treated with 500 or 1,000 mg EGEE/kg per day for 11 days [Foster et al. 1983; Creasy and Foster 1984]; no effects were observed at 250 mg/kg. Decreased sperm counts, abnormal sperm morphology, and decreased epididymal weights were found in rats given oral doses of 936, 1,872, or 2,808 mg EGEE/kg per day for 5 days [Oudiz et al. 1984]. A no-effect level was not included in this study. Stenger et al. [1971] treated male rats orally with 46.5, 93, or 186 mg EGEE/kg per day for 13 wk. Microscopic testicular lesions were found only at doses of 186 mg EGEE/kg per day.

Rats and rabbits of both sexes were exposed to 0, 25, 100, or 400 ppm EGEE for 6 hr/day, 5 days/wk over a 13-wk period [Terrill and Daly 1983a,b; Barbee et al. 1984]. At the highest exposures (400 ppm EGEE), reduced testicular weights and microscopic testicular lesions were observed in rabbits, and reduced pituitary weights were observed in male rats. Reduced body weights were observed in male and female rabbits at 25 and 400 ppm EGEE, and reduced spleen weights were found in nonpregnant female rats at 100 and 400 ppm EGEE.

Studies have demonstrated adverse effects on the dam and the developing fetus. Stenger et al. [1971] treated rats orally with 11.5, 23, 46.5, 93, 186, or 372 mg EGEE/kg per day on g.d. 1 through 21. Decreased fetal body weights and skeletal defects were demonstrated at 93, 186, and 372 mg/kg per day. No effects were noted at 11.5, 23, or 46.5 mg/kg per day.

In rabbits exposed to EGEE for 7 hr/day on g.d. 1 through 18, maternal toxicity and embryolethality were observed at 615 ppm, and embryolethality (22%), skeletal variations, renal and cardiovascular defects, and decreased maternal food consumption were observed at 160 ppm [Andrew et al. 1981; Hardin et al. 1981]. No effects were apparent on fertility or pregnancy outcome when female rats were exposed to 150 or 650 ppm EGEE for 7 hr/day, 5 days/wk during the 3 wk before breeding. Toxic signs were noted in female rats exposed at 650 ppm, but none were observed at 150 ppm. However, when pregnant rats were exposed

to 765 ppm EGEE for 7 hr/day on g.d. 1 through 19, 100% intrauterine death occurred. Similar exposure at 200 ppm EGEE significantly increased fetal cardiovascular and skeletal defects. These effects on development were not influenced by exposures to filtered air or EGEE before pregnancy [Andrew et al. 1981; Hardin et al. 1981].

In rats exposed 6 hr/day to 250 ppm EGEE on g.d. 6 through 15, investigators observed increased postimplantation loss, retarded fetal growth, decreased ossification, and increased skeletal variations; they found no effects on fetuses at 50 or 10 ppm EGEE [Doe 1984a]. Fetal skeletal variations were found in rabbits exposed 6 hr/day to 175 ppm EGEE on g.d. 6 through 18; no effects were found in fetuses at 10 or 50 ppm EGEE [Doe 1984a].

Exposure of pregnant rats to 100 ppm EGEE on g.d. 14 through 20 caused extended gestation (0.7 day), and exposure to 100 ppm EGEE on g.d. 7 through 13 or 14 through 20 caused altered behavioral responses and altered brain neurochemical concentrations in offspring [Nelson et al. 1981].

Effects on the fetus were also demonstrated in a dermal application study of EGEE [Hardin et al. 1982]. Four daily doses of 0.25 or 0.50 ml EGEE were applied to rats on g.d. 7 through 16. The higher dose resulted in decreased maternal body weight gain, ataxia, and 100% fetolethality; the lower dose produced fetotoxicity, 75% fetolethality, and malformations.

7.1.1.3 Basis for Selecting the No Observable Adverse Effect Level (NOAEL)

Acute toxicity data for EGEE (Table 4-2) indicate that CNS and kidney effects occurred at higher EGEE concentrations than adverse reproductive and developmental effects. Smyth et al. [1941] reported narcosis, digestive tract irritation, and kidney damage in guinea pigs and rats exposed to 1,400 or 3,000 mg EGEE/kg. Dyspnea, damaged lungs, and toxic effects on WBCs were reported in mice exposed to 1,130 to 6,000 ppm EGEE [Werner et al. 1943c], and the LC_{50} was 1,820 ppm EGEE.

Adverse effects on the blood and hematopoietic system also occurred at higher EGEE concentrations than adverse reproductive and developmental effects. Data in Table 4-9 indicate that EGEE adversely affects the blood and hematopoietic system at concentrations of 125 to 2,000 ppm. These effects include decreased Hb, Hct, RBCs, WBCs, and increased osmotic fragility of erythrocytes [Werner et al. 1943a,b; Stenger et al. 1971; Carpenter et al. 1956; Nagano et al. 1979; Terrill and Daly 1983a,b; Barber et al. 1984; Doe 1984a].

Limited human data correlate adverse reproductive effects with EGEE exposure [Ratcliffe et al. 1986; Welch et al. 1988].

Table 7-1 presents the reproductive and developmental effects resulting from exposure to EGEE. In rabbits, the LOAEL for male reproductive effects was 400 ppm [Barbee et al. 1984; Terrill and Daly 1983a]. This concentration caused decreased testis weight and microscopic testicular lesions, but 100 ppm and 25 ppm had no effect on the male reproductive system. In the male rat, the LOAEL (500 mg/kg) caused decreased testis weight and microscopic testicular lesions [Foster et al. 1983; Creasy and Foster 1984]; the NOAEL was 250 mg/kg.

Adverse developmental effects (behavioral and neurochemical alterations) were observed in rats exposed at 100 ppm EGEE in a study that did not demonstrate an NOAEL for these effects [Nelson et al. 1981]. The NOAEL for structural malformations in rats and rabbits was 50 ppm EGEE [Doe 1984a]. Carpenter et al. [1956] had previously established a 62-ppm NOAEL for osmotic fragility.

Adverse developmental effects occur at lower EGEE concentrations than reproductive, hematotoxic, CNS, and kidney effects. Thus, limiting exposures to control adverse developmental effects will also control reproductive, hematotoxic, CNS, and kidney effects.

The LOAELs and NOAELs in Table 7-1 indicate that 50 ppm is the highest NOAEL [Doe 1984a] in rats that is also lower than the lowest LOAEL in rats [Nelson et al. 1981]. Because of the lack of human data and because the rat is the species most sensitive to EGEE, it is reasonable to use the rat NOAEL to extrapolate an equivalent dose for humans. NIOSH therefore deems it appropriate to use 50 ppm as the NOAEL for EGEE and to use the body weights of rats [Doe 1984a] for calculating their daily NOAEL and extrapolating an equivalent dose for humans.

7.1.2 EGEEA

No information is available about the toxic effects of EGEEA in humans.

7.1.2.1 Studies in Animals

In mice administered EGEEA orally 5 days/wk for 5 wk, testicular atrophy occurred at 1,000, 2,000, and 4,000 mg/kg per day, and depletion and degeneration of spermatocytes occurred at 4,000 mg/kg per day [Nagano et al. 1979]. When doses were expressed as mmoles/kg per day, the dose-response relationships of EGEE and EGEEA were equivalent. No effects appeared at 500 mg EGEEA/kg per day. Testicular atrophy and spermatocyte depletion developed in rats fed 726 mg EGEEA/kg per day for 11 days [Foster et al. 1984].

Nelson et al. [1984b] examined the effects of EGEEA on rat embryo-fetal development by exposing pregnant rats to 130, 390, or 600 ppm EGEEA for 7 hr/day on g.d. 7 through 15. The highest concentration (600 ppm) caused 100% fetolethality. A 56% increase in resorptions occurred at 390 ppm EGEEA, and fetal weights were significantly reduced at 130 and 390 ppm EGEEA. Visceral malformations of the heart and umbilicus occurred in fetuses at 390 ppm, and one fetus from dams exposed to 130 ppm EGEEA had a heart defect.

In another study, rabbits were exposed to 25, 100, or 400 ppm EGEEA on g.d. 6 through 18 [Doe 1984a]. Adverse effects on the fetus included decreased fetal body weights and retarded ossification at 100 ppm EGEEA, and vertebral column malformations at 400 ppm EGEEA. Decreased maternal body weight gain and food consumption, and increased resorptions also occurred at 400 ppm EGEEA. No adverse maternal effects developed at 25 or 100 ppm EGEEA, and no adverse effects on the fetus appeared at 25 ppm EGEEA.

These studies in animals provide ample evidence of adverse reproductive and developmental effects from EGEEA exposure. The following studies, including the LOAEL and the NOAEL of each, were used in determining the REL for EGEEA.

Tyl et al. [1988] found evidence of maternal toxicity and fetotoxicity in rabbits exposed by inhalation to 100, 200, and 300 ppm EGEEA for 6 hr/day on g.d. 6 through 18. A 100% incidence of malformations occurred at 300 ppm EGEEA, and external, visceral, and skeletal malformations increased significantly at 200 ppm EGEEA. No effects were observed on dams or fetuses at 50 ppm EGEEA.

Tyl et al. [1988] found evidence of maternal toxicity (i.e., decreased body weight gain and food consumption, and increased liver weight) in rats exposed by inhalation to 100, 200, and 300 ppm EGEEA for 6 hr/day on g.d. 6 through 15. Fetotoxicity was also found at 100, 200, and 300 ppm EGEEA, with an increased incidence of visceral, skeletal, and external malformations at 200 and 300 ppm EGEEA. Dams and fetuses showed no effects at 50 ppm EGEEA.

Dermal treatment of pregnant rats on g.d. 7 through 16 with 1.4 ml EGEEA/day caused decreased maternal body weights and adverse developmental effects in offspring, including visceral malformations and skeletal variations [Hardin et al. 1984].

7.1.2.2 Basis for Selecting the No Observable Adverse Effect Level (NOAEL)

Reports in the literature indicate that EGEEA exerts adverse hematologic effects in experimental animals at 62 to 4,000 ppm [von Oettingen and Jirouch 1931; Carpenter et al. 1956; Doe 1984a; Tyl et al. 1988; Truhaut et al. 1979; Nagano et al. 1979]. These effects include hemolysis, reduced RBC and WBC counts, and a reduction in Hb, Hct, and MCV.

Acute toxicity data for EGEEA (Table 4-2) indicate that CNS and kidney effects occur at higher EGEEA concentrations than adverse reproductive and developmental effects. Smyth et al. [1941] reported narcosis and damaged kidneys in guinea pigs and rats treated with 1,910 or 5,100 mg EGEEA/kg. Hemoglobinuria, hematuria, and renal lesions were reported in rats treated with 2,900 to 3,900 mg EGEEA/kg [Truhart et al. 1979], and transient hemoglobinuria and/or hematuria were reported in rabbits exposed to 2,000 ppm EGEEA for 4 hr.

Adverse reproductive and developmental effects generally occur at lower concentrations than hematotoxic, CNS, and kidney effects. Thus, limiting exposures to prevent adverse reproductive and developmental effects will also prevent hematotoxic, CNS, and kidney effects.

Table 7-2 presents reproductive and developmental effects resulting from exposure to EGEEA. These data include the LOAEL for mice (1,000 mg/kg), rats (130 ppm), and rabbits (100 ppm). In the study by Tyl et al. [1988], 50 ppm EGEEA caused no effects in rabbits. The LOAELs and NOAELs presented in Table 7-2 indicate that 50 ppm is the highest

NOAEL in rabbits that is also lower than the lowest LOAEL in rabbits [Tyl et al. 1988]. Because human data are lacking and because the rabbit is the animal species most sensitive to EGEEA, it is reasonable to use the rabbit NOAEL to extrapolate an equivalent dose for humans. NIOSH therefore deems it appropriate to use 50 ppm as the NOAEL for EGEEA and to use the body weights of rabbits studied by Tyl et al. [1988] for calculating their daily NOAEL and extrapolating an equivalent dose for humans.

7.1.3 EGME

7.1.3.1 Studies in Humans

As reported in Chapter 4 (Section 4.3), adverse CNS effects (headache, forgetfulness, fatigue, personality change, nausea, and neurologic abnormalities) and hematotoxic effects (anemia and lymphopenia) were observed in workers exposed to EGME-containing solvents in shirt factories [Donley 1936; Parsons and Parsons 1938]. Greenburg et al. [1938] studied workers fusing shirt collars at the same factory as Parsons and Parsons [1938] and observed similar effects (i.e., anemia, neurologic abnormalities, drowsiness, and fatigue). Industrial hygiene measurements taken after the report of adverse health effects in workers indicated that the airborne concentration of EGME was about 25 ppm with windows open and 75 ppm with windows partially closed. Greenburg et al. [1938] stated that worker exposures to EGME had been higher than the measured concentrations because improvements had been made to exhaust and ventilation systems after the report of adverse health effects in workers.

Severe anemia [Zavon 1963; Cohen 1984], major encephalopathy, and bone marrow depression [Ohi and Wegman 1978; Cohen 1984] were observed in workers exposed to EGME dermally and by inhalation in the printing and microfilm industries. In one study [Zavon 1963], EGME was used as a cleaning agent and as a solvent, but the workers seldom wore gloves. No means were available to measure possible dermal absorption. Workers were exposed to 60 to 3,960 ppm EGME during the various cleaning operations, but after airborne EGME concentrations were reduced to the order of 20 ppm EGME, no further ill effects were noted. No mention was made about preventing skin exposure.

Nitter-Hauge [1970] reported general weakness, disorientation, nausea, and vomiting in two men who had each ingested about 0.1 liter of pure EGME, believing it to be ethyl alcohol. Upon admittance to the hospital, the men were suffering from cerebral confusion, pronounced hyperventilation, and profound metabolic acidosis. After i.v. treatment with sodium bicarbonate and ethyl alcohol, both patients made an uneventful recovery over a 4-wk period.

Limited evidence shows the adverse effects of EGME on the male reproductive system. Data suggest that testicle size may have been reduced in male workers with potential exposure to EGME (see Section 4.1.2.2) [Cook et al. 1982]. Welch et al. [1988] noted lowered sperm counts in shipyard painters exposed to EGME and EGEE; airborne EGME ranged from nondetectable concentrations to 5.6 ppm. Details of this study, which are presented in Chapter 4, indicated that lead and epichlorohydrin (also present in the work environment) had no effect on semen quality.

When hematologic parameters were studied in the same group of shipyard painters [Welch and Cullen 1988], several cases of anemia were reported. Exposure to EGME and EGEE was suspected as the cause of the hematologic disorders, but no dose-response relationship was established.

7.1.3.2 Studies in Animals

Chapter 4 summarizes experimental studies demonstrating reproductive and developmental toxicity resulting from EGME exposure (see Appendix B for the complete studies). Doses of 62.5, 125, 250, 500, 1,000, or 2,000 mg EGME/kg per day were administered to mice 5 days/wk for 5 wk [Nagano et al. 1979]. Testicular atrophy was found at 250, 500, 1,000, and 2,000 mg EGME/kg per day, but not at lower doses.

In a study to determine temporal development and the site of the testicular lesion, rats were treated orally with 50, 100, 250, or 500 mg EGME/kg per day for up to 11 days [Foster et al. 1983]. Testis weights were significantly reduced after 2 days at 500 mg/kg per day and after 7 days at 250 mg/kg per day. The lesion appeared localized in the primary spermatocyte 24 hr after a single dose of 100 mg/kg. Partial depletion and degeneration of spermatids and spermatocytes were also observed in rats treated with 100 mg EGME/kg per day for 11 days. No effects were noted over the 11-day treatment period at 50 mg EGME/kg per day.

Treatment of rats with 50 mg EGME/kg per day for 5 days in another study caused a reduction in epididymal sperm counts [Chapin et al. 1985a] and the appearance of abnormal sperm morphology at wk 4, followed by recovery at wk 8 [Chapin et al. 1985b].

Adverse reproductive effects were noted in male rats exposed to ≥100 ppm EGME by inhalation for 6 hr/day, 5 days/wk during a 10-day to 13-wk period [Miller et al. 1983a; Rao et al. 1983; Doe et al. 1983]. At 300 ppm, rats showed decreased male fertility [Rao et al. 1983], testicular atrophy [Doe et al. 1983], microscopic testicular lesions, and decreased testis weights [Miller et al. 1983a]; at 100 ppm, male rats showed no effects. Miller et al. [1983a] observed testicular effects in rabbits exposed to 100 or 300 ppm EGME and slight microscopic changes in testicular tissue in 1 of 5 rabbits exposed to 30 ppm EGME. These investigators considered 30 ppm to be the NOAEL in rabbits.

The effects of EGME on rat reproductive performance were studied by exposing males or females to 30, 100, or 300 ppm EGME for 6 hr/day, 5 days/wk for 13 wk before mating with unexposed animals [Rao et al. 1983]. At 300 ppm, EGME completely suppressed male fertility for 2 wk after exposure; fertility was partially restored 13 to 19 wk after exposure ended. No effects were observed on female reproductive performance at any concentration of EGME, or on male reproductive performance at 30 or 100 ppm. No neonatal effects were found in this study at any EGME concentration.

Nagano et al. [1981] administered doses of 31.25, 62.5, 125, 250, 500, or 1,000 mg EGME/kg per day to rats on g.d. 7 through 14. Skeletal variations consisting of bifurcated and split cervical vertebrae were observed at the lowest dose, and increased malformations (spina bifida occulta) occurred at 62.5 mg EGME/kg per day.

Heart function was also evaluated in rat fetuses from dams treated orally on g.d. 7 through 13 with 25 or 50 mg EGME/kg per day [Toraason et al. 1985]. At 25 mg/kg per day, EGME caused a significant increase in the number of fetuses with abnormal QRS wave complexes; and at 50 mg/kg per day, it caused an increase in cardiovascular defects.

Oral treatment of nonhuman primates with 36 mg EGME/kg during gestation resulted in one embryo that was missing a digit on each forelimb [Scott et al. 1989]. Three of thirteen pregnancies (23%) at the 12-mg/kg dose ended in embryonic death.

Rats and rabbits were exposed by inhalation to 3, 10, or 50 ppm EGME for 6 hr/day on g.d. 6 through 15 (rats) or 6 through 18 (rabbits) [Hanley et al. 1984a]. Maternal toxicity (decreased body weight) in dams of both species was noted at 50 ppm EGME. A significant increase in the resorption rate was also noted in pregnant rabbits exposed to 50 ppm EGME. Significant increases in the incidence of two minor skeletal variations (i.e., lumbar spurs and delayed ossification) indicated slight fetotoxicity in rat fetuses from dams exposed to 50 ppm EGME. Rabbit fetuses from dams exposed to 50 ppm EGME exhibited a significant increase in the incidence of malformations of all organ systems and a significant decrease in the mean body weight. No effects were noted in either species for dams and fetuses at 3 or 10 ppm EGME.

Hanley et al. [1984a] found minimally decreased body weight gains in mice exposed to 50 ppm EGME 6 hr/day on g.d. 6 through 15. Examination of fetuses from dams exposed to 50 ppm EGME revealed statistically significant increases in the incidence of extra lumbar ribs and of unilateral testicular hypoplasia. No adverse effects were noted in dams or fetuses at 10 ppm EGME.

In another study, pregnant rats were exposed to 100 or 300 ppm EGME for 6 hr/day on g.d. 6 through 17, and males were exposed to 100 or 300 ppm EGME for 6 hr/day during a 10-day period [Doe et al. 1983]. At 100 ppm, EGME increased gestation time and decreased the number of pups and live pups. At 300 ppm, EGME decreased maternal body weight and produced 100% fetolethality. Male rats showed testicular effects after 10 exposures to 300 ppm, but not after exposures to 100 ppm EGME.

In a dominant lethal study, male rats were exposed by inhalation to 25 or 500 ppm EGME for 6 hr/day over 5 days [McGregor et al. 1983]. Rats exposed to 500 ppm showed decreased fertility during wk 3 through 8, and rats exposed to 25 ppm EGME showed no adverse effects on fertility.

Nelson et al. [1984a] exposed male rats to 25 ppm EGME for 7 hr/day, 7 days/wk during a 6-wk period. These rats were then mated with untreated females that were allowed to deliver and rear their young. In the same study, pregnant females were exposed to EGME for 7 hr/day on g.d. 7 through 13 or 14 through 20 and allowed to deliver and rear their young. Significant differences in avoidance conditioning were observed in offspring of dams exposed on g.d. 7 through 13, but not in offspring of dams exposed on g.d. 14 through 20. Brain neurochemical deviations were noted in offspring from the paternally exposed group and in offspring from both maternally exposed groups.

In a dermal exposure study, female rats were exposed to solutions of 3%, 10%, 30%, or 100% EGME (10 ml/kg) in physiological saline [Wickramaratne 1986]. Reduced litter sizes were observed at the 10% concentration, 100% fetolethality occurred at the 30% concentration, and 100% maternal death was observed at the 100% concentration.

A single dermal application of 500, 1,000, or 2,000 mg EGME/kg on g.d. 12 caused statistically significant increases ($P<0.05$) in external, visceral, and skeletal malformations [Feuston et al. 1990]. In the same study, dermal exposure of female rats to EGME (1,000 mg/kg on g.d. 12 or 2,000 mg/kg on g.d. 10 and 12) caused a statistically significant decrease in fetal body weights ($P<0.05$). The investigators determined 250 mg EGME/kg to be the NOAEL for adverse developmental effects.

7.1.3.3 Basis for Selection of No Observable Adverse Effect Level (NOAEL)

Adverse CNS effects (encephalopathy) and hematotoxic effects (bone marrow depression, anemia, and leukopenia) were observed in workers exposed to EGME [Donley 1936; Parsons and Parsons 1938; Greenburg et al. 1938; Zavon 1963; Ohi and Wegman 1978; Cohen 1984]. However, there is limited evidence of an adverse effect on the male reproductive system as a result of EGME exposure [Welch et al. 1988].

Acute toxicity data for EGME (Table 4-2) indicate that CNS, liver, and kidney effects occur at higher EGME concentrations than adverse reproductive and developmental effects. Wiley et al. [1938] reported tissue damage to the kidneys and liver in dogs and rabbits exposed to 2,130 mg EGME/kg. Narcosis, lung, and kidney damage were reported in rats (3,250 to 3,400 mg/kg), rabbits (890 mg/kg), and guinea pigs (950 mg/kg) [Carpenter et al. 1956], and digestive tract irritation and damaged kidneys were reported in rats and guinea pigs exposed to 246 and 950 mg EGME/kg, respectively.

Adverse effects on the blood and hematopoietic system also occurred at higher EGME concentrations than adverse reproductive or developmental effects. Data in Table 4-9 indicate that 32 to 2,000 ppm EGME adversely affects the blood and hematopoietic system. These effects include increased osmotic fragility, decreased Hb, Hct, RBC and WBC counts [Carpenter et al. 1956; Nagano et al. 1979; Grant et al. 1985; Werner et al. 1943a,b; Miller et al. 1981; Miller et al. 1983a].

Table 7-3 presents the reproductive and developmental effects caused by exposure to EGME. In rats, the LOAEL of 50 mg EGME/kg per day caused decreased sperm counts and abnormal sperm morphology in two separate studies that did not demonstrate a NOAEL [Chapin et al. 1985a,b]. In rabbits, the LOAEL (100 ppm EGME) caused microscopic testicular lesions and decreased testis weights, and the NOAEL was 30 ppm EGME [Miller et al. 1983a]. In mice, the LOAEL (250 mg/kg per day) caused testicular atrophy, and the NOAEL was 125 mg/kg per day [Nagano et al. 1979].

Behavioral defects and neurochemical deviations were observed in the offspring of rats exposed to 25 ppm EGME [Nelson et al. 1984a]. Retarded fetal ossification was observed

in the offspring of mice treated with 31.25 mg EGME/kg per day (LOAEL) [Nagano et al. 1981]. Adverse developmental effects were observed in the offspring of rats, rabbits, and mice exposed to an LOAEL of 50 ppm EGME [Hanley et al. 1984a]; the NOAEL for these species was 10 ppm EGME. In the same study, the NOAEL for maternal effects in these species was 10 ppm EGME.

Feuston et al. [1990] observed an increase ($P<0.05$) in external, visceral, and skeletal malformations in the fetuses of rats exposed to single dermal applications of 500, 1,000, or 2,000 mg EGME/kg on g.d. 12. The authors determined 250 mg EGME/kg to be the NOAEL for adverse developmental effects in this study.

Adverse developmental effects occur at lower EGME concentrations than reproductive, hematotoxic, CNS, liver, and kidney effects. Thus, limiting exposure to control adverse developmental effects will also control reproductive, hematotoxic, CNS, liver, and kidney effects.

The data that demonstrate reproductive and developmental toxicity, and the LOAELs and NOAELs presented in Table 7-3 indicate that in several species (rats, rabbits, and mice), 10 ppm is the highest NOAEL that is also lower than the lowest LOAEL [Hanley et al. 1984a]. Because of the lack of human data, it is reasonable to use the NOAEL of 10 ppm [Hanley et al. 1984a] to extrapolate an equivalent dose for humans.

7.1.4 EGMEA

Few data are available on the toxicity of EGMEA. Bolt and Golka [1990] reported the occurrence of hypospadias at birth in two boys whose mother had been exposed to EGMEA during her pregnancies. The authors concluded that the hypospadias were caused by exposure to EGMEA. Testicular atrophy was observed in mice exposed orally for 5 days/wk during a 5-wk period to 500, 1,000, or 2,000 mg EGMEA/kg per day; no reproductive effects were noted at 62.5, 125, or 250 mg EGMEA/kg per day [Nagano et al. 1979]. When doses were expressed as mmol/kg per day, the dose-response relationships of EGMEA and EGME were almost identical. The toxic effects caused by EGMEA are likely to be similar to those caused by EGME because EGMEA is metabolized to EGME and then to the active metabolite (see Section 4.2). Therefore, it is reasonable to use the NOAELs for EGME to extrapolate NOAELs for EGMEA. On the basis of the Hanley et al. [1984a] study, a NOAEL of 10 ppm was used for EGMEA.

7.2 BASIS FOR RECOMMENDED STANDARDS FOR EGEE, EGME, AND THEIR ACETATES

7.2.1 Data Available from Studies in Humans and Animals

Toxic effects of human exposure to EGEE and EGME include personality change, memory loss, drowsiness, blurred vision, hearing loss, anemia, and leukopenia. However, data are

limited on possible adverse reproductive and developmental effects of worker exposure to EGEE, EGME, and EGMEA, and no human data are available on EGEEA exposure. Cook et al. [1982] suggested that testicle size in males may have been reduced because of EGME exposure. Welch et al. [1988] concluded that exposure to EGEE and EGME caused functional impairment in males by lowering sperm counts. The occurrence of hypospadias in two boys at birth was attributed to the mother's exposure to EGMEA during her pregnancies [Bolt and Golka 1990].

Ballew and Hattis [1989] performed a quantitative risk analysis under contract to NIOSH to determine the risk of developmental effects in the offspring of pregnant women exposed to EGEE and EGME. Table 7-4 summarizes the concentrations of EGEE and EGME that the authors associated with developmental risks in humans at a frequency of 1 per 1 million or 1 per 10,000. Because the estimates presented in this table are based on a series of assumptions and carry considerable uncertainty, and because this was an exploratory analysis, NIOSH does not deem it appropriate to base RELs for EGEE, EGME, or their acetates on this risk analysis.

Although data for humans are limited, ample evidence from studies in animals indicates that EGEE, EGME, and their acetates adversely affect reproduction and development. In the absence of sufficient human data, NIOSH deems it appropriate to base the RELs for EGEE, EGME, and their acetates on animal data. The following procedure was therefore used to calculate equivalent human doses from animal data.

7.2.2 Procedure for Calculating Equivalent Human Doses from Animal Data

No mechanistic models exist to describe the relationship of reproductive and developmental toxicity to exposure; only empirical models are available to use in a quantitative risk assessment (QRA). Because a threshold is assumed to exist for reproductive and developmental toxicity, a QRA model is inappropriate since these models assume a no-threshold effect. Therefore, the following method was used to determine the RELs for EGEE, EGME, and their acetates.

Both humans and animals were assumed to retain 100% of inhaled EGEE, EGME, or their acetates. The retained dose for animals exposed at the NOAEL was calculated as follows by using the inhalation rate and the average body weights of the animals (see Table 7-5):

$$\text{Retained dose for animals} = \text{NOAEL } (\text{mg/m}^3) \times \frac{\text{inhalation rate } (\text{m}^3/\text{day})}{\text{animal body weight}} \times 0.25 \text{ day} \qquad (1)$$

That dose was converted to an equivalent exposure for humans by assuming a 70-kg body weight and an inhalation rate of 10 m^3 in an 8-hr workday [45 Fed. Reg. 79318 (1980); EPA 1987]:

$$\text{Equivalent exposure for humans} = \frac{\text{retained dose for animals (mg/kg per day)} \times 70 \text{ kg}}{10 \text{ m}^3/\text{day}} \qquad (2)$$

Table 7–4.—Concentrations of EGME and EGEE associated with developmental risks in humans at a frequency of 1 per 1 million or 1 per 10,000* (ppm)

Developmental effect	EGEE		EGME	
	Lower limit†	Best estimate‡	Lower limit†	Best estimate‡
	Concentrations associated with projected risk of 1 per 1 million for each effect			
Miscarriages	0.00056	0.53	0.00026	0.067
Minor skeletal defects	0.0000044	0.022	---	---
External malformations	0.0011	1.1	---	---
Digit or limb malformations	---	---	0.00013	0.15
Total malformations	---	---	0.000046	0.042
Infant mortality§ (projected from fetal weight changes)	---	0.069	---	0.0085
	Concentrations associatedwith projected risk of 1 per 10,000 for each effect			
Miscarriages	0.0061	1.8	0.0029	0.22
Minor skeletal defects	0.000048	0.073	---	---
External malformations	0.012	3.5	---	---
Digit or limb malformations	---	---	0.0014	0.48
Total malformations	---	---	0.0005	0.14
Infant mortality§ (projected from fetal weight changes)	---	6.8	---	0.84

*Adapted from Ballew and Hattis [1989].
†Concentrations of EGEE or EGME associated with the indicated effect under a more pessimistic assumption about the degree of interindividual variability in susceptibility of the human population (log probit slope of 1).
‡Best-estimate assumption of the degree of interindividual variability in susceptibility for the quantal developmental effects (log probit slope of 2).
§Death in the first year after birth. In the case of this hypothesized effect, only best estimates have been made.

Table 7-5.—Data for inhalation studies

Glycol ether and species studied	NOAEL ppm	NOAEL mg/m^3	Exposure duration	Average body weight (kg)	Inhalation rate*
EGEE:†					
Rat	50	184.25	6 hr/day on g.d. 6-15	0.240	0.184 m^3/day
Rabbit	50	184.25	6 hr/day on g.d. 6-18	2.25	1.23 m^3/day
EGEEA:‡					
Rabbit	50	270	6 hr/day on g.d. 6-18	3.25	1.61 mg/m^3
EGME:§					
Rabbit	10	31.12	6 hr/day on g.d. 6-18	4.17	1.94 mg/m^3
Rat	10	31.12	6 hr/day on g.d. 6-15	0.22	0.172 mg/m^3
Mouse	10	31.12	6 hr/day on g.d. 6-15	0.0499	0.07 mg/m^3

*Data from Guyton [1947] and Adolph [1949].
†Data from Doe [1984a].
‡Data from Tyl et al. [1988].
§Data from Hanley et al. [1984a].

To allow for potential interspecies variability, an uncertainty factor of 10 was applied to the equivalent exposure for humans. An additional uncertainty factor of 10 was then applied to allow for potential intraspecies variablility. The resulting concentration was converted to parts per million:

$$\frac{\text{Equivalent exposure for humans}}{100} \times \frac{24.45}{\text{mol wt of particular glycol ether}} = \text{ppm} \qquad (3)$$

7.2.2.1 REL for EGEE and EGEEA

Although limited data in humans have shown adverse reproductive or developmental effects from exposure to EGEE [Ratcliffe et al. 1986; Welch et al. 1988], sufficient data have demonstrated these effects in animals exposed to EGEE [Nagano et al. 1979; Stenger et al. 1971; Andrew et al. 1981; Hardin et al. 1981, 1982; Nelson et al. 1981; Terrill and Daly 1983a; Foster et al. 1983; Doe 1984a; Barbee et al. 1984; Oudiz et al. 1984] and EGEEA [Nagano et al. 1979; Doe 1984a; Foster et al. 1984; Nelson et al. 1984b; Tyl et al. 1988]. These animal data provide the basis for determining the RELs for worker exposure to EGEE and EGEEA and for instituting controls to reduce worker exposure. On the basis of the calculations presented in Equations 4 through 12, NIOSH recommends that occupational

exposure to EGEE and EGEEA be limited to 0.5 ppm as a TWA for up to a 10-hr workshift during a 40-hr workweek. Because both EGEE and EGEEA can be absorbed percutaneously [Dugard et al. 1984], dermal contact is prohibited. The data in Table 7-5 were used in Equations 4 through 12 to calculate the human equivalents to the daily animal NOAELs for EGEE and EGEEA as follows:

$$\text{Daily rat NOAEL for EGEE} = 184.25\ \text{mg/m}^3 \times \frac{0.184\ \text{m}^3/\text{day} \times 0.25\ \text{day})}{0.240\ \text{kg}} = 35.3\ \text{mg/kg per day} \quad (4)$$

$$\text{Human equivalent to daily rat NOAEL for EGEE} = \frac{35.3\ \text{mg/kg per day} \times 70\ \text{kg}}{10\ \text{m}^3/\text{day}} = 247\ \text{mg/m}^3 \quad (5)$$

$$\frac{247\ \text{mg/m}^3}{100} \times \frac{24.45}{90.1} = 0.67\ \text{ppm} \quad (6)$$

$$\text{Daily rabbit NOAEL for EGEE} = 184.25\ \text{mg/m}^3 \times \frac{1.23\ \text{m}^3/\text{day} \times 0.25\ \text{day})}{2.25\ \text{kg}} = 25.18\ \text{mg/kg per day} \quad (7)$$

$$\text{Human equivalent to daily rabbit NOAEL for EGEE} = \frac{25.18\ \text{mg/kg per day} \times 70\ \text{kg}}{10\ \text{m}^3/\text{day}} = 176.26\ \text{mg/m}^3 \quad (8)$$

$$\frac{176.26}{100} \times \frac{24.45}{90.1} = 0.478\ \text{ppm} = 0.5\ \text{ppm} \quad (9)$$

$$\text{Daily rabbit NOAEL for EGEEA} = 270\ \text{mg/m}^3 \times \frac{(1.61\ \text{m}^3/\ \text{day} \times 0.25\ \text{day})}{3.25} = 33.4\ \text{mg/kg per day} \quad (10)$$

$$\text{Human equivalent to daily rabbit NOAEL for EGEEA} = \frac{33.4\ \text{mg/kg per day} \times 70\ \text{kg}}{10\ \text{m}^3/\text{day}} = 234\ \text{mg/m}^3 \quad (11)$$

$$\frac{234}{100} \times \frac{24.45}{132.16} = 0.43\ \text{ppm} \quad (12)$$

7.2.2.2 REL for EGME and EGMEA

Case reports and clinical studies demonstrated adverse CNS and hematotoxic effects on workers exposed to EGME [Donley 1936; Parsons and Parsons 1938; Greenburg et al. 1938; Zavon 1963; Ohi and Wegman 1978; Cohen 1984], but data demonstrating adverse reproductive and developmental effects in offspring of EGME-exposed workers are limited [Welch et al. 1988]. Bolt and Golka [1990] reported hypospadias at birth in two boys whose mother was exposed to EGMEA during her pregnancies.

Sufficient evidence in animal studies indicates that EGME exerts adverse reproductive and developmental effects [Nagano et al. 1979; Nagano et al. 1981; Doe et al. 1983; Foster et al. 1983; McGregor et al. 1983; Miller et al. 1983a; Rao et al. 1983; Hanley et al. 1984a; Nelson et al. 1984a; Chapin et al. 1985a; Chapin et al. 1985b; Toraason et al. 1985; Scott et al. 1989; Wickramaratne 1986]. EGMEA was also shown to have such effects by Nagano et al. [1979], who found that this glycol ether caused testicular atrophy in mice. Data from these animal studies warrant concern that EGME and EGMEA are capable of inducing similar adverse effects in exposed workers.

Based on information presented in Table 7-3, a 10-ppm NOAEL was determined for EGME in rats, rabbits, and mice [Hanley et al. 1984a]. Any effects that EGMEA might cause would be likely to occur through the initial conversion of EGMEA to EGME (see Section 4.2). Therefore, it is reasonable to propose the same REL for both compounds. An equivalent human dose was determined for EGME using the information presented in the study by Hanley et al. [1984a]. On the basis of the calculations presented in Equations 13 through 21, NIOSH recommends that occupational exposure to EGME and EGMEA be limited to 0.1 ppm as a TWA for up to a 10-hr workday during a 40-hr workweek. Because EGME and EGMEA can be absorbed percutaneously [Dugard et al. 1984], dermal contact is prohibited. The data in Table 7-5 were used in Equations 13 through 21 to calculate the human equivalents to the daily animal NOAELs for EGME and EGMEA as follows:

$$\text{Daily rabbit NOAEL for EGME} = 31.12\ \text{mg/m}^3 \times \frac{(1.94\ \text{m}^3/\text{day} \times 0.25\ \text{day})}{4.17\ \text{kg}} = 3.62\ \text{mg/kg per day} \quad (13)$$

$$\text{Human equivalent to daily rabbit NOAEL for EGME} = \frac{3.62\ \text{mg/kg per day} \times 70\ \text{kg}}{10\ \text{m}^3/\text{day}} = 25.34\ \text{mg/m}^3 \quad (14)$$

$$\frac{25.34\ \text{mg/m}^3}{100} \times \frac{24.45}{76.1} = 0.08\ \text{ppm} = 0.1\ \text{ppm} \quad (15)$$

$$\text{Daily rat NOAEL for EGME} = 31.12\ \text{mg/m}^3 \times \frac{(0.172\ \text{m}^3/\text{day} \times 0.25\ \text{day})}{0.22\ \text{kg}} = 6.08\ \text{mg/kg per day} \quad (16)$$

$$\text{Human equivalent to daily rat NOAEL for EGME} = \frac{6.08\ \text{mg/kg per day} \times 70\ \text{kg}}{10\ \text{m}^3/\text{day}} = 42.56\ \text{mg/m}^3 \quad (17)$$

$$\frac{42.56\ \text{mg/m}^3}{100} \times \frac{24.45}{76.1} = 0.137\ \text{ppm} = 0.14\ \text{ppm} \quad (18)$$

$$\text{Daily mouse NOAEL for EGME} = 31.12\ \text{mg/m}^3 \times \frac{0.07\ \text{m}^3/\text{day} \times 0.25\ \text{day})}{0.0499\ \text{kg}} = 10.9\ \text{mg/kg per day} \quad (19)$$

$$\text{Human equivalent to daily mouse NOAEL for EGME} = \frac{10.9 \text{ mg/kg per day} \times 70 \text{ kg}}{10 \text{ m}^3\text{/day}} = 76.3 \text{ mg/m}^3 \quad (20)$$

$$\frac{76.3 \text{ mg/m}^3}{100} \times \frac{24.45}{76.1} = 0.245 \text{ ppm} \quad (21)$$