5 HAZARD IDENTIFICATION

Each employer who manufactures, transports, packages, stores, or uses EGBE and EGBEA 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

Environmental sampling for EGBE and EGBEA can be conducted by using NIOSH Method No. 1403 [NIOSH 1984] and collecting a total air volume of 10 liters with a charcoal tube at a flow rate of 0.01 to 0.05 liter/min. Sampling can also be conducted by using OSHA Method No. 83 and collecting a total air volume of 48 liters with a coconut charcoal shell tube at a flow rate of 0.1 liter/min [OSHA 1990].

5.2 ANALYTICAL METHODS

Laboratory analysis for EGBE can be performed by NIOSH Method No. 1403, which is described in detail in Appendix A; the quantitation limit of the analytical procedure is 2 ppm in 10 liters of air. NIOSH Method No. 1403 may be adapted for EGBEA [Kennedy and Belinky 1990]. The following steps should be taken to adapt Method No. 1403 for EGBEA: (1) analytical conditions should be developed for capillary column gas chromatographic analysis, and (2) the limits of detection and quantitation should be evaluated at concentrations below the proposed NIOSH REL. The recovery of EGBEA from charcoal should be studied to determine whether the analyte is adequately recovered (>75%). The capacity of the charcoal tube sampler should be checked to ensure that an adequate amount of analyte can be collected to allow quantitation at or below the proposed REL. Finally, the stability of the analyte on the charcoal tube sampler should be verified [Kennedy and Belinky 1990].

Laboratory analysis for EGBE and EGBEA can also be performed by using OSHA Method No. 83, which is described in detail in Appendix A. The quantitation limits of the analytical procedure are 0.031 ppm for EGBE and 0.024 ppm for EGBEA [OSHA 1990]. Although the method states that the presence of a glycol ether should be confirmed by gas chromatography/mass spectrometry (GC/MS), NIOSH recommends that all samples be analyzed by GC/MS because of the number of potential interferences present in the sample [Kennedy et al. 1990]. To better define the potential interferences, NIOSH also recommends that bulk samples of the solutions containing EGBE/EGBEA be returned to the laboratory for analysis. To prevent potential contamination, these samples should be shipped separately. A material safety data sheet should also accompany each bulk sample returned to the laboratory.

5.3 MEDICAL MONITORING

EGBE and EGBEA have been shown to have adverse effects on the central nervous, hematopoietic, and renal systems in humans and animals; furthermore, exposure to these glycol ethers may impair liver function. Preplacement and periodic medical examinations should therefore be instituted for workers who may be exposed to EGBE and EGBEA. 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 preexisting 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 EGBE and EGBEA on the blood and hematopoietic system, workers with blood diseases may be at increased risk from exposure to EGBE or EGBEA.

  —Skin. Because EGBE and EGBEA are readily absorbed through the skin, workers with chronic skin disease characterized by eczema or fissures may be at increased risk of absorption of these substances.

  —Liver. Although glycol ethers are not known as liver toxins in humans, the detoxification properties of this organ should place workers with impaired liver function under special consideration.

  —Kidneys. A urinalysis should be done to ascertain whether impaired renal function exists. Because of the importance of the kidneys in eliminating toxic substances, special consideration should be given to workers with impaired renal function who may be exposed to EGBE or EGBEA.

  —Central nervous system. The need for examinations of the central nervous system should be stressed.

- Periodic medical examinations. The aforementioned medical examinations should be performed annually for all workers occupationally exposed to EGBE and EGBEA at or above the action levels, especially those 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 EGBE and EGBEA. Biological monitoring takes into account the influence of workload and percutaneous absorption.

5.4.1 Justification for Biological Monitoring

Johanson et al. [1986] and Van Vlem [1987] described the uptake of EGBE by humans in experimental inhalation studies. The study that included different workloads in the experimental design [Van Vlem 1987] demonstrated a linear relationship between workload and uptake of EGBE. A linear relationship was also found for exposure concentration and uptake.

In vitro dermal absorption of EGBE has been shown in human abdominal skin [Dugard et al. 1984]. The rate of absorption for EGBE was 0.198 mg/cm^2 ± 0.7. Bartnik et al. [1987] demonstrated in vitro dermal absorption of EGBE through forearm skin. In vivo studies in humans have also demonstrated uptake of EGBE through the skin. Johanson et al. [1988] compared the inhalation and dermal uptake rates of EGBE. Humans exposed by inhalation to 4 ppm (20 mg/m^3) EGBE for 2 hr at 50 W of exercise had uptake similar to subjects with four fingers immersed in pure EGBE for 2 hr (see Section 4.2).

Metabolism studies in animals (described in Section 4.2) demonstrated that EGBE is metabolized to its corresponding alkoxyacetic acid, BAA, which is excreted in the urine. This urinary metabolite has been shown to produce hematologic toxicity in rats [Bartnik et al. 1987; Ghanayem 1989]. Thus measurement of this metabolite 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 EGBE and EGBEA 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 a principal route of exposure, and workload can dramatically affect the actual inhalation uptake of EGBE and EGBEA. Therefore, biological monitoring should be considered an additional technique to assess the total exposure of the worker.

5.4.2 Selection of Monitoring Medium

Johanson et al. [1986, 1988] studied blood and expired air concentrations in subjects exposed to EGBE under controlled experimental conditions. Johanson [1988] concluded that the small concentrations of EGBE found in blood and expired air, and the rapid elimination of EGBE precluded the use of blood and expired air for biological monitoring.

According to Johanson [1988], the concentration of the alkoxyacetic acid BAA in the urine is the best indicator of exposure by all routes. The advantages of using the urinary alkoxyacetic acid for biological monitoring of EGBE and its acetate are as follows:

- The acid metabolite BAA is not normally present in human urine.
- The expected concentration for this metabolite at the proposed REL can be measured by the recommended analytical method (see Appendix C).

- BAA exerts hematologic toxicity and may reflect the concentration of the "active agent" at the target sites.
- The elimination half-life of EGBE (4 to 7 hr) reflects the integrated exposure over a workday [Johanson et al. 1986, 1988; Van Vlem 1987].
- 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 metabolite of EGBE and EGBEA. Biological monitoring primarily assesses uptake and not exposure concentration. In addition to the lack of well designed field evaluations of workers exposed to EGBE and EGBEA, the following factors limit the use of biological monitoring to assess exposure [Johanson 1988]:

- Variability in uptake through inhalation caused by workload-dependent uptake
- Intraindividual variations in excretion rates of metabolites, possibly caused by fluid intake or the effects of alcohol consumption
- Interindividual variations in excretion rates of 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 the acid metabolite in the urine is appropriate even if the uptake or metabolism is influenced by other factors. The concentration of BAA 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 EGBE Uptake with BAA Excretion

BAA was found in the urine of male subjects exposed to EGBE during light physical exercise [Johanson et al. 1988]. The authors concluded that BAA in urine is suitable for biological monitoring of humans exposed to EGBE. However, because of the large variability of BAA concentrations in individuals, the collection of several urine specimens was suggested.

5.4.5 Assessment of Biological Monitoring Results in Various Studies

Johanson [1986] conducted physiologically-based pharmacokinetic modeling of EGBE inhalation exposure. The model, based on 20 ppm exposures with exercise at 50 W for 2 hr, agreed well with experimental studies conducted in humans [Johanson et al. 1986]. The model predicted the potential for large increases in EGBE uptake with increased workload. In the presence of 1% blood alcohol (ethanol), the model predicts increased blood concentrations of EGBE and presumably decreased BAA concentrations in the urine. This finding

agrees with previous animal research and may occur because of competitive inhibition of EGBE metabolism by alcohol dehydrogenase, an enzyme involved in the metabolism of ethanol and ethylene glycol ethers. The model also predicted the even distribution of EGBE to body compartments based on water content and linear exposure kinetics at occupationally relevant exposures.

Johanson et al. [1988] studied the dermal absorption of EGBE in five healthy males who had also participated in inhalation studies [Johanson et al. 1986]. The subjects kept four fingers immersed for 2 hr in a container of undiluted EGBE, which was placed in a ventilated area to eliminate exposure via inhalation. Finger volume, skinfold thickness, and finger diameter were determined for each subject. A series of 12 experiments was conducted. At the conclusion of the exposure period, both hands were washed with soap and water. Arterialized capillary blood samples were collected from the unexposed hand before, during, and up to 4 hr after the EGBE exposure, and analyzed for EGBE by gas chromatography using an electron-capture detector. Urine samples were collected as described in Section 4.2 for 24 hr and analyzed for BAA by a high-sensitivity, gas chromatography method developed for this study.

The authors concluded that detection of EGBE in the blood of all subjects indicated systemic in vivo dermal absorption. The total percutaneous uptake averaged 384 μmol/subject with a range of 127 to 1,891 μmol/subject. The subject that showed 1,891 μmol uptake was included even though two separate repeat doses did not confirm the high uptake. The next highest uptake was 743 μmol/subject. The uptake rate averaged 20 μmol/min with a range of 7.1 to 95.8, including the unconfirmed highest uptake. The next highest uptake rate was 38.5 μmol/min. The urinary excretion rate of BAA increased during the first hour after exposure ended and reached a peak 3 hr after exposure. The excretion rate then declined with an average BAA half-life of 3.1 hr. The accumulated excretion of BAA averaged 94.3 μmol and ranged from 8.7 to 313 μmol, corresponding to an average percutaneous uptake of 17% with a range of 2.5% to 39%. The relationship between EGBE uptake and total 24-hr BAA excretion was linear (excretion = 0.17 × uptake, $r = 0.78$).

The authors noted that the wide variations in uptake rates of EGBE might have been caused by individual differences in the stratum corneum, but they acknowledged that other factors may have also been important. They stated that the uptake rate of EGBE was comparable to that obtained in vitro using human skin [Dugard et al. 1984; Bartnik et al. 1987]. The authors concluded that their study clearly showed that EGBE is absorbed through human skin in vivo and enters the systemic circulation. A comparison of the dermal uptake rate (1 to 16 μmol/min for four fingers exposed to liquid EGBE for 2 hr) with the inhalation uptake rate (8 to 14 mol/min in subjects exposed to 20 ppm for 2 hr at 50 W of exercise) suggested that uptake of EGBE by these two exposure routes was approximately equivalent. The authors further concluded that both skin and respiratory uptake should be considered when workers are exposed to EGBE. They cautioned that their comparison of uptake rates for dermal and inhalation exposures be used with care because of different uptake rates with different skin areas, interindividual variation in dermal penetration of EGBE, use of other solvents in the workplace, and the small number of subjects used in this study [Johanson et al. 1988].

Studies done by Johanson and Fernstrom [1988] on the dermal penetration of aqueous solutions of EGBE in guinea pigs may have some significance to human dermal uptake. Aqueous solutions of EGBE between 20% and 80% were more readily absorbed through the skin of guinea pigs than pure EGBE or solutions of less than 20% EGBE. The high water-solubility of EGBE may therefore make it possible for EGBE vapor to be absorbed through wet human skin at a faster rate than pure liquid EGBE.

Van Vlem [1987] conducted two studies evaluating human exposure to EGBE using the methods of Groeseneken et al. [1986b]. The first was an experimental laboratory exposure of three male subjects to two levels of EGBE at rest and with exercise. Retention, uptake, and elimination of EGBE and BAA were studied. The second study was an evaluation of occupational exposure of five females performing silk-screening operations [Veulemans et al. 1987a].

In the first study, three male subjects were exposed by face mask to 120 mg/m^3 (25.2 ppm) EGBE at rest, 60 mg/m^3 (12.6 ppm) EGBE at rest, and 60 mg/m^3 (12.6 ppm) EGBE at 30 W of exercise, 50 min/hr for 4 hr. The experimental design was similar to that of Groeseneken et al. [1986b]. It is important to note that these exposures were by face mask, in contrast to inhalation chamber exposures conducted by Johanson et al. [1986]. Retention averaged 67.0%, 68.9%, and 77.6% for the three exposure conditions (difference not significant). Respiratory elimination of EGBE averaged 0.66% to 0.69% at rest and 0.24% at 30 W. The average percentage of BAA recovered was 27%, 27%, and 13.6% of the absorbed EGBE for the three exposure conditions; wide individual variation was observed. Table 5-1 summarizes the uptake, respiratory elimination, BAA half-life, and total BAA excreted in 62 hr.

These results generally agree with those from other Groeseneken studies that examined different ethylene glycol ethers and different exposure concentrations and workloads [Groeseneken et al. 1986b, 1987b]. However, the group of three subjects exposed to 12.6 ppm at 30 W showed lower respiratory elimination of EGBE and total elimination of BAA; thus the increased uptake under this exposure condition was not reflected in similarly increased respiratory or urinary elimination. Studies conducted with only three subjects per group may produce unreliable data because of the interindividual variability in glycol ether uptake and elimination seen in similar studies.

Table 5-1.–Summary of EGBE uptake* and elimination†

Exposure concentration (ppm)	Work-load (W)	Uptake (mg)	Respiratory elimination (mg)	Half-life BAA (hr)	Total BAA elimination in 62 hr (mg)
25.2	0	122.3 ± 23.6	0.79 ± 0.27	6.3 ± 1.8	35.7 ± 1.9
12.6	0	61.8 ± 4.8	0.40 ± 0.08	7.1 ± 1.9	18.4 ± 2.5
12.6	30	131.6 ± 8.5	0.32 ± 0.06	9.7 ± 3.1	19.6 ± 9.9

*Determined through a 4-hr exposure by face mask.
†Determined throughout a 4-hr exposure period and 62 hr following exposure.

The relationship of BAA excretion and EGBE exposure was evaluated by Van Vlem [1987] in the group of five women studied by Veulemans et al. [1987a] at a silk screening operation. Half-shift personal monitoring was conducted for 5 days. Following a 12-day halt in production, monitoring continued for an additional 7 days. Mean weekly exposures to EGBE averaged 0.65 ppm (3.1 mg/m^3).

BAA was measured preshift and postshift for each of the work days as described by Veulemans et al. [1987a]. The urine showed higher postshift concentrations of BAA in all cases compared with preshift concentrations. Preshift concentrations ranged from less than 1 to 5.5 mg/liter, whereas postshift values ranged from approximately 8 to 11 mg/liter. No accumulation of BAA was seen during the workweek. On the third Monday morning of monitoring, following two days off, no BAA was detected, indicating complete clearance of BAA over the weekend. The calculated half-life of EGBE was 8.3 hr, a value consistent with experimental findings. The field study did not show a dose-response relationship, probably because of the narrow range of low exposures.

The author dismissed the value of BAA as an exposure monitor because of the unexplained variability of urinary BAA concentrations, particularly with exercise. The use of three subjects per group does not impart much statistical power to studies of this type, which have been shown to have large individual variability in response. In addition, the author dismissed the value of measuring BAA in urine to monitor occupational exposure. In this study, exposures were very low and uniform, so calculation of a dose-response curve would be difficult. The author proposed that BAA may be a good monitor for toxic effects because it exerts adverse hemolytic effects.

Table 5-2 compares several of the EGBE studies discussed. The ranges or standard deviations in the data are not shown in the table. All research groups cited reported large individual variability regardless of the experimental conditions. Table 5-2 also shows that uptake, eliminated BAA, recovery of BAA, and half-life of BAA are comparable given the different conditions of exposure and workload. The 12.6-ppm exposure at 30 W of exercise [Van Vlem 1987] showed a much lower urinary excretion of BAA than seen by Johanson et al. [1986]. The half-lives are remarkably close considering the diversity of exposure routes (inhalation and dermal), exposure conditions (experimental and workplace), exposure concentrations (0.65 to 25.2 ppm), and sex (male experimental and female work site).

If EGBE can be absorbed through wet skin, then exposure-chamber inhalation studies at 50 W continuous exercise for 2 hr might be expected to show greater uptake of EGBE and greater excretion of BAA than inhalation exposures by face mask. Examination of Table 5-2 shows that inhalation chamber exposure to 20 ppm EGBE for 2 hr at 50 W of exercise produced a total uptake of 143 mg EGBE, and a total excretion of 65.5 mg BAA. Assuming linear kinetics, exposure for 4 hr would be expected to produce a corresponding uptake of 284 mg EGBE and a total excretion of 131 mg BAA. These projected values are much higher than those seen for face mask exposure for 200 min to 25.2 ppm EGBE at rest (122 mg uptake, 35.7 mg BAA excretion) and for exposure for 4 hr to 12.6 ppm EGBE at 30 W (132 mg uptake, 19.6 mg BAA excreted). Although exercise increases pulmonary ventilation and uptake, the higher values seen in the chamber study are consistent with the hypothesis that EGBE vapor can be absorbed through wet skin.

Table 5-2.—Summary of EGBE exposure studies

Type of exposure	No. of subjects and sex	Concentration (ppm)	Workload (W)	Time (hr)	Total EGBE uptake* (mg)	Total BAA excretion† (mg)	EGBE retention (%)	BAA recovery (%)	BAA half-life (hr)	Post-exposure concentration of BAA (μg/min)	BAA (mg/g creatinine)	Reference
Face mask inhalation	3 males	25.2	0	4	122	35.7	67.0	27	6.3	50§	48	Van Vlem [1987]
	3 males	12.6	0	4	62	18.4	---	27	7.1	36	34	
	3 males	12.6	30	4	132	19.6	77.6	13.6	9.7	40	38	
Occupational	5 females	0.65	60	8/day (5 days)	---	---	---	---	8.3	**	---	
Inhalation chamber	7 males	20	50	2	143	65.5	57.3	41.0	5.8	67††	176	Johanson et al. [1986]
Dermal, 4 fingers	5 males	---	0	2	45.3	12.4	---	17.0	3.1	35§§	---	Johanson [1988]

*Uptake is based on the molecular weight (mw) of 118.2 g for EGBE and represents total uptake.

†Excretion is based on the molecular weight of 132 g for BAA and represents the total amount of BAA excreted during the experiment.

§Urine BAA data were estimated from plots in the reference and represent urine specimens collected at the end of exposure.

**Urine data were estimated from a plot in the cited reference and represent urine specimens collected following 3 days of exposure. Urine data were corrected to a specific gravity of 1.016.

††Urine BAA data were estimated from a plot in the cited reference and represent a urine specimen collected at the end of exposure.

§§Urine BAA data were estimated from a plot in the cited reference and reflect the concentrations in urine samples collected at the end of exposure.

5.4.6 Method for Analyzing Urinary BAA

A variety of methods have been developed for the analysis of BAA in human urine. The gas chromatographic procedures employed are based on either fluoranhydride derivatization following the extraction of the acid tetrabutylammonium ion-pair [Smallwood et al. 1984, 1988; Johanson et al. 1986, 1988] or diazomethane derivatization following lyophilization of the urine [Groeseneken et al. 1986a]. Groeseneken et al. [1989] later developed a method that combined the best attributes of the two basic models. Detailed descriptions of the above methods are presented in Appendix C.

5.4.7 Summary

BAA has been shown to produce hematotoxic effects noted for EGBE and EGBEA. Because EGBE can be absorbed through the skin [Johanson 1988], monitoring of BAA may serve as a measure of EGBE uptake and of potential adverse health effects.

BAA may be analyzed by a variety of sensitive and specific methods. The recent method by Groeseneken et al. [1989] has sufficient sensitivity to monitor excretion of this metabolite after EGBE or EGBEA exposure at the REL.

Exposure of male subjects to EGBE vapor in an inhalation chamber during light physical exercise resulted in 57% retention of inspired EGBE [Johanson et al. 1986]. BAA was rapidly excreted in urine with an elimination half-life of 5.8 hr. Excretion rates varied widely among individuals. Percutaneous exposure of male subjects to EGBE resulted in uptake of EGBE, with BAA excreted in the urine [Johanson et al. 1988]. A comparison of dermal and inhalation uptake suggested that both should be considered when workers are potentially exposed to EGBE [Johanson et al. 1988].

Van Vlem [1987] exposed male subjects to EGBE by face mask both at rest and during exercise. BAA was excreted in the urine with an elimination half-life of 6 to 9 hr. Less uptake and elimination were found in this study using mask inhalation exposures compared with the inhalation chamber studies of Johanson et al. [1986] performed during light work. This finding provides some evidence for the possible absorption of EGBE vapor through wet skin.

Insufficient information is currently available to construct statistically sound guidelines for determining the concentration of BAA in urine that would correlate with an airborne exposure to EGBE or EGBEA. However, biological monitoring should be considered because the metabolite measured is also an indicator of potential toxicity. General guidelines for biological monitoring of EGBE and EGBEA are presented in Appendix D.

6 OTHER STANDARDS AND RECOMMENDATIONS

OSHA adopted the current Federal standard for occupational exposure to EGBE (there is no standard for EGBEA) in 1989. At that time, OSHA lowered the permissible exposure limit (PEL) for EGBE from 50 ppm (240 mg/m^3) to 25 ppm (120 mg/m^3) as an 8-hr TWA with a skin notation [54 Fed. Reg.* 2554 (1989)]. OSHA considers the PEL of 25 ppm to reduce the risk of irritant, hematologic, and other systemic effects because this limit is below the concentration at which these toxic effects are observed in animals and humans. This lower limit also prevents the discomfort experienced by workers at concentrations of 40 ppm.

In 1946, ACGIH established a maximum allowable concentration (m.a.c.) of 200 ppm for EGBE [ACGIH 1984]. Although the value remained unchanged, the term "threshold limit value" (TLV®) was substituted for m.a.c. in 1948. ACGIH lowered the TLV for EGBE from 200 to 50 ppm in 1961 on the basis of a study by Carpenter et al. [1956]. These investigators concluded that humans exposed to single 8-hr exposures of 100 and 200 ppm EGBE suffered discomfort and mild irritation [ACGIH 1962].

In 1968, the notation "skin" (indicating the potential for skin absorption of toxic amounts of the compound) was added to the TLV for EGBE. In 1981, the ACGIH adopted a TLV of 25 ppm EGBE with a short-term exposure limit (STEL) of 75 ppm. However, the STEL was eliminated in 1987 [ACGIH 1988b]. The TLV was lowered because of adverse hematologic effects observed in laboratory animals [Carpenter et al. 1956]. Exposure to 62 ppm EGBE increased the osmotic fragility of rat erythrocytes, and exposure to 32 ppm EGBE exerted no effect. The ACGIH deemed it prudent to limit chemical exposures to concentrations below those found to cause blood changes in experimental animals [ACGIH 1980].

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

Federal Register. See Fed. Reg. in references.

Table 6-1.—Occupational exposure limits for EGBE and EGBEA in various countries[*,†]

Country	Type of standard	EGBE		EGBEA	
		ppm	mg/m^3	ppm	mg/m^3
USA	OSHA PEL—TWA [skin]	25	120	---	---
	ACGIH TLV—TWA [skin]	25	120	---	---
	TLV—STEL [skin]	75[§]	360	---	---
Belgium	---	100	480	---	---
Denmark	---	25	120	---	---
Finland	---	25	120	---	---
France	---	25	120	---	---
GRF (W. Germany)	mak [skin]	20	100	20	135
Holland	mac	(100[**])	(480[**])	---	---
Italy	---	††	††	---	---
Japan	---	50	240	---	---
Norway	[skin]	100	480	---	---
Sweden	[skin]	20	100	---	---
Switzerland	mak [skin]	100	480	---	---
United Kingdom	TWA [skin]	(25[**])	(120[**])	---	---
	STEL [skin]	(75[**])	(360[**])	---	---

[*]Data from ECETOC [1985].

[†]Abbreviations: mac and mak = maximum allowable concentration; GFR = German Federal Republic; PEL = permissible exposure limit; TLV = threshold limit value; TWA = time-weighted average.

[§]ACGIH deleted the STEL in 1987.

[**]Values are subject to change.

[††]No exposure limit has been established.

7 ASSESSMENT OF EFFECTS

The principal human health effects attributed to EGBE and EGBEA exposure involve the central nervous system, the blood and hematopoietic system, and the kidneys. No evidence from animal studies indicates that EGBE or EGBEA causes adverse reproductive or developmental effects. Summaries of the adverse effects of EGBE and EGBEA on the hematopoietic system are presented in Table 7-1.

7.1 CORRELATION OF EXPOSURE AND EFFECTS

7.1.1 EGBE

7.1.1.1 Studies in Humans

Rambourg-Schepens et al. [1988] reported hemoglobinuria and erythropenia in a woman who had ingested 250 to 500 ml of a cleaning solution containing 12% EGBE. Gijsenbergh et al. [1989] reported a suicide attempt in which a woman ingested a window cleaning agent containing an unknown amount of EGBE. Upon admittance to the hospital, the woman was comatose and suffering from hypotension. Severe metabolic acidosis followed. The patient recovered after forced diuresis and hemodialysis. Human volunteers exposed to 98 to 200 ppm EGBE for 4 to 8 hr reported nasal and ocular irritation and disturbed taste [Carpenter et al. 1956]; no abnormalities were detected in blood pressure, pulse rate, erythrocytic fragility, urinary glucose, or albumin. However, increased osmotic fragility was found in vitro with human erythrocytes. In vitro, EGBE (200, 225, and 250 mmol/liter) induced complete lysis of human erythrocytes, whereas 3.75 and 7.5 mmol BAA/liter failed to cause lysis of human erythrocytes [Bartnik et al. 1987]. Ghanayem [1989] also examined the in vitro effect of BAA on human blood obtained from healthy young male and female volunteers. At 8 mM BAA, there was a slight but significant increase in Hct ($P \leq 0.05$) followed by slight but significant hemolysis ($P \leq 0.05$) of human erythrocytes. No other information is available on the toxic effects of EGBE in humans.

7.1.1.2 Studies in Animals

Data obtained from studies in animals indicate that EGBE and EGBEA do not cause adverse reproductive or developmental effects [Nagano et al. 1979; Doe 1984; Schuler et al. 1984; Tyl et al. 1984; Nelson et al. 1984; Hardin et al. 1984; Krasavage 1986]. However, these compounds do adversely affect the blood and hematopoietic system in animals (see Section 4.3) [Werner et al. 1943a; Carpenter et al. 1956; Nagano et al. 1979; Dodd et al. 1983; Tyl et al. 1984; Grant et al. 1985].

Table 7-1.—Hematologic effects of EGBE and EGBEA

Studies and references	Sex and species	Route of administration and dose	LOAEL*	NOAEL*	Observed effects
EGBE:					
Nagano et al. [1979]	Male mice	Oral: 500, 1,000 or 2,000 5 days/wk for 5 wk	500 mg	---	Decreased RBC
Grant et al. [1985]	Male rats	Oral: 500 or 1,000 mg/kg for 4 days	500 mg	---	Decreased RBC, WBC, and Hb; increased MCV, reticulocytes, and MCHb
Werner et al. [1943a]	Rats	Inhalation: 135 or 320 ppm, 7 hr/day, 5 days/wk for 5 weeks	320 ppm	135 ppm	Increased circulating immature granulocytes; increased reticulocytes, Hb, and RBC
Carpenter et al. [1956]	Rats	Inhalation: 62 ppm for 4 hr	62 ppm	---	Increased osmotic fragility
	Male and female rats	Inhalation: 107, 203, 314, or 342 ppm for 7 hr	107 ppm	---	Increased osmotic fragility
	Male and female rats	Inhalation: 54 ppm, 7 hr/day, 5 days/wk for 30 days	54 ppm	---	Increased osmotic fragility
	Male dogs	Inhalation: 100 ppm, 6 hr/day for 90 days	100 ppm	---	Transitory increase in WBC and Hct
	Male and female monkeys	Inhalation: 100 ppm, 6 hr/day for 90 days	100 ppm	---	Transitory increase in osmotic fragility and RBC

(continued)

See footnote at end of table.

Table 7-1 (Continued).—Hematologic effects of EGBE and EGBEA

Studies and references	Sex and species	Route of administration and dose	LOAEL*	NOAEL*	Observed effects
EGBE (continued):					
Dodd et al. [1983]	Female rats	Inhalation: 20, 86, or 245 ppm, 6 hr/day for 9 days	86 ppm	20 ppm	Decreased Hb and MCHb, and increased Hct and MCV
	Male rats	Inhalation: 20, 86, or 245 ppm, 6 hr/day for 9 days	86 ppm	20 ppm	Increased number of lymphocytes
	Female rats	Inhlalation: 5, 25, or 77 ppm, 7 hr/day for 90 days	77 ppm	25 ppm	Decreased RBC and Hb, increased MCHb
	Male rats	Inhalation: 5, 25, or 77 ppm, 7 hr/day for 90 days	77 ppm	25 ppm	50% reduction in RBC
Tyl et al. [1984]	Rats	Inhalation: 25, 50, 100, or 200 ppm, 6 hr/day on g.d.* 6-15	100 ppm	50 ppm	Decreased RBC and MCHC, and increased MCV and MCHb
	Rabbits	Inhalation: 25, 50, 100, or 200 ppm, 6 hr/day on g.d. 6-18	---	200 ppm	No effects at any concentration
EGBEA:					
Truhaut et al. [1979]	Male and female rabbits	Inhalation: 40 ppm	400 ppm	---	Transient hematuria and hemoglobinuria

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

A decrease in WBCs, RBCs and Hb, and an increase in MCV, reticulocytes, and MCHb were noted in male rats treated by gavage with 500 or 1,000 mg EGBE/kg per day for 4 days [Grant et al. 1985]. RBC counts were decreased in male mice treated by gavage with 500, 1,000, 2,000, or 4,000 mg EGBE/kg per day, 5 days/wk for 5 wk [Nagano et al. 1979]; no effects were noted at 62.5, 125, or 250 mg/kg per day. Ghanayem et al. [1987] demonstrated that adult rats (9 to 13 wk old) were more susceptible to EGBE-induced hematotoxicity than young rats (4 to 5 wk old).

Increased numbers of circulating immature granulocytes, reticulocytes, and RBCs, and increased Hct were observed in rats exposed by inhalation to 320 ppm EGBE for 7 hr/day, 5 days/wk for 5 wk [Werner et al. 1943a].

Inhalation studies by Carpenter et al. [1956] showed increased osmotic fragility in rats at 54 ppm EGBE, a transitory increase in WBCs and a decrease in Hct in dogs at 100 ppm, and a transitory increase in osmotic fragility and RBCs in monkeys at 100 ppm.

Inhalation exposure to 86 or 245 ppm EGBE for 6 hr/day for 9 days caused increased numbers of lymphocytes in male rats, and decreased Hb and MCHb and increased Hct and MCV in female rats; no effects were noted at 20 ppm [Dodd et al. 1983]. The effect of EGBE on the hematopoietic system was also assessed by the same investigators in a chronic study of rats exposed to EGBE for 7 hr/day, 5 days/wk for 90 days [Dodd et al. 1983]. No effects were observed at 5 or 25 ppm EGBE. At 77 ppm EGBE, male rats had decreased RBCs, and female rats had decreased RBCs and Hb and increased MCHb.

A decrease in RBCs and MCHC, and an increase in MCV and MCHb were noted in rats exposed to 100 or 200 ppm EGBE for 6 hr/day on g.d. 6 to 15, whereas no adverse effects were noted at 25 or 50 ppm [Tyl et al. 1984]. The same study showed no effects on the hematopoietic systems of rabbits exposed to 25, 50, 100, or 200 ppm EGBE for 6 hr/day on g.d. 6 to 18.

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

Acute toxicity data for EGBE (see Chapter 4, Tables 4-1 and 4-2) indicate that CNS, kidney, and liver effects occur at higher exposure concentrations than hematotoxic effects. In the Carpenter et al. [1956] study, early death in rats exposed to 2,400 and 2,500 mg EGBE/kg was attributed to narcotic effects, and delayed death was attributed to lung and kidney damage. However, in the same study, increases in osmotic fragility occurred at the lower concentrations of 62 and 54 ppm EGBE (see Table 7-1). CNS, kidney, and liver effects occur at higher EGBE exposures than hematotoxic effects. Therefore, limiting exposures to prevent hematotoxic effects will also prevent CNS, kidney, and liver effects.

Table 7-1 presents hematotoxic effects resulting from exposure to EGBE. These data include the lowest observable adverse effect level (LOAEL) for mice (500 mg/kg), rats (54 ppm), and dogs and monkeys (100 ppm). In the study by Tyl et al. [1984], no effects on rabbits were noted at any concentration tested. Thus it appears that on the basis of available data, the rat is the most sensitive species.

Data presented in Section 4.3 (see Tables 4-5 and 4-6) demonstrate that the rat is more susceptible than humans to the hematotoxic effects of EGBE and its metabolite BAA [Bartnik et al. 1987; Ghanayem 1989]. Whereas 175 mmol EGBE/liter caused complete lysis of rat erythrocytes, 200 mmol EGBE/liter caused complete lysis of human erythrocytes [Bartnik et al. 1987]. In the Ghanayem [1989] study, 20 mM EGBE caused significant hemolysis of rat erythrocytes. In vitro, 0.5 to 8 mM BAA caused complete lysis of rat erythrocytes. With human erythrocytes in vitro, 8 mM BAA caused a slight but significant increase in Hct ($P \leq 0.05$) followed by slight but significant hemolysis ($P \leq 0.05$) [Ghanayem 1989]. Because there is a lack of adequate human data and because the rat is the animal species most sensitive to EGBE, it is reasonable to use the rat NOAEL to extrapolate an equivalent dose for humans.

The data that demonstrate adverse effects on the blood and hematopoietic system, and the LOAELs and NOAELs presented in Table 7-1 indicate that 50 ppm is the highest NOAEL in rats that is also lower than the lowest LOAEL in rats [Tyl et al. 1984]. NIOSH therefore deems it appropriate to use 50 ppm as the NOAEL for EGBE in rats and to use the body weights of rats studied by Tyl et al. [1984] for calculating the daily NOAEL for rats and extrapolating an equivalent dose for humans.

7.1.2 EGBEA

Few data are available on the toxicity of EGBEA. Transient hematuria and hemoglobinuria were noted in rabbits exposed by inhalation for 4 hr to 400 ppm EGBEA [Truhaut et al. 1979]. The toxic effects of EGBEA are likely to be similar to those caused by EGBE as a result of the metabolism of EGBEA to EGBE (see Section 4.2 for the analogy to EGEEA, EGEE, and EAA). Therefore, it is reasonable to use NOAELs for EGBE to extrapolate the NOAEL for EGBEA.

7.2 BASIS FOR THE RECOMMENDED STANDARD FOR EGBE AND EGBEA

A limited number of studies describe the effects of EGBE exposure on humans. The following toxic effects have been reported in humans exposed by inhalation to 100 to 200 ppm EGBE: ocular and nasal irritation, disturbed taste, vomiting, headache, and belching [Carpenter et al. 1956]. In separate incidents, two women attempted suicide by ingesting window cleaners containing EGBE [Rambourg-Schepens et al. 1988; Gijsenbergh et al. 1989]. Their symptoms included hemoglobinuria, erythropenia, and hypotension. Both women recovered fully.

Experimental results indicate that rats are more susceptible than humans to the hemolytic effects of EGBE and BAA. When rats and men were exposed simultaneously to 200 ppm EGBE, osmotic fragility of rat erythrocytes increased appreciably, but that of human erythrocytes did not [Carpenter et al. 1956]. The same study revealed that human erythrocytes have increased osmotic fragility in vitro. Therefore, the osmotic fragility of human erythrocytes would be expected to increase after inhalation of EGBE at concentrations above 200 ppm. Later investigators demonstrated that in vitro lysis of human

erythrocytes requires higher concentrations of EGBE and BAA than lysis of rat erythrocytes [Bartnik et al. 1987; Ghanayem 1989].

Data obtained from animal studies indicate that EGBE and EGBEA do not cause adverse reproductive or developmental effects [Nagano et al. 1979; Doe 1984b; Krasavage 1986; Schuler et al. 1984; Tyl et al. 1984; Nelson et al. 1984; Hardin et al. 1984]. However, both compounds adversely affect the blood and hematopoietic system in animals (rodents) [Werner et al. 1943a; Carpenter et al. 1956; Nagano et al. 1979; Truhaut et al. 1979; Dodd et al. 1983; Tyl et al. 1984; Grant et al. 1985]. Adult rats appear to be more susceptible to EGBE-induced hematotoxicity than young rats [Ghanayem et al. 1987]. No significant hematologic effects were observed in young rats receiving 125 mg EGBE/kg, but significant decreases in RBCs, Hct, and Hb were detected in adult rats receiving the same dose of EGBE.

Limited data exist to characterize the effects of EGBE on human erythrocytes; however, studies in animals clearly demonstrate that EGBE adversely affects the hematopoietic system and that these effects are age-dependent. Because the rat appears to be more sensitive to hematologic effects than humans, NIOSH deems it appropriate to base the REL on animal data in the absence of sufficient human data. Data from the Tyl et al. [1984] study (Table 7-1) were used to determine the human dose corresponding to a 50-ppm NOAEL in rats.

No mechanistic models exist to describe the relationship of hematotoxicity to exposure; only empirical models are available to use in a quantitative risk assessment (QRA). Because a threshold is assumed to exist for hematotoxicity, a QRA model is inappropriate since such models assume a no-threshold effect. Therefore, the following method was used to determine the REL for EGBE.

Both humans and rats were assumed to retain 100% of inhaled EGBE. The retained dose (44.9 mg/kg per day) for rats exposed at the NOAEL (50 ppm [241.5 mg/m^3]) was calculated by using the inhalation rate and the average body weight of the rats (see Table 7-2):

$$241.5 \text{ mg/m}^3 \times \frac{(0.161 \text{ m}^3\text{/day} \times 0.25 \text{ day})}{0.215 \text{ kg}} = 44.9 \text{ mg/kg per day}^*$$

That dose was converted to an equivalent exposure concentration 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]:

$$\frac{44.9 \text{ mg/kg per day} \times 70 \text{ kg}}{10 \text{ m}^3\text{/day}} = 314 \text{ mg/m}^3 \text{ (equivalent daily exposure for humans)}$$

The adverse hematologic effects observed are reversible [Rambourg-Schepens et al. 1988; Gijsenbergh et al. 1989], and the available data indicate that humans are less sensitive than

*The values in this equation were rounded to obtain 44.9.

rats to the hematotoxic effects of EGBE [Carpenter et al. 1956; Bartnik et al. 1987; Ghanayem 1989]. In consideration of this interspecies variation, an uncertainty factor was not deemed appropriate. In consideration of potential intraspecies variability, an uncertainty factor of 10 was applied to the concentration calculated as the human equivalent to the NOAEL for rats. The resulting concentration was converted to parts per million:

$$\frac{314\ mg/m^3}{10} \times \frac{24.45}{118.2} = 6.5\ ppm$$

On the basis of these calculations, NIOSH recommends that occupational exposure to EGBE be limited to a TWA of 5 ppm for up to a 10-hr workshift and a 40-hr workweek.

Because any effects of EGBEA would be likely to occur after it is metabolized to EGBE, the same exposure limit is recommended for EGBEA. Both EGBE and EGBEA can be absorbed percutaneously [Dugard et al. 1984; Johanson et al. 1988]; thus skin and eye contact should be avoided through the use of good work practices and personal protective clothing and equipment.

Table 7-2.—Data for rat inhalation study

Item	Description
Compound studied	EGBE
Reference	Tyl et al. [1984]
Inhalation rate*	0.161 m^3/day
Exposure duration	6 hr/day on g.d. 6-15
Average body weight of rats	0.215 kg
NOAEL†	50 ppm (241.5 mg/m^3)

*Rat inhalation rate = $0.105 \times \left(\frac{0.215}{0.113}\right)^{2/3} = 0.16\ m^3$/day

Calculation is based on the average body weight for rats (0.215 kg) [55 Fed. Reg. 4066 (1990); Anderson et al. 1983].

†Daily NOAEL for rats = $241.5\ mg/m^3 \times \frac{(0.161\ m^3/day \times 0.25\ day)}{0.215\ kg} = 44.9$ mg/kg per day

The values in this equation were rounded to obtain 44.9.