5 RECOGNITION OF THE HAZARD

Each employer who manufactures, transports, packages, stores, or uses EGME, EGEE, or their acetates in any capacity should determine the potential for occupational exposure of any worker at or above the action level (one-half the REL).

5.1 ENVIRONMENTAL SAMPLING

Exposure monitoring and environmental sampling for EGME, EGEE, and their acetates can be performed according to OSHA Method No. 79 [OSHA 1990]. The sampling procedure involves the use of activated coconut shell charcoal sampling tubes connected by flexible tubing to a sampling pump. A total air volume of 48 liters is drawn by the pump through the charcoal tube at a flow rate of 0.1 liter/min.

5.2 ANALYTICAL METHODS

Laboratory analyses for EGME, EGEE, and their acetates can be performed by OSHA Method No. 79 [OSHA 1990], which is based on OSHA Method No. 53 [OSHA 1985]. Prior knowledge of certain types of interfering compounds will help the analyst select the appropriate analytical conditions for sample analysis. This list of compounds can be compiled from the material safety data sheets for the compounds that are used in or around the process where the sampling will occur. The principles of the method are as follows:

- The charcoal in the sampling tube is transferred to a small, stoppered sample container, and the analyte is desorbed. EGME, EGEE, EGMEA, and EGEEA may be desorbed from the charcoal with methylene chloride and 5% (v/v) methanol.
- An aliquot of the desorbed sample is injected into a gas chromatograph with a flame ionization detector.
- The area of the resulting peak is determined and compared with areas obtained from the injection of standards.

The detailed analytical method is described in Appendix A. Table 5-1 lists the quantitation limits of this analytical procedure for a 48-liter air sample.

5.3 MEDICAL MONITORING

EGME, EGMEA, EGEE, and EGEEA exert adverse effects on the blood and the reproductive, central nervous, hematopoietic, and renal systems in humans and animals; furthermore,

Table 5-1.—Quantitation limits of OSHA Method No. 79[*,†]

Compound	Limits of quantitation (ppm)
EGME	0.0067
EGMEA	0.0017
EGEE	0.0021
EGEEA	0.0012

[*]Source: OSHA [1990].
[†]48-liter air sample.

exposure to these glycol ethers may impair liver function. Workers who may be exposed to them should therefore receive preplacement and periodic medical examinations. Medical monitoring should include the following:

- An initial medical examination. A complete medical history and examination will establish a baseline for further monitoring and detect any pre-existing conditions that may place the exposed worker at increased risk. Special attention should be given to tests of the following systems and organs:

  —Blood and hematopoietic system. A complete blood count should be done. Because of adverse effects of glycol ethers on the blood and the hematopoietic system, workers with blood diseases may be at increased risk from exposure to these glycol ethers.

  —Skin. These glycol ethers are readily absorbed through the skin, but workers with chronic skin disease characterized by eczema or fissures may be at increased risk of absorbing them.

  —Liver. Although these glycol ethers are not known as liver toxins in humans, they are metabolized primarily in this organ, and workers with impaired liver function should receive special consideration.

  —Kidneys. A urinalysis should be done to ascertain whether renal function is impaired. Because of the importance of the kidneys in the elimination of toxic substances, special consideration should be given to workers with impaired renal function who may be exposed to glycol ethers.

  —Central nervous system. The need for examinations of the central nervous system should be emphasized because of the adverse effects of glycol ethers on this system.

  —Reproductive system. The need for examinations of the reproductive system should be stressed (i.e., semen quality, sperm count).

- Periodic medical examinations. The aforementioned medical examinations should be performed annually for all workers occupationally exposed to EGEE, EGME, or their acetates at or above the action levels, and for all who have the potential for significant skin exposure.

5.4 BIOLOGICAL MONITORING

Biological monitoring may be a useful adjunct to environmental monitoring in assessing worker exposure to EGME, EGEE, and their acetates. Biological monitoring includes the influence of workload and percutaneous absorption.

5.4.1 Justification for Biological Monitoring

Human experimental inhalation studies have demonstrated the uptake of EGEE [Groeseneken et al. 1986b], EGEEA [Groeseneken et al. 1987a], and EGME [Groeseneken et al. 1989a]. Studies that included different workloads in the experimental design [Groeseneken et al. 1986b, 1987a] demonstrated a linear relationship between the workload and uptake of each glycol ether; a linear relationship was also found for the exposure concentration and uptake. Table 5-2 illustrates the effects of a 4-hr inhalation exposure to EGEE under a variety of exposure and exercise conditions. Each group consisted of five subjects; experimental details are provided in Appendix B of this document [Groeseneken et al. 1986b].

Data presented in Table 5-2 show that an exposure to EGEE at 5.4 ppm (20 mg/m^3) with exercise at 30 W is comparable to an exposure of 10.8 ppm (40 mg/m^3) at rest. Johanson [1988] concluded that the uptake of glycol ethers by inhalation is directly related to pulmonary ventilation.

EGME, EGEE, and their acetates exhibit high solubilities in both lipids and in water. These characteristics make them candidates for significant absorption through the skin. In vitro dermal absorption of EGME, EGEE, and EGEEA has been shown in human abdominal skin [Dugard et al. 1984]. Relative absorption rates are shown in Table 5-3.

Table 5-2.—Absorption of EGEE at various workloads

Group	EGEE exposure		Workload	Total EGEE absorbed
	ppm	mg/m^3	(W)	(mg)
1	2.7	10	0*	16.7 ± 4.2
	5.4	20	0	35.1 ± 7.6
	10.8	40	0	64.1 ± 14.5
2	5.4	20	0	33.3 ± 8.3
	5.4	20	30	57.0 ± 11.8
	5.4	20	60	94.4 ± 13.9

*0 watts is defined as "at rest."

Table 5-3.—In vitro skin absorption of selected glycol ethers in humans

Compound	Rate of absorption (mg/cm^2 per hr)	Relative rate (EGBE = 1)
EGME	2.82 ± 2.63	14.2
EGEE	0.796 ± 0.460	4.02
EGEEA	0.800 ± 0.430	4.04

Nakaaki et al. [1980] demonstrated that 10 times more EGME was absorbed through the forearm than acetone or methanol.

Johanson [1988] described the relative importance of the inhalation of EGME, EGEE, and EGEEA at 5 ppm or at 1% of the saturation concentration at room temperature compared with the dermal route of absorption. Uptake rates were calculated by assuming a pulmonary ventilation of 10 liters/min and a relative respiratory uptake of 60% for inhalation exposure, and by extrapolation of in vitro human skin penetration rates to an area of 50 cm^2 (an area of about 4 × 2 in.) for dermal exposure.

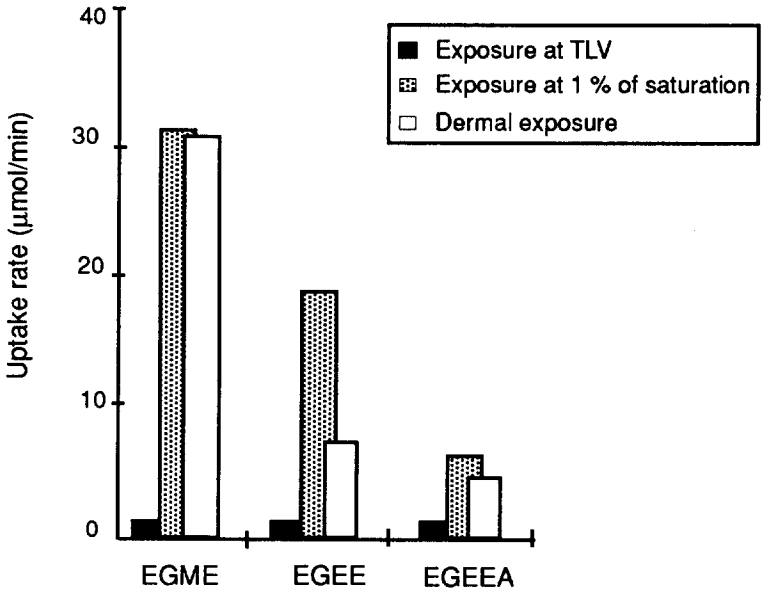

Figure 5-1. Relative uptake rates of glycol ethers under different exposure routes. Source: Johanson [1988].

Examination of Figure 5-1 shows that, based on uptake rates, absorption through the skin is a major route of absorption of EGME, EGEE, and EGEEA. The rate of absorption through this small 8-$in.^2$ area of skin would be far greater than pulmonary absorption in an atmosphere containing 5 ppm of these glycol ethers.

Metabolism studies in animals (described in Section 4.2) demonstrated that EGEE and EGME are metabolized to their corresponding alkoxyacetic acids, EAA and MAA, which

are excreted in the urine. These metabolites produced reproductive and hematologic toxicity in a variety of animal species. Thus measurement of these metabolites can be viewed as an indicator of potential health effects as well as an assessment of total uptake through inhalation and dermal absorption.

Assessment of worker exposure to EGEE, EGME, and their acetates should include biological monitoring. Industrial hygiene measurements are used to assess the workroom concentrations, and the inhalation exposures may be measured with personal breathing zone samples. However, dermal absorption may be the principal route of exposure, and workload can dramatically affect the actual inhalation uptake of EGEE, EGME, and their acetates. Therefore biological monitoring should be considered an additional technique to assess the total exposure of the worker.

5.4.2 Selection of Monitoring Medium

A variety of biological monitoring media can be used to assess uptake (e.g., expired air, blood, urine). Groeseneken et al. [1986b, 1987a, 1989a] studied the respiratory elimination of EGEE, EGEEA, and EGME, and concluded that less than 0.5% of the dose was eliminated by the lungs. Respiratory elimination half-lives were short and the expired air concentrations low. These glycol ethers were not found in the blood.

According to Johanson [1988], the concentrations of alkoxyacetic acids (EAA and MAA) in urine are the best indicators of exposure by all routes. The advantages of using urinary alkoxyacetic acids for biological monitoring of EGEE, EGME, and their acetates are:

- The acid metabolites EAA and MAA are not normally present in human urine.
- Expected concentrations for these metabolites at the proposed RELs can also be measured by the recommended analytical method (see Appendix F).
- The acid metabolites are associated with the reproductive and hematologic toxicity of EGEE, EGME, and their acetates, and may reflect the concentration of the "active agent" at the target sites.
- The half-lives of the acid metabolites in urine are suitable for exposure monitoring and can reflect integrated exposures over a workweek [Groeseneken et al. 1989a, 1988]. The half-life for MAA is 77 hr and for EAA is 42 to 48 hr.
- Collection of urine samples is a noninvasive procedure.

5.4.3 Limitations of Biological Monitoring

Limitations and possible sources of error exist in the biological monitoring of the acid metabolites of these glycol ethers. Biological monitoring assesses uptake and not exposure concentration. In addition to the lack of well-designed field evaluations of workers exposed to EGME, EGEE, and their acetates, the following factors limit the use of biological monitoring to assess exposure [Johanson 1988]:

- Variability in uptake through inhalation caused by workload-dependent uptake
- Variability in extent of skin exposure
- Intraindividual variations in excretion rates of the metabolites, possibly caused by fluid intake or the effects of alcohol consumption
- Interindividual variations in excretion rates of the acid metabolites, possibly caused by differences in body fat, sex, personal habits (e.g., smoking, dietary factors, ethanol consumption), and coexposure to other chemicals

Johanson [1988] concluded that monitoring acid metabolites in the urine is appropriate even if the uptake or metabolism is influenced by other factors. The concentration of the acid metabolite in the urine may not be linearly correlated to the absorbed dose, but it may be well correlated to the concentration at the target sites and thus related to the potential toxicity.

5.4.4 Correlation of Glycol Ethers' Uptake with Acid Metabolite Excretion

Urinary EAA excretion in subjects exposed to EGEE at rest and during physical exercise was described in Section 4.2 [Groeseneken et al. 1986c]. The relationship between total uptake of EGEE (pulmonary ventilation × concentration of retained EGEE × exposure time) and urinary excretion of EAA is shown in Figure 5-2.

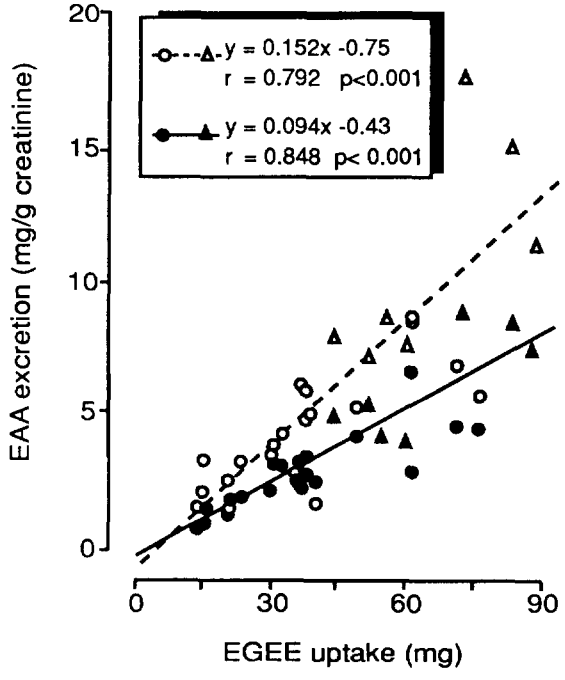

Figure 5-2. Relationship between uptake of EGEE and EAA excretion. Correlation between time-weighted individual uptake of EGEE at rest (o, ●) and during physical exercise (Δ, ▲), and urinary excretion of ethoxyacetic acid at maximal excretion (open symbols) and next morning (closed symbols). Source: Groeseneken et al. [1986c].

Figure 5-2 shows the linear relationship between the uptake of EGEE during rest and physical exercise and the concentration of EAA, expressed as mg/g creatinine, in urine samples collected 4 hr after exposure and 18 hr after exposure (prior to the next shift). Good correlations between EAA excretion and EGEE uptake were found 4 hr postexposure ($r=0.792$, $P<0.001$), and 18 hr postexposure ($r=0.848$, $P<0.001$). A better correlation was shown 18 hr postexposure (corresponding to a preshift urine sample collected the next day), based on the observed correlation coefficients. Biological monitoring using the preshift specimen the next day may be preferred because of the long elimination half-time of EAA in the urine. In addition, as a result of its long biological half-life, EAA will not be cleared from the urine before the next shift and accumulation can be expected through repetitive exposures [Groeseneken et al. 1986c].

Groeseneken et al. [1986c] also showed the relationship between exposure, workload, uptake, and urinary EAA (expressed as mg/g creatinine) for urine samples collected at the end of the exposure period and 18 hr after the end of the exposure period (Table 5-4). The 5.4-ppm exposure group at 0 W represents the combined data from both groups, n=10 [Groeseneken et al. 1986c]. This table reveals the impact of physical exercise on the uptake of EGEE and the amount of EAA excreted in the urine. Note that volunteers exposed to 5.4 ppm EGEE at 30 W exercise excreted slightly more EAA in urine samples than subjects exposed to twice the concentration of EGEE while at rest.

Urinary EAA excretion in subjects exposed to EGEEA both at rest and during physical exercise was described in Section 4.2 [Groeseneken et al. 1987a]. Figure 5-3 shows the linear relationship between uptake of EGEEA during rest and physical exercise, and the concentration of EAA, expressed as mg/g creatinine, in urine samples collected 4 hr and 18 hr postexposure. Good correlations were found between EAA excretion and EGEEA uptake 4 hr after exposure ($r=0.82$, $P<0.001$) and 18 hr postexposure ($r=0.77$, $P<0.001$). Similar correlations were seen with EGEE [Groeseneken et al. 1986c]. Although the correlation is slightly lower for urine specimens collected 18 hr after exposure, collection at this time may be preferred for biological monitoring because of the long EAA elimination half-life. As with EGEE, EAA would be expected to accumulate with repeated daily exposures.

Table 5-4.—Relationship between exposure to EGEE, workload, uptake, and EAA in urine

EGEE exposure (ppm)	Workload (W)	EGEE uptake (mg)	EAA (mg/g creatinine)	
			End of exposure	18 hr postexposure
2.7	0	16.7 ± 4.2	1.72 ± 0.58	1.12 ± 0.34
5.4	0	35.1 ± 7.6	3.85 ± 1.73	2.61 ± 0.50
10.8	0	64.1 ± 14.5	5.23 ± 1.67	4.54 ± 1.36
5.4	0	33.3 ± 8.3	3.85 ± 1.73	2.61 ± 0.50
5.4	30	57.0 ± 11.8	7.42 ± 2.84	6.26 ± 1.92
5.4	60	94.4 ± 13.9	10.49 ± 4.18	8.64 ± 3.05

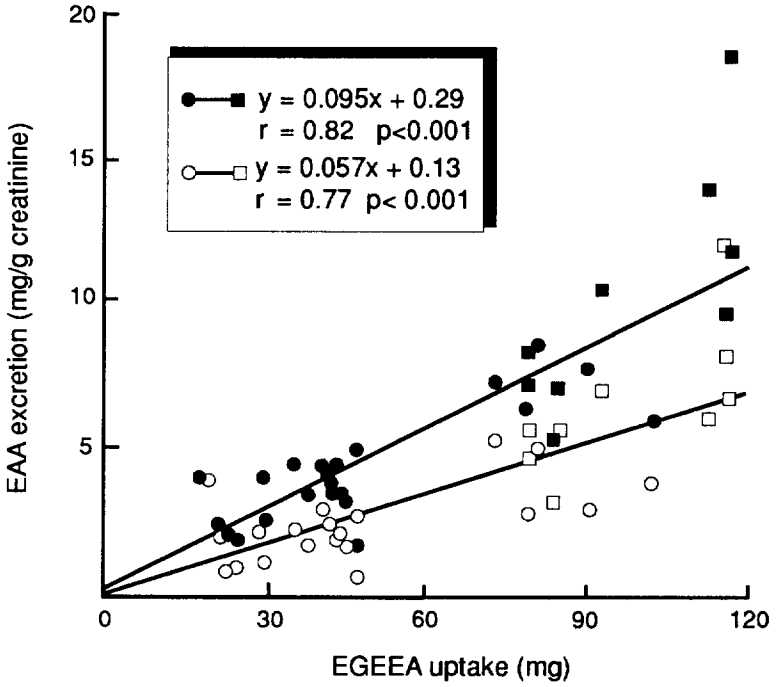

Figure 5–3. Relationship between EGEEA uptake and urinary excretion of EAA. Source: Groeseneken et al. [1987b].

Groeseneken et al. [1987b] also showed the relationship between exposure, workload, uptake, and urinary EAA (expressed as mg/g creatinine) for urine samples collected at the end of exposure and 18 hr after exposure (Table 5–5). The 5.2-ppm exposure group at 0 W represents the combined data from both groups, n=10.

The data in Table 5–5 show the influence of exercise on EGEEA uptake and EAA excretion in the urine. Note that subjects exposed to 5.2 ppm EGEEA at a 30-W workload produce about the same amount of EAA as subjects exposed to almost twice the concentration (9.3 ppm) at rest.

Table 5–5.—Relationship between exposure to EGEEA, workload, uptake, and EAA in urine

EGEEA exposure (ppm)	Workload (W)	EGEEA uptake (mg)	EAA (mg/g creatinine)	
			End of exposure	18 hr postexposure
2.6	0	23.3 ± 2.1	2.35 ± 0.50	1.81 ± 0.60
5.2	0	44.9 ± 1.3	3.20 ± 0.35	2.12 ± 0.20
9.3	0	85.1 ± 5.5	5.87 ± 0.57	4.15 ± 0.52
5.2	0	37.1 ± 2.4	3.20 ± 0.35	2.12 ± 0.20
5.2	30	84.4 ± 2.5	6.04 ± 1.45	5.32 ± 0.62
5.2	60	121.5 ± 5.4	9.82 ± 2.23	7.78 ± 1.21

In spite of the differences in respiratory uptake and elimination between EGEE [Groeseneken et al. 1986b] and EGEEA [Groeseneken et al. 1987a], the same relationships existed between EAA excretion and time-weighted uptake of EGEE or EGEEA (expressed as EGEE equivalents, abbreviated as $EGEE_{eq}$ below) [Groeseneken et al. 1987b]. These relationships for urine samples collected 4 hr after the cessation of exposure were expressed by the following equations:

$$\text{EAA (mg/g creatinine)} = -0.75 + 0.152 \text{ mg EGEE uptake} \quad \text{[Groeseneken et al. 1986c]} \tag{1}$$

$$\text{EAA (mg/g creatinine)} = 0.29 + 0.140 \text{ mg } EGEE_{eq} \quad \text{[Groeseneken et al. 1987b]} \tag{2}$$

$$\text{EAA (mg/g creatinine)} = 0.29 + 0.095 \text{ mg EGEEA} \quad \text{[Groeseneken et al. 1987b]} \tag{3}$$

Equation 3 was taken from Figure 5-3 and demonstrates the relationship between EAA excretion and EGEEA uptake, expressed as EGEEA. The similarity of the slopes and intercepts for equations 1 and 2, which are expressed in equivalent units, supports the authors' conclusions that EAA can be used as an index of exposure to both EGEE and EGEEA, and that the same relationship exists when EGEEA uptake is calculated as EGEE equivalents. The authors suggested that these relationships are probably valid only for single exposures to EGEE and EGEEA because of the long elimination half-lives for EAA and the likelihood of accumulation of EAA during repeated exposures.

MAA was found in the urine of male volunteers exposed at rest to 5 ppm EGME [Groeseneken et al. 1989a]. This study was described in Appendix B, Section B.4.1, and is discussed in Section 5.4.5.2.

5.4.5 Assessment of Biological Monitoring Results in Various Studies

5.4.5.1 EGEE and EGEEA

Urinary EAA excretion was examined in female silk-screen printing operators exposed to a mixture of EGEE and EGEEA [Veulemans et al. 1987a]. Veulemans et al. [1987a] stated that the half-life of elimination of EAA was longer (42 hr) than previously determined (21 to 24 hr) by Groeseneken et al. [1986c, 1987b]. In a subsequent publication, Groeseneken et al. [1988] reported that the half-life in this occupational exposure study was up to 48 hr, which is in agreement with the average 42-hr half-life recalculated by Groeseneken et al. [1988]. Veulemans et al. [1987a] concluded that the increasing EAA concentrations seen during the workweek were caused by accumulation of EAA. The higher preshift EAA concentrations seen in the majority of week-1 specimens may have been due to the slow release of EAA from a fat compartment caused by buildup from exposure in previous weeks. The lack of such a pattern in the second observation period, after 12 days with no exposure, supports this hypothesis.

Few details are included about the level of work activity by the females working in the silk screen operation [Veulemans et al. 1987a]. Based on the assumption that silk screening operations involve standing and moderate work with both hands, this activity can be classified as light to moderate work and is approximately equivalent to the expenditure of 4 kilocalories (kcal)/min [ACGIH 1988]. Groeseneken et al. [1986b, 1987a] reported that males exercising at 30 W had an average oxygen uptake of 0.6 liter/min, while those exercising at 60 W had an average of 0.82 liter/min, approximately equivalent to 3 and 4 kcal/min, respectively [McArdle et al. 1981]. Therefore, one can assume that the women working on the silk screening process were working at the equivalent of 60 W.

The experimental studies in males exposed to EGEE [Groeseneken et al. 1986c] or EGEEA [Groeseneken et al. 1987b] demonstrated end-of-exposure concentrations of EAA that were much lower than those seen in the occupational study with women [Veulemans et al. 1987a]. For example, the mean concentration of EAA was 10.5 mg/g creatinine in urine specimens from male subjects exposed once to 5.2 ppm (20 mg/m^3) for 4 hr at 60 W of exercise [Groeseneken et al. 1986c]. Silk screen operators exposed to 3.9 ppm (14.4 mg/m^3) for 5 workdays showed an average end-of-week urine EAA concentration of 105.7 mg/g creatinine. In order to reconcile the apparent discrepancies between the experimental data developed for males and the workplace data for females, the following assumptions were made:

- Women working in the silk screen process were exposed to EGEE and EGEEA levels, as EGEE equivalents, of 14.4 mg/m^3 (3.9 ppm), and exerted the equivalent of 60 W of energy.
- The only EAA data that were comparable with experimental exposure data were EAA concentrations in urine samples collected after the 12-day break. The 42 to 48 hr half-life of EAA elimination resulted in significant EAA accumulation during the week and possibly from week to week. Preshift urine samples on the first day following the 12-day break were the lowest observed during the entire study (1.2 to 2.6 mg/g creatinine). Data from these days thus were suitable for comparison to the experimental exposure data for males.
- The metabolism of EGEE and EGEEA was linear at occupationally relevant exposures. Groeseneken et al. [1988] demonstrated linear kinetics with EGEE at exposures expected in the workplace.
- The EAA elimination half-lives of females were similar to those of males. Groeseneken et al. [1988] stated that the EAA elimination half-life for males was 42 hr, and that the estimate of EAA half-life for females in the silk screening operation was about 48 hr.
- Skin absorption by the female employees was not significantly different from skin absorption by the male subjects exposed under experimental conditions.

Using these assumptions, one can extrapolate the expected EAA concentration in urine from experimental exposure data for males exposed to 5.4 ppm (20 mg/m^3) EGEE for 4 hr at

60 W of exercise, to exposure for 8 hr by using the principle of superposition [Gibaldi and Perrier 1982]. This principle assumes that the kinetics of EAA excretion do not change with EAA concentration. Using this extrapolation technique, the estimated EAA urinary concentration following an 8-hr exposure is equal to the urinary concentration 4 hr after the end of a 4-hr exposure, plus the urinary concentration at the end of the second 4-hr exposure. Actual data from Groeseneken et al. [1986c] are 14.38 and 10.49 mg EAA/g creatinine, respectively, for a total of 24.87 mg EAA/g creatinine.

A pharmacokinetic approach can be used to extrapolate the 4-hr exposure data to a full-shift exposure. If simple first-order EAA kinetics are assumed following a 4-hr EGEE exposure, the estimated EAA urinary half-life can be used to project urinary EAA concentrations at time points later than the peak urinary EAA concentration (which occurred 8 hr after the start of a 4-hr exposure period). Estimated EAA urine concentrations (see Table 5-6) were determined by using a 42-hr half-life [Groeseneken et al. 1988] to extrapolate the urinary EAA concentration following a 4-hr EGEE exposure, and then applying the principle of superposition [Gibaldi and Perrier 1982] to combine two extrapolated 4-hr exposures into one extrapolated 8-hr exposure. (An 8-hr workday beginning at 8:00 a.m. and ending at 4:00 p.m. was assumed.) Under these conditions, the projected maximal EAA urinary concentration would occur at approximately 8:00 p.m., reaching 27.84 mg/g creatinine. The estimated urinary EAA concentration 16 hr after an 8-hr work exposure is 22.84 mg/g creatinine.

Data from the occupational study by Veulemans et al. [1987a] were for the first Thursday. The average EAA concentration was 22 mg/g creatinine (range of 10 to 39.5) and the average

Table 5-6.—Estimated EAA urine concentrations from 8-hr EGEE exposures*

		EAA concentration (mg/g creatinine)		
Time	Elapsed hours	First 4-hr exposure	Second 4-hr exposure	Total EAA† from 8-hr exposure
8 a.m.	0	0		0.00
10 a.m.	2	5.25		5.25
Noon	4	10.49	0.00	10.49
2 p.m.	6	12.44	5.25	17.68
4 p.m.	8	14.38	10.49	24.87
6 p.m.	10	13.91	12.44	26.35
8 p.m.	12	13.46	14.38	27.84
10 p.m.	14	13.02	13.91	26.94
Midnight	16	12.60	13.46	26.06
2 a.m.	18	12.19	13.02	25.22
4 a.m.	20	11.80	12.60	24.40
6 a.m.	22	11.41	12.19	23.61
8 a.m.	24	11.04	11.80	22.84

*Source: Groeseneken et al. [1986c].
†10- to 24-hr EAA concentrations were estimated using 42 hr as the EAA half-life.

exposure concentration (expressed as EGEE) was 14.1 mg/m^3 (range of 11 to 18.9 mg/m^3). The estimated value of 22.84 mg EAA/g creatinine is consistent with the workplace measurements of Veulemans et al. [1987a]. Furthermore, this estimate suggests that the urinary EAA concentration would be expected to drop very little from the end of 1 8-hr workday to the start of the next (i.e., from 24.87 to 22.84 mg/g creatinine, under the test conditions), and that EAA would be expected to accumulate from day to day. This is also consistent with the observation of Veulemans et al. [1987a] that urinary EAA levels in occupationally exposed workers tended to rise throughout the workweek. Although there is some general similarity between EAA concentrations found in the urine of workers exposed to EGEE [Veulemans et al. 1987a] and EAA concentrations extrapolated from single 4-hr experimental exposures, one should not infer that these results are in agreement. Extrapolations of experimental data are based on assumptions that have not been experimentally verified. Data for EAA concentrations in preshift urine samples collected on the following day (Friday morning) were approximately 42 mg/g creatinine (range of 13 to 66), compared with the extrapolated concentration of approximately 23 mg/g creatine from the same experimental studies.

Veulemans [1989] presents the following explanation for the lack of agreement between the field study data and experimental data. The high urinary concentrations in the field study compared with the experiments can largely be explained by the combination of repeated exposures and the long biological half-life of excretion. A rough approximation by a single compartment model with a half-life of 42 hr already gives an agreement within 70% of the observed results. To explain all the observed facts (e.g., delayed excretion maxima, circadian variations) a more complex model is needed. The design and testing of such a model, however, requires data on the plasma concentrations of the metabolite and its parent compound. At the time of the experiments the available analytical methods were not sensitive enough to measure the plasma concentrations at low exposure concentrations.

The following exposure assessments at two worksites were conducted by NIOSH during two health hazard evaluations.

1. A study of worker exposure to EGEE was conducted at a plant where precision cast metal parts were produced using the "lost-wax" process [Ratcliffe et al. 1986; Clapp et al. 1987].

2. A study was conducted of the potential exposure to EGEE and EGME for workers associated with various types of painting operations in a shipyard. This study included a health hazard evaluation [McManus et al. 1989] and a separate research study [Sparer et al. 1988; Welch et al. 1988]. Preliminary biological monitoring results were published separately [Lowry 1987].

NIOSH conducted a health hazard evaluation (described in Section 4.1) to determine possible adverse reproductive effects in male workers potentially exposed to EGEE in the preparation of ceramic shells used to cast metal parts ("lost-wax" process) [Ratcliffe et al. 1986]. The binder slurry included 50% EGEE and 50% ethanol. About 80 workers were employed in the investing departments at each of the two sites where these ceramic shells were prepared. The potentially exposed male workers included those engaged in the preparation

of binder slurry, hand dippers and grabbers who dipped molds into the slurry, shell processors who prepared and handled ceramic shells, supervisors, and process engineers. Although gloves were worn by some workers, no other chemical protective clothing or respirators were used. Air samples, most of which were breathing zone, were collected. Because the potential for skin exposure existed, spot urine samples were taken at intervals and analyzed for EAA [Smallwood et al. 1984]. Surveys were conducted in April 1984 and June 1984 [Clapp et al. 1987].

In the April survey, general area air samples revealed higher concentrations of EGEE (10 to 17 ppm) in the investment rooms, which contained open tanks of slurry, compared with the mixing and storage rooms (5 to 7 ppm). Full-shift personal breathing zone exposures of EGEE ranged from 3 to 14.5 ppm for workers in the investing areas. Ratcliffe et al. [1986] reported that recoveries of EGEE in three quality control samples were as low as 69% indicating that the measured airborne concentrations could have been underestimated.

Urine samples were collected as voided during a 24-hr period from three EGEE-exposed workers and two controls (unexposed workers). Table 5-7 presents personal breathing zone EGEE data and urinary EAA concentrations. Environmental data represent the mean value for all workers in the specific job classification; urinary EAA data present the average and range found in each subject [Ratcliffe et al. 1986; Clapp et al. 1987]. No EAA was detected in the urine of the two control subjects.

In the June survey, area samples averaged 2.4 to 14.9 ppm. Personal breathing zone samples averaged 8.1 ppm for grabber operators, 4.5 ppm for shell processors, and 5.0 ppm for investment room supervisors. In this case, spot urine samples were collected at random over a 7-day period. Table 5-8 summarizes the findings. EGEE values represent the geometric mean values for a job classification, while the urinary EAA results represent the average of all urine specimens collected during the 7-day period for one worker [Ratcliffe et al. 1986; Clapp et al. 1987].

This study [Ratcliffe et al. 1986; Clapp et al. 1987] is not well-designed for biological monitoring because it provides no appropriate match of environmental samples with urine samples and no information on the time of urine collection in relationship to exposure. In addition, it includes no documentation concerning the extent of skin exposure or the assessment of work practices. The potentially low recovery of EGEE from personal samples,

Table 5-7.—Comparison of EGEE exposure concentrations and urinary EAA

Job classification	EGEE (ppm, geometric mean)	EAA (mg/g creatinine)	
		Mean	Range over 24 hr
Hand dipper A	14.5	40.8	26-66
Hand dipper B	14.5	30.2	21-40
Investment supervisor	6.0	28.0	18-35

Table 5-8.—Comparison of worker exposure to EGEE and urinary EAA

Job classification and worker ID	EGEE (ppm, geometric mean)	EAA (mg/g creatinine)	
		Mean	Range over 7 days
Grabber operator 1	8.1	88	59-108
Grabber operator 2	8.1	95	52-163
Grabber operator	8.1	58	52-121
Shell processor 1	4.5	79	
Shell processor 2	4.5	83	78-87
Shall processor 3	4.5	60	
Investment supervisor	5.0	25	16-40

identified through a quality control problem with "spiked" EGEE samples, placed the environmental data in question. Nevertheless, this study does indicate that EAA in urine reflects exposure to EGEE in the workplace at full-shift exposure concentrations in the range of 4 to 14.5 ppm.

Studies were recently conducted to determine the effects of combined EGME and EGEE exposure on the reproductive potential of 600 men who worked in a large shipbuilding facility [Sparer et al. 1988; Welch et al. 1988]. NIOSH also conducted a health hazard evaluation of 36 male painters at the same site using environmental and biological monitoring to assess their potential exposure to EGEE and EGME [McManus et al. 1989; Lowry 1987].

Work conditions and practices described in the health hazard evaluation varied considerably among painters. Some painters worked in confined spaces below deck, while others worked in the open. The study was conducted in the winter, and the temperatures varied depending on the painters' work areas. Information on work practices, such as the number of hours spent painting, the type of paint used, the work area locations, the use of respirators, and the potential for skin contact, was gathered from questionnaires. Personal environmental breathing zone samples were collected for each worker for 3 days and expressed as 8-hr TWAs. Table 5-9 provides a summary of the environmental exposure data. Urine samples were collected for 1 week at the beginning and end of each workday [McManus et al. 1989; Lowry 1987]. EAA concentrations were determined using the method devised by Smallwood et al. [1988]. Approximately six urine specimens were collected from each worker. Table 5-10 presents the highest concentration of EAA recovered. MAA was detected in only one specimen.

Table 5-9.—Summary of environmental data

Type of data	EGEE (ppm)	EGME (ppm)
Mean	2.6 ± 4.2	0.8 ± 1.0
Median	1.2	0.44
Range	0-21.5	0-5.6

Table 5-10.—Summary of urinary EAA data

Worker group	Number of workers	Maximum EAA (mg/g creatinine)
Controls, shipyard workers	20	Not detected
Painters not using EGEE	5	6.6 ± 3.91
Painters using EGEE	27	25.0 ± 20.7

A wide range of EAA concentrations was noted in workers using EGEE-containing paints; this was probably caused by variation in work assignments, work areas, work practices, and in the use of personal protective equipment. The author concluded that there appeared to be a relationship between urinary EAA excretion and the use of paints containing EGEE [Lowry 1987].

The health hazard evaluation demonstrated that the potential existed for exposure of painters to EGEE and EGME. Because of the complexity of the work environment and the variable use of personal protective equipment, no dose-response relationship could be developed. However, at the exposure concentrations measured, painters who used paints with EGEE did excrete more EAA in the urine than painters who did not use EGEE-containing paints.

Sparer et al. [1988] and Welch et al. [1988] examined some of the same workers from the health hazard evaluation. (These studies are discussed in detail in Section 4.1.) The authors concluded that exposure to EGEE and EGME lowered sperm counts in the painters. In addition, they concluded that when smoking was controlled the painters had an increased odds ratio for a lower sperm count per ejaculate [Welch et al. 1988].

However, it would be inappropriate to conclude that the EGEE and EGME exposure concentrations presented in the health hazard evaluation [McManus et al. 1989] were representative of the chronic exposure of shipyard workers who participated in the semen study [Welch et al. 1988]. In addition, it cannot be concluded that marginally (but not statistically significant) lowered sperm counts were caused by exposure concentrations measured in the health hazard evaluation [McManus et al. 1989].

5.4.5.2 EGME

No studies have evaluated the relationship between EGME exposure in the workplace and urinary MAA concentration. Results of the study by Groeseneken et al. [1989a] have provided the following information regarding MAA excretion in urine.

- The relatively long urinary elimination half-life of MAA (77 hr) suggests that MAA would be expected to accumulate during the workweek. If biological monitoring were done, urine specimens collected at the end of the week, or possibly prior to the first shift of the week, would be appropriate.

- Sixty percent of the urine specimens from this study contained MAA at concentrations below 2 mg/liter. If 4-hr exposures are extrapolated to 8-hr exposures, based on linear kinetics, then subjects exposed to 5.1 ppm at rest would be expected to have 60% of their urine samples with MAA concentrations below 4 mg/liter. If exposures were 1/10 of those from this study (i.e., 0.5 ppm) then 60% of the urine specimens would be expected to have less than 0.4 mg/liter of MAA [Groeseneken et al. 1989a]. The limit of quantitation for MAA was reported to be 0.1 mg/liter [Groeseneken et al. 1989b]. Higher concentrations of MAA would be expected with exercise.

Although dermal absorption was not studied, dermal uptake of EGME is a potential route of exposure. Dugard et al. [1984] demonstrated in vitro absorption of EGME through human abdominal skin. Nakaaki et al. [1980] also demonstrated dermal penetration of EGME through the forearm of human volunteers. Johanson [1988] suggested that dermal uptake of EGME is possibly the major route of exposure.

Thus, in spite of the lack of quantitative relationships between EGME exposure and MAA excretion in urine, measurement of MAA in urine is warranted. The potential for extensive skin absorption, and the potential buildup of the active urinary metabolite MAA during the workweek, are reasons to measure MAA in urine as an exposure index. In addition, measurement of MAA in urine may be useful as an indicator of the potential for adverse reproductive effects.

5.4.6 Methods for Analyzing Urinary EAA and MAA

A variety of methods have been developed for the analysis of EAA and MAA in human urine. Gas chromatographic procedures are based on either fluoranhydride derivatization following the extraction of the acid tetrabutylammonium ion-pair [Smallwood et al. 1984, 1988] or diazomethane derivatization following lyophilization of the urine [Groeseneken et al. 1986a]. Groeseneken et al. [1989b] developed a method that combined the best attributes of the two basic existing models. Detailed descriptions of the above methods are presented in Appendix H.

5.4.7 Summary

EGEE, EGME, and their acetates are metabolized to their respective alkoxyacetic acid metabolites, EAA and MAA, which are excreted in the urine. EAA and MAA have produced reproductive and hematotoxic effects noted for glycol ethers. These glycol ethers can also be absorbed through the skin. In fact, the major route of exposure to EGME and EGEE may be through the skin [Johanson 1988]. Thus, monitoring of these acids may serve not only as a measure of exposure or uptake, but also as a measure of potential adverse health effects.

The alkoxyacetic acid metabolites may be analyzed by a variety of sensitive and specific methods. The recently developed method of Groeseneken et al. [1989b] has sufficient sensitivity to monitor excretion of these metabolites at the recommended RELs.

Results from human laboratory inhalation exposure studies indicated that EAA in urine could be used to monitor uptake of EGEE and EGEEA [Groeseneken et al. 1986c, 1987b]. The total amount of urinary EAA was related to EGEE and EGEEA uptake, and was influenced by pulmonary ventilation and the concentration of EGEE and EGEEA in inspired air. EAA excretion in urine peaked about 4 hr after cessation of exposure and was eliminated in the urine with a half-life of 42 hr [Groeseneken et al. 1988].

Investigations of occupational exposure also revealed a correlation between urinary EAA excretion and repeated daily inhalation exposure of workers to a mixture of EGEE and EGEEA [Veulemans et al. 1987a]. Data showed the accumulation of EAA following repeated daily exposures to EGEE and EGEEA. The estimated elimination half-life of EAA was 48 hr.

Two other worksite investigations of occupational exposure to EGEE demonstrated the utility of EAA in urine to assess uptake of EGEE regardless of the route of exposure [Ratcliffe et al. 1986; Clapp et al. 1987; Lowry 1987; McManus et al. 1989; Sparer et al. 1988; Welch et al. 1988].

Experimental studies were conducted in which humans were exposed to EGME. Results of these studies indicated that measurement of urinary MAA could be used to assess uptake of EGME. The concentration of MAA peaked several hr after exposure ended, and MAA was eliminated with a half-life of 77 hr. Examination of the elimination kinetics showed that MAA would accumulate following repeated daily exposures, and could also accumulate over extended exposure periods.

Insufficient information is available at present to construct a dose-response plot that would provide statistically sound guidelines for the concentration of alkoxyacetic acid metabolites in urine that would correspond to an airborne exposure to glycol ethers. Table 5-11 presents a summary of the laboratory and occupational dose-response data.

Table 5-11.—Summary of EGEE, EGEEA, and EGME exposure studies

Glycol ether	Type of exposure	No. of subjects and sex	Concentration (ppm)	Workload (W)	Time (hr)	Total glycol ether uptake (mg)	Total metabolite excretion (mg/g creatinine)	Reference
EGEE	Face mask inhalation	10 males	2.7	0	4	16.7± 4.2	1.12±0.34*	Groeseneken et al. 1986c
			5.4	0	4	35.1± 7.6	2.61±0.50	
			10.8	0	4	64.1±14.5	4.54±1.36	
			5.4	0	4	33.3± 8.3	2.61±0.50	
			5.4	30	4	57.0±11.8	6.26±1.92	
			5.4	60	4	94.4±13.9	8.64±3.05	
EGEEA	Face mask inhalation	10 males	2.6	0	4	23.3± 2.1	1.81±0.60†	Groeseneken et al. 1987b
			5.2	0	4	44.9± 1.3	2.12±0.20	
			9.3	0	4	85.1± 5.5	4.15±0.52	
			5.2	0	4	37.1± 2.4	2.12±0.20	
			5.2	30	4	84.4± 2.5	5.32±0.62	
			5.2	60	4	121.5± 5.4	7.78±1.21	
EGEE/ EGEEA	Occupational	5 females	3.9	60	8‡	—	42	Veulemans et al. 1987a
			3.9	60	1 week§	—	106	
EGME**	Face mask inhalation	7 males	5.1	0	4	19.4± 2.1	—	Groeseneken et al. 1989a

*Urine EAA data are from 18 hr postexposure (before next shift).

†Urine EAA data are from 18 hr postexposure (before next shift).

‡Data represent 8-hr exposure to EGEE and EGEEA by female silk screen workers on the first day following 12 days without exposure. Workloads were estimated. Urine EAA data were estimated from samples collected before the shift on the second day of exposure following 12 days without exposure.

§Data represent 1-week exposure to EGEE and EGEEA after regular weekly exposure in previous weeks. Urine EAA data were stated by the author as the average end-of-the-week concentrations.

**Urine MAA (2.4 μg/min) was estimated from the plot in the cited reference and represents a urine sample collected 18 hr after the end of exposure.

6 OTHER STANDARDS AND RECOMMENDATIONS

In 1971, OSHA adopted the current Federal standards for worker exposure to EGME, EGMEA, EGEE, and EGEEA, which are based on the American Conference of Governmental Industrial Hygienists (ACGIH) 1968 Threshold Limit Values (TLVs®). These TLVs® were based on the hematotoxic and neurotoxic effects and exposure concentrations reported in the early case reports of human health effects [Donley 1936; Parsons and Parsons 1938; Greenburg et al. 1938]. The OSHA PELs include a "skin" notation, indicating the potential for skin absorption of toxic amounts of these glycol ethers.

The OSHA PELs for occupational exposure to the glycol ethers are as follows: 25 ppm (80 mg/m^3) for EGME, 25 ppm for EGMEA (120 mg/m^3), 200 ppm (740 mg/m^3) for EGEE, 100 ppm (540 mg/m^3) for EGEEA, as TWAs for an 8-hr workshift [29 CFR 1910.1000]. OSHA is considering a revision of these PELs.

NIOSH has previously recommended that EGME and EGEE be regarded in the workplace as having the potential to cause adverse reproductive effects in male and female workers and embryotoxic effects, including teratogenesis, in the offspring of the exposed pregnant female, and that occupational exposure to them should be reduced to the lowest extent possible [NIOSH 1983a]. These recommendations were based on the results of animal studies that demonstrated dose-related embryotoxicity and other reproductive effects in several species of animals exposed by different routes of administration [Stenger et al. 1971; Nagano et al. 1979; Nagano et al. 1981; Andrew et al. 1981; Miller et al. 1981, 1983a; Nelson et al. 1981, 1984b; Hardin et al. 1982; McGregor et al. 1983; Rao et al. 1983; Hanley et al. 1984a].

In 1946, ACGIH established maximum allowable concentrations (m.a.c.s) of 100 ppm for EGME, EGMEA, and EGEEA, and 200 ppm for EGEE [ACGIH 1984]. In 1947, the m.a.c.s for EGME and EGMEA were lowered to 25 ppm because of the Greenburg et al. [1938] study in which neurologic and hematologic changes were observed in men exposed to EGME at concentrations estimated to be as low as 25 ppm. The m.a.c. for EGMEA was lowered because the toxic effects caused by it were likely to be similar to those caused by EGME as a result of EGMEA's metabolism to EGME and then to the active metabolite [ACGIH 1962, 1984]. Although the values remained unchanged, the term "threshold limit value" was substituted for m.a.c. in 1948.

In 1968, the notation "skin" (indicating the potential for skin absorption of toxic amounts of a compound) was added to the TLVs® for EGME, EGEE, EGMEA, and EGEEA. In 1971, ACGIH lowered the TLV® for EGEE from 200 to 100 ppm to prevent irritation of the nose and eyes [ACGIH 1980]. In 1981, the ACGIH adopted TLVs® of 50 ppm for

EGEE and EGEEA, each with a short-term exposure limit (STEL) of 100 ppm; in 1987-88, the STELs were deleted [ACGIH 1991]. The TLVs® were lowered because of adverse hematologic effects observed in laboratory animals [Carpenter et al. 1956]. Changes in rat erythrocyte fragility were produced by 125 ppm EGEE but not by 62 ppm. ACGIH deemed it prudent to maintain chemical exposures below levels found to cause blood changes in experimental animals. Because the TLV® of 100 ppm for EGEEA was based on analogy with EGEE, it was logical to establish a similar TLV® of 50 ppm for its acetate [ACGIH 1980].

Reports of adverse testicular effects in experimental animals treated with EGME, EGEE, and their acetates [Nagano et al. 1979] led ACGIH to lower the TLVs® for these compounds. The 5-ppm TLV® for EGME, EGMEA, EGEE, and EGEEA as an 8-hr TWA was adopted in 1984, and the "skin" notation was retained.

Table 6-1 presents a compilation of occupational exposure limits of various countries for these glycol ethers.

Table 6-1.—Occupational exposure limits for EGME, EGEE, and their acetates in various countries[*,†]

Country	Type of standard	EGME		EGMEA		EGEE		EGEEA	
		ppm	mg/m^3	ppm	mg/m^3	ppm	mg/m^3	ppm	mg/m^3
USA									
	OSHA PEL TWA [skin]	25[‡]	80	25[‡]	120	200[‡]	740	100[‡]	540
	ACGIH TLV®-TWA [skin]	5	16	5	24	5	19	5	27
Belgium		25	80	—	—	50	185	25	135
GRF (Germany)	mak [skin]	5	15	5	25	20	75	20	110
Denmark		25	80	25	120	100	370	50	270
						50[‡]	185[‡]	50	270
Finland		25	80	25	120	100	370	25	135
		5	16	5	24	5	19	5	27
Holland	mac	5[‡]	15[‡]	—	—	5[‡]	19[‡]	—	—
Italy		—	—	—	—	—	—	—	—
Japan		25	80	25	120	100	370	—	—
Norway	[skin]	25	80	—	—	50	185	—	—
Sweden[§]	LLV [skin]	5	16	5	25	5	19	5	30
	STV [skin]	10	30	10	50	10	40	10	50
Switzerland	mak [skin]	5[‡]	15[‡]	—	—	20[‡]	75[‡]	100	540
United kingdom	TWA [skin]	25(5[**])	80(15[**])	25(5[**])	120(25[**])	100(10[**])	370(37[**])	10[‡]	55[‡]
	STEL [skin]	35(15[**])	120(45[**])	35(15[**])	170(75[**])	150(30[**])	560(115[**])	30[‡]	175[‡]

[*]Data from ECETOC [1985].
[†]Abbreviations: PEL = Permissible exposure limit; STEL = Short term exposure limit; LLV = Level limit value; STV = Short term value; TWA = Time weighted average; mak, mac = Maximum allowable concentration.
[‡]Value is subject to be changed.
[§]NBOSH [1989].
[**]Intended change.