NIOSH

Criteria For A Recommended Standard

Occupational Exposure to Ethylene Glycol Monomethyl Ether, Ethylene Glycol Monoethyl Ether, and Their Acetates

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Centers for Disease Control
National Institute for Occupational Safety and Health

CDC

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Division of Standards Development and Technology Transfer
Cincinnati, Ohio

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FOREWORD

The purpose of the Occupational Safety and Health Act of 1970 (Public Law 91-596) is to assure safe and healthful working conditions for every working person and to preserve our human resources. The Act authorizes the National Institute for Occupational Safety and Health (NIOSH) to develop and recommend occupational safety and health standards and to develop criteria that will ensure that no worker will suffer diminished health, functional capacity, or life expectancy as a result of his or her work experience.

Through criteria documents, NIOSH communicates recommended standards to regulatory agencies, including the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA). In addition, NIOSH distributes these documents to health professionals in academia, industry, organized labor, public interest groups, and other appropriate government agencies. Criteria documents provide the scientific basis for the occupational safety and health standards. These documents generally contain a critical review of the scientific and technical information available on the prevalence of hazards, the existence of safety and health risks, and the adequacy of control methods.

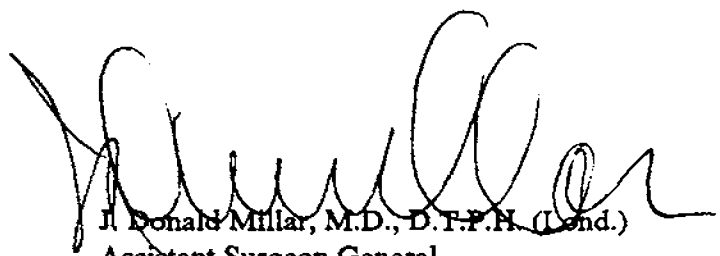
This criteria document reviews available information about the health risks for workers engaged in the manufacture and use of ethylene glycol monomethyl ether (EGME), ethylene glycol monoethyl ether (EGEE), and their acetates, ethylene glycol monomethyl ether acetate (EGMEA) and ethylene glycol monoethyl ether acetate (EGEEA). Evidence from case reports clearly establishes the risk of adverse effects on the blood, central nervous and hematopoietic systems, liver, and kidneys. The results of studies in animals have demonstrated dose-related embryotoxicity and other reproductive effects in several species of animals exposed to EGME, EGEE, and their acetates by different routes of administration. Of particular concern are studies in which exposure of pregnant animals to airborne concentrations of EGME or EGEE at or below their current OSHA permissible exposure limits (PELs) led to increased incidences of malformations, growth retardation, and embryonic death. Concern was also caused by testicular atrophy and infertility resulting from exposure of male animals to airborne concentrations of EGME or EGEE at or below their PELs.

A known metabolism precedes the reproductive and developmental toxicity of EGME and EGEE in animals. Because the same metabolic pathways exist in humans, NIOSH considers it prudent to assume that humans and animals are similarly subject to the reproductive and developmental effects of these chemicals. EGMEA and EGEEA have the same potential for reproductive and developmental effects as the parent compounds because they are metabolized to EGME and EGEE, respectively.

Because limited data are available from studies in humans, NIOSH bases its recommended exposure limits (RELs) for EGME, EGEE, and their acetates on data from studies in animals. The data were adjusted to allow for uncertainties in the extrapolation from animals to humans. NIOSH recommends that worker exposure to EGME and EGMEA in the workplace be limited to 0.1 part per million parts of air (0.1 ppm) (0.3 mg EGME/m^3 and 0.5 mg

EGMEA/m^3) as a time-weighted average for up to 10 hr/day during a 40-hr workweek (10-hr TWA). Exposure to EGEE and EGEEA in the workplace shall be limited to 0.5 ppm (1.8 mg/m^3 for EGEE and 2.7 mg/m^3 for EGEEA) as a 10-hr TWA. Exposure to these glycol ethers shall be reduced using state-of-the-art engineering controls and work practices. Dermal contact is prohibited because EGME, EGEE, and their acetates are readily absorbed through the skin.

The Institute takes sole responsibility for the conclusions and recommendations presented in this document. All reviewers' comments are being sent with this document to OSHA and MSHA for consideration in standard setting.



J. Donald Millar, M.D., D.T.P.H. (Lond.)
Assistant Surgeon General
Director, National Institute for
Occupational Safety and Health
Centers for Disease Control

ABSTRACT

This document examines the occupational health risks associated with exposure to ethylene glycol monomethyl ether (EGME), ethylene glycol monoethyl ether (EGEE), and their acetates, ethylene glycol monomethyl ether acetate (EGMEA) and ethylene glycol monoethyl ether acetate (EGEEA). Criteria are also provided for eliminating or minimizing the risks encountered by workers during the manufacture and use of these glycol ethers.

These glycol ethers adversely affect the blood, central nervous and hematopoietic systems, liver, and kidneys. Studies in animals have demonstrated dose-related malformations, growth retardation, and embryonic death in the offspring of pregnant animals exposed to airborne concentrations of EGME or EGEE at or below their current Occupational Safety and Health Administration (OSHA) permissible exposure limits (PELs). In addition, testicular atrophy and infertility occurred in male animals exposed to airborne concentrations of EGME or EGEE at or below their current PELs. EGMEA and EGEEA have the same potential for reproductive and developmental effects as the parent compounds because they are metabolized to EGME and EGEE, respectively.

The National Institute for Occupational Safety and Health (NIOSH) therefore recommends that exposure to EGME and EGMEA in the workplace be limited to 0.1 part per million parts of air (0.1 ppm) (0.3 mg EGME/m^3 and 0.5 mg EGMEA/m^3) as a time-weighted average for up to 10 hr/day during a 40-hr workweek (10-hr TWA).

NIOSH also recommends that exposure to EGEE and EGEEA be limited to 0.5 ppm (1.8 mg EGEE/m^3 and 2.7 mg EGEEA/m^3) as a 10-hr TWA. Exposure to these glycol ethers shall be reduced using state-of-the-art engineering controls and work practices. Dermal contact is prohibited because EGME, EGEE, and their acetates are readily absorbed through the skin.

CONTENTS

ABBREVIATIONS

ABP	androgen binding protein
ACGIH	American Conference of Governmental Industrial Hygienists
Ach	acetylcholine
ADH	alcohol dehydrogenase
Cal OSHA	California Occupational Safety and Health Administration
CAS	Chemical Abstracts Service
cc	cubic centimeter
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CK	creatinine kinase
cm	centimeter
CNS	central nervous system
CY	cyclophosphamide
DA	dopamine
DEGBE	diethylene glycol butyl ether
DEGME	diethylene glycol monomethyl ether
DPGME	dipropylene glycol monomethyl ether
DTH	delayed type hypersensitivity
EAA	ethoxyacetic acid
EC_{50}	concentration that allowed 50% of the seeded cells to form colonies
EGEE	ethylene glycol monoethyl ether
EGEEA	ethylene glycol monoethyl ether acetate
EGME	ethylene glycol monomethyl ether
EGMEA	ethylene glycol monomethyl ether acetate
EMH	extramedullary hemopoiesis
FSH	follicle-stimulating hormone
g	gram
g.d.	gestation day

Hb	hemoglobin
Hct	hematocrit
HPLC	high performance liquid chromatography
5-HT	5-hydroxytryptamine
IDLH	immediately dangerous to life and health
IgG	immunoglobulin G
i.p.	intraperitoneal
i.v.	intravenous
kcal	kilocalorie
kg	kilogram
KLH	keyhole limpet hemocyanin
LC_{50}	lethal concentration for 50% of the animals
LD_{50}	lethal dose for 50% of the animals
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest observable adverse effect level
m	meter
MAA	methoxyacetic acid
M.A.C.	maximum allowable concentration
MCHb	mean corpuscular (cell) hemoglobin
MCHC	mean cell hemoglobin concentrations
MCV	mean corpuscular (cell) volume
MEK	methylethyl ketone
mg	milligram
MIBK	methyl isobutyl ketone
min	minute
ml	milliliter
mM	millimolar
mmol	millimole
4-MP	4-methylpyrazole
MSDS	material safety data sheet
MSHA	Mine Safety and Health Administration
NAD	nicotinamide adenine
NADPH	nicotinamide adenine diphosphate

NE	norepinephrine
NFPA	National Fire Protection Association
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observable adverse effect level
NOES	National Occupational Exposure Survey
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PCV	packed cell volume
PEL	permissible exposure limit
ppe	personal protective equipment
ppm	parts per million
RBC	red blood cell or erythrocyte
REL	recommended exposure limit
RTECS	Registry of Toxic Effects of Chemical Substances
s.c.	subcutaneous
SRBC	sheep erythrocyte
STEL	short-term exposure limit
TDI	toluene diisocyanate
TLV	threshold limit value
TNP-LPS	trinitrophenyl-lipopolysaccharide
TWA	time-weighted average
UCC	Union Carbide Corporation
UDS	unscheduled DNA synthesis
µmol	micromole
v/v	volume to volume
WBC	white blood cell
wk	week

GLOSSARY

***Biological monitoring*:** The measurement and evaluation of hazardous substances or their metabolites in the body tissues, fluids, or exhaled air of exposed workers.

***Developmental toxicity*:** Any adverse effects on normal growth, development, or acquisition of organ function in (1) the conceptus of a pregnant woman exposed to a chemical or physical agent, or (2) an immature (prepubertal) individual exposed to a chemical or physical agent.

***Lowest observable adverse effect level (LOAEL)*:** The lowest concentration of a chemical or physical agent that produces an observable adverse health effect in exposed animals or workers.

***No observable adverse effect level (NOAEL)*:** The concentration of a chemical or physical agent that produces no observable adverse health effect in exposed animals or workers.

***Recommended exposure limit (REL)*:** An occupational exposure limit recommended by NIOSH as being protective of worker health and safety over a working lifetime; the REL is used in combination with engineering and work practice controls, exposure and medical monitoring, labeling, posting, worker training, and personal protective equipment. The REL is frequently expressed as a time-weighted average (TWA) exposure for up to 10 hr/day during a 40-hr workweek. The REL may also be expressed as (1) a short-term exposure limit (STEL) that should never be exceeded and is to be determined in a specified sampling time (usually 15 min), or (2) a ceiling limit (C) that should never be exceeded even instantaneously unless specified over a given time period.

***Reproductive hazard*:** Any chemical or physical agent capable of causing an adverse effect on reproduction.

***Reproductive toxicity*:** Any adverse effects on gametogenesis, fecundity, or sexual functions (e.g., libido, menstrual cyclicity, potency) that result when a postpubertal individual of either sex is exposed to certain chemical or physical agents.

***Skin*:** The notation "skin" indicates that airborne or direct exposure by the cutaneous route (including mucous membranes and eyes) contributes to overall exposure.

***Time-weighted average (10-hr TWA)*:** An airborne concentration of a chemical or physical agent in the worker's breathing zone for up to 10 hr/day during a 40-hr workweek.

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We wish to thank the following consultants for their review of this document:

Dr. Frank Mirer
Director, Health and Safety Department
United Auto Workers
8000 E. Jefferson
Detroit, MI 48214

Dr. Joan McCuen
ARCO Chemical Company
3801 West Chester Pike
Newtown Square, PA 19073

Mr. Matthew Gillen
for the AFL-CIO
Director
Worker's Institute for Safety and Health
Washington, DC 20036

Mr. Walter Lypka
Graphic Communications
International Union
1900 L Street, N.W.
Washington, DC 20036

Mr. Frank Burkhardt
for Mr. William Duval
International Brotherhood of
Builders and Allied Trades
United Unions Building
1750 New York Avenue, N.W.
Washington, DC 20006

Dr. H. Veulemans
Laboratorium voor arbeidshygienne
en-toxicologie
Provisorium 1, Minderbroedersstraat
17, B-3000
Leuven, Belgium

Dr. E. Marshall Johnson
Daniel Baugh Institute
Jefferson Medical College
1020 Locust Street
Philadelphia, PA 19107

Chemical Manufacturers Association
Dr. Joseph V. Rodricks
Dr. Jeffrey S. Ferguson
Dr. Resha M. Putzrath
Mr. Matthew Fitzgerald
2501 M Street, N.W.
Washington, DC 20037

Dr. Laura Welch
George Washington University
Department of Medicine,
Occupational Medicine Program
6th Floor
2150 Pennsylvania Avenue, N.W.
Washington, DC 20039

Dr. P. Sharma
for William Kelley of ACGIH
Utah State University
College of Agriculture Toxicology
Program
Department of Animal, Dairy, and
Veterinary Sciences
Logan, UT 84322-5600

Dr. Robert Elves
for the Department of Defense
Department of the Air Force
Harry G. Armstrong Aerospace
Medical Research Laboratory
Wright-Patterson Air Force Base
OH 45433-6573

Dr. Frank Welsch
Chemical Industry Institute
of Toxicology
P. O. Box 12137
Research Triangle Park
NC 27709

1 RECOMMENDATIONS FOR STANDARDS

The National Institute for Occupational Safety and Health (NIOSH) recommends that worker exposure to ethylene glycol monomethyl ether (EGME), ethylene glycol monoethyl ether (EGEE), and their acetates, ethylene glycol monomethyl ether acetate (EGMEA) and ethylene glycol monoethyl ether acetate (EGEEA), be controlled in the workplace by complying with the recommendations presented in this Chapter. These recommendations are designed to protect the health and provide for the safety of workers for up to a 10-hr workshift and a 40-hr workweek over a working lifetime. Compliance with all sections of the recommended standard, including the recommended exposure limits (RELs), should prevent or greatly reduce the risk of adverse effects on exposed workers.

SECTION 1.1 RECOMMENDED EXPOSURE LIMITS FOR EGME, EGEE, AND THEIR ACETATES

1.1.1 Exposure

Exposure to EGME and EGMEA in the workplace shall be limited to 0.1 part per million parts of air (0.1 ppm, or 0.3 mg EGME/m^3 and 0.5 mg EGMEA/m^3) as a time-weighted average for up to 10 hr/day during a 40-hr workweek (10-hr TWA). Exposure to EGEE and EGEEA in the workplace shall be limited to 0.5 ppm (1.8 mg EGEE/m^3 and 2.7 mg EGEEA/m^3) as a 10-hr TWA. Exposure to these glycol ethers shall be reduced using state-of-the-art engineering controls and work practices.

Dermal contact shall be prohibited because EGME, EGEE, and their acetates are readily absorbed through the skin.

1.1.2 Sampling and Analysis

Workplace air samples shall be collected and analyzed for EGME, EGEE, and their acetates as described by Occupational Safety and Health Administration (OSHA) Method No. 79 [OSHA 1990] (discussed in Section 5.2 and Appendix A) or by any other methods with at least equal accuracy, precision, and sensitivity. The NIOSH Occupational Exposure Sampling Strategy Manual [Leidel et al. 1977] provides guidance for the number of samples to be collected and is discussed in Section 8.8.

SECTION 1.2 EXPOSURE MONITORING

Exposure monitoring shall be conducted as specified in Sections 1.2.1 and 1.2.2. Results of all exposure monitoring shall be recorded and maintained as specified in Section 1.9.

1.2.1 Industrial Hygiene Surveys

In work areas where airborne exposures to EGME, EGEE, or their acetates may occur, the employer shall conduct initial industrial hygiene surveys to determine the magnitude of exposure by using personal sampling techniques for an entire workshift. The employer shall keep records of these surveys. If the employer concludes that exposure concentrations for all glycol ethers are less than one-half the REL, the records must show the basis for this conclusion. Surveys shall be repeated at least annually and whenever any process change is likely to increase concentrations of airborne EGEE, EGME, EGEEA, and EGMEA. The employer shall also look for, evaluate, and record the potential for dermal exposure.

1.2.2 Personal Monitoring

If workers are exposed to any glycol ether at or above one-half the REL, a program of personal monitoring shall be instituted to identify and to measure or calculate the exposure of each worker (see Section 8.8). Source and area monitoring may be a useful supplement to personal monitoring. In all personal monitoring, samples representative of the TWA exposures to airborne glycol ethers shall be collected in the breathing zone of the worker. Procedures for sampling and analysis shall be in accordance with Section 1.1.2. For each determination of an occupational exposure concentration, a sufficient number of samples (as determined in Leidel et al. [1977]), shall be collected to characterize each worker's exposure during each workshift. Although not all workers must be monitored, a sufficient number of samples must be collected to characterize the exposure of all workers. Variations in work and production schedules as well as worker locations and job functions shall be considered when determining sampling locations, times, and frequencies.

If a worker is exposed to EGME, EGEE, or their acetates at concentrations below the REL but at or above one-half the REL, the exposure of that worker shall be monitored at least once every 6 months or more frequently, as indicated by a professional industrial hygienist. If a worker is exposed to one of these glycol ethers at concentrations exceeding the REL, the worker must wear a respirator until adequate engineering controls and/or work practices are instituted. Controls shall then be initiated, the worker shall be notified of the exposure and of the control measures being implemented, and the worker's exposure shall be evaluated at least once a week. Such monitoring shall continue until two consecutive determinations at least 1 week apart indicate that the worker's exposure no longer exceeds the REL. At that time, semiannual monitoring can be resumed; if concentrations of the glycol ethers are less than one-half the REL after two consecutive semiannual surveys, sampling can be conducted annually.

All episodes of skin contact shall be reported to a supervisor. These reports and the results of any investigation or corrective action are to be retained with other records.

1.2.3 Biological Monitoring

Measurement of two glycol ether metabolites—ethoxyacetic acid (EAA, the metabolite of EGEE and EGEEA) and methoxyacetic acid (MAA, the metabolite of EGME and EGMEA)—

may help characterize occupational exposure to EGEE, EGME, and their acetates when the potential exists for airborne concentrations at or above one-half the REL, or for dermal contact from accidental exposure or breakdown of chemical protective clothing (see Section 5). Guidelines for biological monitoring are presented in Appendix G.

SECTION 1.3 MEDICAL MONITORING

The employer shall provide the following information to the physician performing or responsible for the medical monitoring program:

- The requirements of the applicable standard
- An estimate of the worker's potential exposure to glycol ethers, including any available results from workplace sampling
- A description of the worker's duties as they relate to exposure
- A description of any protective equipment the worker may be required to use

1.3.1 General

- The employer shall institute a medical monitoring program for all workers who are exposed to airborne concentrations of EGEE, EGME, or their acetates at or above one-half the REL, or who have the potential for dermal exposure.
- If a worker has had a dermal exposure, the employer shall provide this information to the physician responsible for or performing the medical monitoring program.
- The employer shall ensure that all medical examinations and procedures are performed by or under the direction of a licensed physician.
- The employer shall provide the required medical monitoring at a reasonable time and place without loss of pay or other cost to the workers.
- The employer shall institute a biological monitoring program for all workers who are exposed to airborne concentrations of EGME, EGEE, or their acetates at or above one-half the REL, or who have the potential for dermal exposure. Guidelines for biological monitoring are presented in Appendix G.

1.3.2 Preplacement Medical Examinations

Preplacement medical examinations shall include at least the following:

- A comprehensive medical, work, and reproductive history that emphasizes identification of existing medical conditions (e.g., those affecting the reproductive, hematopoietic, and central nervous systems, skin, liver, and kidneys) and previous occupational exposure to chemical or physical agents

- A medical examination giving special attention to the reproductive, hematopoietic, and central nervous systems, skin, liver, and kidneys
- Routine urinary monitoring for MAA and EAA before job placement, which may be a useful adjunct to environmental monitoring because it indicates both airborne and dermal exposures
- A judgment of the worker's ability to use positive- and negative-pressure respirators

1.3.3 Periodic Medical Examinations

Periodic medical examinations shall be provided at least annually to all workers occupationally exposed to airborne concentrations of EGME, EGEE, and their acetates at or above one-half the REL, and to workers with the potential for dermal exposure. These examinations shall include at least the following:

- An update of medical and work histories
- A medical examination and tests as outlined above

1.3.4 Medical Consultation

Workers who have a dermal exposure or who are exposed to concentrations of EGME, EGEE, or their acetates above the REL should be given the opportunity to consult with a physician regarding possible adverse health effects, including reproductive and developmental effects. OSHA Form 200 shall be modified to include any reports of dermal exposure.

SECTION 1.4 LABELING AND POSTING

All labels and warning signs shall be printed both in English and the predominant language of workers who do not read English. Workers unable to read the labels and warning signs shall be informed verbally regarding the instructions printed on labels and signs in the hazardous work areas of the plant.

1.4.1 Labeling

Containers of EGME, EGMEA, EGEE, or EGEEA used or stored in the workplace shall carry a permanently attached label that is readily visible. The label shall identify the glycol ether and give information regarding its effects on human health and emergency procedures (see Figure 1-1).

1.4.2 Posting

Signs bearing information about the health effects of EGME, EGMEA, EGEE, or EGEEA shall be posted in readily visible positions in work areas and at entrances to work areas or

building enclosures where the potential exists for exposures at or above the REL or where skin exposures may occur (see Figure 1-2).

If respirators and personal protective clothing are needed during the manufacturing or handling of these glycol ethers or during the installation or implementation of required engineering controls, the following statement shall be added in large letters to the signs required in this section:

Respirators and protective clothing are required in this area.

In any area where emergency situations may arise, the required signs shall be supplemented with emergency first-aid procedures and the locations of emergency showers and eyewash fountains.

SECTION 1.5 PROTECTIVE CLOTHING AND EQUIPMENT

Engineering controls and good work practices shall be used to keep the airborne concentrations of EGME, EGEE, and their acetates below the REL and to prevent skin and eye contact. When protective clothing and equipment are needed, they shall be provided by the employer at no cost to the worker.

1.5.1 Eye and Face Protection

The employer shall provide chemical splash-proof safety goggles or face shields (20-cm minimum) with goggles and shall ensure that workers wear the protective equipment during any operation in which splashes of these glycol ethers are likely to occur. Devices for eye and face protection shall be selected, used, and maintained in accordance with 29 CFR* 1910.133 and 30 CFR 56.150004, and 57.150004.

1.5.2 Skin Protection

- Workers at risk of dermal exposure to these glycol ethers shall be provided with appropriate protective clothing such as gloves and disposable clothing. Information presented in Section 8.6.1 provides guidance in the selection of appropriate materials for gloves and clothing.
- Clothing contaminated with these glycol ethers shall be cleaned before reuse. Anyone who handles contaminated clothing or is responsible for its cleaning shall be informed of the hazards of these glycol ethers and the proper precautions for their safe handling and use.

* *Code of Federal Regulations.* See CFR in references.

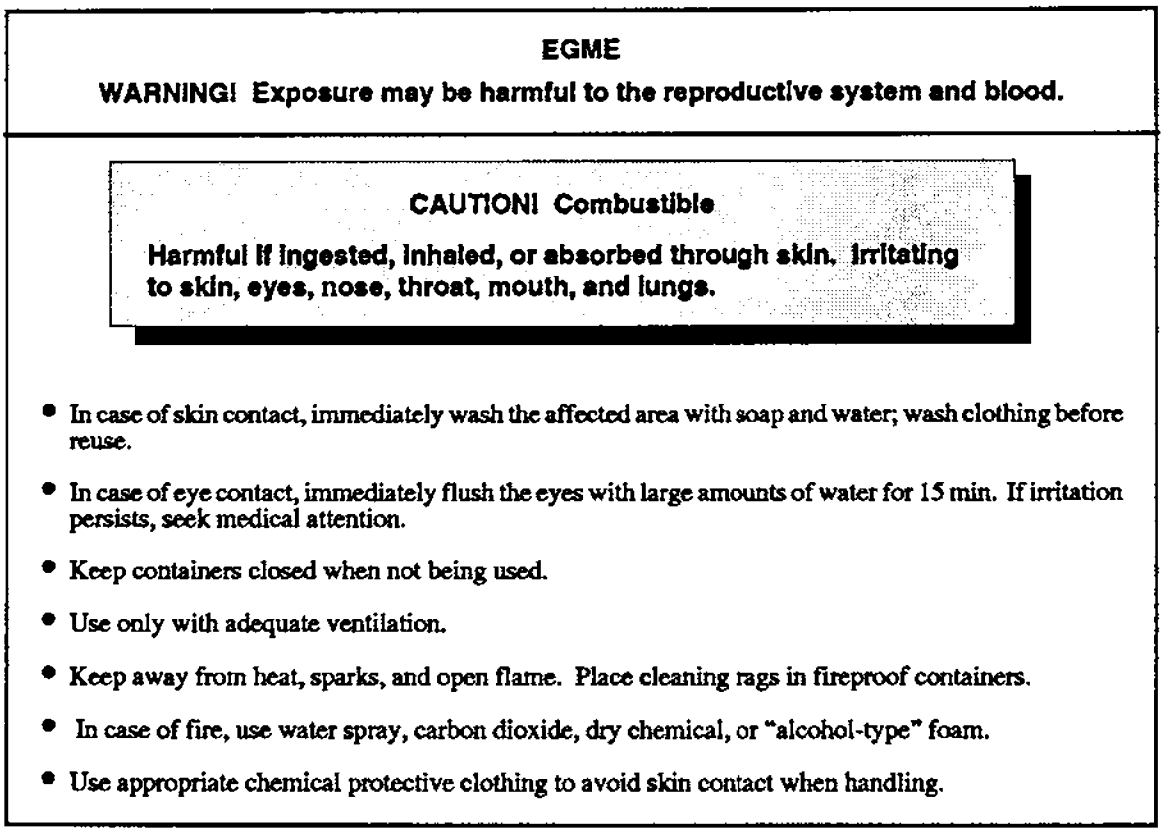

Figure 1–1. Example of a container label identifying the glycol ether and listing information about its effects of human health and emergency procedures.

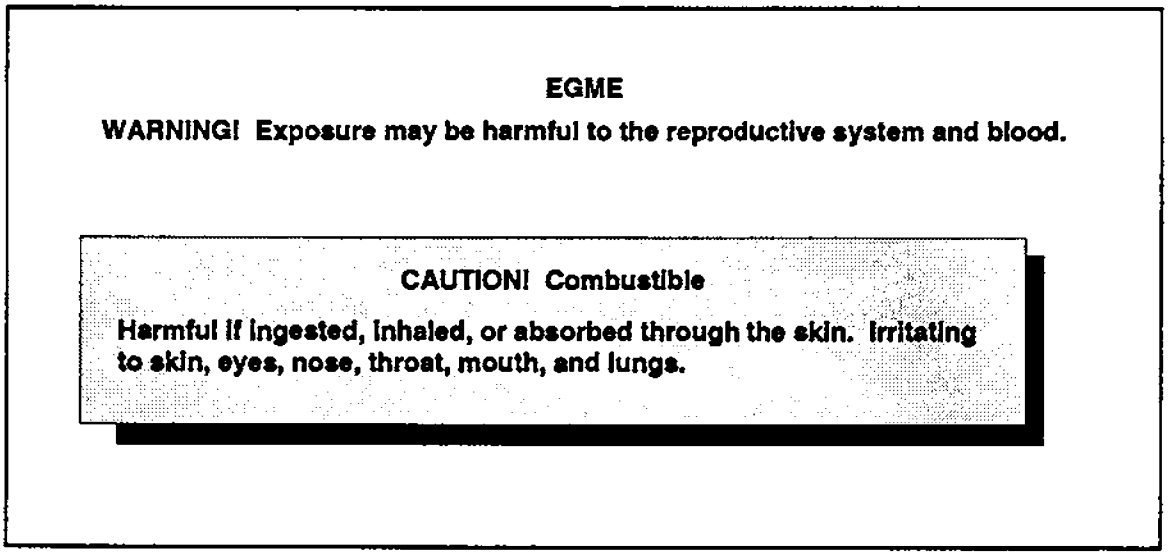

Figure 1–2. Example of a sign containing information about the health effects of a glycol ether.

- The employer shall ensure that all personal protective clothing and equipment is inspected regularly and maintained in a clean and satisfactory working condition.
- Protective clothing or gloves shall be evaluated on a routine basis to ensure that they are in good condition and no breakthrough has occurred.

1.5.3 Respiratory Protection

Engineering controls and good work practices shall be used to control respiratory exposure to airborne contaminants. The use of respirators is the least desirable method of controlling worker exposures and should not be used as the primary control method during routine operations. However, NIOSH recognizes that respirators may be required to provide protection in certain situations such as implementation of engineering controls, short-duration maintenance procedures, and emergencies. Respirator selection guides for protection against EGEE, EGME, and their acetates are presented in Tables 1-1 through 1-3.

- Respirators shall be provided by the employer when such equipment is necessary to protect the health of the worker. The worker shall use the provided respiratory protection in accordance with instructions and training received.
- The employer shall ensure that respirators are properly fitted and that workers are instructed at least annually in the proper use and testing for leakage of respirators assigned to them.
- Workers should not be assigned to tasks requiring the use of respirators unless it has been determined that they are physically able to perform the work and use the equipment. The respirator user's medical status should be reviewed at least annually or more frequently as recommended by the physician responsible for the physical examination. See Appendix H for additional information about the medical aspects of wearing respirators.
- The employer shall be responsible for establishing and maintaining a respiratory protection program as follows:*

  1. Written standard operating procedures governing selection and use of respirators shall be established.

  2. The worker shall be instructed and trained in the proper use of respirators and their limitations.

  3. Where practicable, the respirators should be assigned to individual workers for their exclusive use.

*The OSHA minimum requirements for a respiratory protection program for general industry may be found in 29 CFR 1910.134, and the minimum Mine Safety and Health Administration (MSHA) requirements for the mining industry may be found in 30 CFR 56.5005, 57.5005, 70.305, and 70.305-1.

Table 1–1.—NIOSH-recommended respiratory protection for workers exposed to EGME and EGMEA

Condition	Minimum respiratory protection*
1 ppm or less (10 × REL)	Any supplied-air respirator equipped with a half-mask†
2.5 ppm or less (25 × REL)	Any supplied-air respirator equipped with a hood or helmet and operated in a continuous-flow mode
5.0 ppm or less (50 × REL)	Any supplied-air respirator with a full facepiece, or Any self-contained breathing apparatus with a full facepiece
100 ppm or less (1,000 × REL)	Any supplied-air respirator equipped with a half-mask† and operated in a pressure-demand or other positive-pressure mode
200 ppm or less (2,000 × REL)	Any supplied-air respirator equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode
Greater than 200 ppm	Any self-contained breathing apparatus equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode, or Any supplied-air respirator equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained breathing apparatus operated in a pressure-demand or other positive-pressure mode
Fire fighting	Any self-contained breathing apparatus equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode
Escape	Any air-purifying,‡ full-facepiece respirator (gas mask) with a chin-style or front- or back-mounted organic vapor canister, or Any appropriate escape-type, self-contained breathing apparatus

*Only NIOSH/MSHA-approved equipment shall be used.
†If eye irritation occurs, a respirator equipped with full facepiece, helmet, or hood shall be used.
‡Air-purifying respirators are used for escape only because EGME and EGMEA do not have good odor-warning properties.

Table 1–2.—NIOSH-recommended respiratory protection for workers exposed to EGEE

Condition	Minimum respiratory protection*
5 ppm or less (10 × REL)	Any supplied-air respirator equipped with a half-mask†
12.5 ppm or less (25 × REL)	Any supplied-air respirator equipped with a hood or helmet and operated in a continuous-flow mode
25 ppm or less (50 × REL)	Any supplied-air respirator with a full facepiece, or Any self-contained breathing apparatus with a full facepiece
500 ppm or less (1,000 × REL)	Any supplied-air respirator equipped with a half-mask† and operated in a pressure-demand or other positive-pressure mode
1,000 ppm or less (2,000 × REL)	Any supplied-air respirator equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode
Greater than 1,000 ppm	Any self-contained breathing apparatus equipped with a full facepiece operated in a pressure-demand or other positive-pressure mode, or Any supplied-air respirator equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained breathing apparatus operated in a pressure-demand or other positive-pressure mode
Fire fighting	Any self-contained breathing apparatus with a full facepiece and operated in a pressure-demand or other positive-pressure mode
Escape	Any air-purifying,‡ full-facepiece respirator (gas mask) with a chin-style or front- or back-mounted organic vapor canister, or Any appropriate escape-type, self-contained breathing apparatus

*Only NIOSH/MSHA-approved equipment shall be used.
†If eye irritation occurs, a respirator equipped with full facepiece, helmet, or hood shall be used.
‡Air-purifying respirators are used for escape only because EGEE does not have good odor-warning properties.

Table 1-3.—NIOSH-recommended respiratory protection for workers exposed to EGEEA

Condition	Minimum respiratory protection*
5.0 ppm or less (10 × REL)	Any air-purifying respirator† equipped with organic vapor cartridges,‡ or
	Any supplied-air respirator equipped with a half-mask‡
12.5 ppm or less (25 × REL)	Any supplied-air respirator operated in a continuous flow mode,‡ or
	Any powered, air-purifying respirator† equipped with a loose-fitting hood or helmet and an organic vapor cartridge or canister
25 ppm or less (50 × REL)	Any powered, air-purifying respirator† equipped with a tight-fitting facepiece and organic vapor cartridges, or
	Any air-purifying, full-facepiece respirator† equipped with organic vapor cartridges or canisters, or
	Any supplied-air respirator with a full facepiece, or
	Any self-contained breathing apparatus with a full facepiece
500 ppm or less (1,000 × REL)	Any supplied-air respirator equipped with a half-mask‡ and operated in a pressure-demand or other positive-pressure mode
1,000 ppm or less (2,000 × REL)	Any supplied-air respirator equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode
Greater than 1,000 ppm	Any self-contained breathing apparatus equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode, or
	Any supplied-air respirator equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode in combination with an auxiliary self-contained breathing apparatus operated in a pressure-demand or other positive-pressure mode
Fire fighting	Any self-contained breathing apparatus equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode
Escape	Any air-purifying, full-facepiece respirator† (gas mask) with a chin-style or front- or back-mounted organic vapor canister, or
	Any appropriate escape-type, self-contained breathing apparatus

*Only NIOSH/MSHA-approved equipment shall be used.
†Air-purifyiing respirators should be used with EGEEA (which has good odor-warning properties) only when the other glycol ethers (which have poor odor-warning properties) are not present in the workplace.
‡If eye irritation occurs, a respirator equipped with a full facepiece, helmet, or hood shall be used.

4. Respirators shall be regularly cleaned and disinfected.

5. Respirators shall be stored in a convenient, clean, and sanitary location.

6. Respirators used routinely shall be inspected during cleaning. Worn or deteriorated parts shall be replaced. Respirators for emergency use (e.g., self-contained devices) shall be thoroughly inspected at least once a month and after each use.

7. The respiratory protection program shall be regularly evaluated by the employer to determine its continued effectiveness.

8. Additional information about the selection, maintenance, and use of respirators can be found in the *NIOSH Respirator Decision Logic* [NIOSH 1987b] and the *NIOSH Guide to Industrial Respiratory Protection* [NIOSH 1987a].

SECTION 1.6 INFORMING WORKERS ABOUT THE HAZARDS OF GLYCOL ETHERS

1.6.1 Hazard Communication

If workers have the potential for dermal exposure or are assigned to areas where airborne exposures to EGME, EGEE, EGMEA, and EGEEA are one-half or more of the REL, they shall be kept informed of the hazards, relevant signs and symptoms of toxicity, and proper conditions and precautions for the safe use and handling of these glycol ethers. Workers shall be made aware of possible reproductive, developmental, and hematologic effects of exposure to these glycol ethers.

The employer shall notify the worker when exposure exceeds the REL in the work area to which he is assigned.

1.6.2 Training

The employer shall institute a continuing education program conducted by persons qualified by experience or training in occupational safety and health. The program shall ensure that all workers exposed to EGME, EGEE, or their acetates have current knowledge of glycol ether hazards, proper maintenance, cleanup methods, and proper use of protective clothing and equipment, including respirators. The instructional program shall include oral and written descriptions of the environmental and medical monitoring programs and of their advantages to the worker. The employer shall maintain a written plan of these training and monitoring programs. In addition, employers shall follow the OSHA regulations in 29 CFR 1910.1200, Hazard Communication.

Workers shall also be instructed about their responsibilities for following proper work practices and sanitation procedures to help protect their health and provide for their safety and that of their fellow workers.

All workers in areas where exposure to EGME, EGEE, or their acetates may occur during spills or emergencies shall be trained in proper emergency and evacuation procedures.

1.6.3 File of Written Hazard Communication

Required information shall be recorded on the material safety data sheet (see example in Appendix D) or on a similar OSHA form that describes the relevant toxic, physical, and chemical properties of the glycol ethers and mixtures of glycol ethers that are used or otherwise handled in the workplace. This information shall be kept on file and shall be readily available to workers for examination and copying.

SECTION 1.7 ENGINEERING CONTROLS AND WORK PRACTICES

1.7.1 Engineering Controls

Engineering controls shall be used as needed to maintain exposure to airborne glycol ethers within the limits prescribed in Chapter 1.

1.7.1.1 Local Exhaust Ventilation

Local exhaust ventilation may be effective when used alone or in combination with process enclosure. When a local exhaust ventilation system is used, it shall be designed and operated to prevent accumulation or recirculation of airborne glycol ethers in the workplace. Exhaust ventilation systems discharging to outside air shall conform with applicable local, State, and Federal air pollution regulations and shall not constitute a hazard to workers or to the general population. Before maintenance work on control equipment begins, the generation of airborne glycol ethers shall be eliminated to the greatest extent feasible.

1.7.1.2 Maintaining Design Airflow

Enclosures, exhaust hoods, and ductwork shall be kept in good repair to maintain designed airflows. Measurements such as capture velocity, duct velocity, or static pressure shall be made at least semiannually, and preferably monthly, to demonstrate the effectiveness (quantitatively, the ability of the control system to maintain exposures below the REL) of the mechanical ventilation system. NIOSH recommends the use of continuous airflow indicators such as water or oil manometers marked to indicate acceptable airflow. A record shall be kept showing design airflow and the results of all airflow measurements. Measurements of the effectiveness of the system in controlling exposures shall also be made as soon as possible after any change in production, process, or control devices that may increase airborne concentrations of EGME, EGEE, and their acetates.

1.7.1.3 Forced-draft Ventilation

Forced-draft ventilation systems shall be equipped with remote manual controls and should be designed to shut off automatically in the event of a fire.

1.7.2 General Work Practices

- Operating instructions for all equipment shall be developed and posted where EGME, EGEE, and their acetates are handled or used.
- Transportation, use, and disposal of these glycol ethers shall comply with all applicable local, State, and Federal regulations.
- These glycol ethers shall be stored in tightly closed containers and in well-ventilated areas.
- Containers shall be moved only with the proper equipment and shall be secured to prevent loss of control or dropping during transport.
- Storage facilities shall be designed to prevent contamination of workroom air and to contain spills completely within surrounding dikes.
- Ventilation switches and emergency respiratory equipment shall be located outside storage areas in readily accessible locations.
- Process valves and pumps shall be readily accessible and shall not be located in pits or congested areas.
- Glycol ether containers and systems shall be handled and opened with care. Approved protective clothing and equipment as specified in Section 1.5 shall be worn by workers who open, connect, and disconnect glycol ether containers and systems. Adequate ventilation shall be provided to minimize exposures of such workers to airborne glycol ethers.
- Glycol ether storage equipment and systems shall be inspected daily for signs of leakage. All equipment, including valves, fittings, and connections, shall be checked for leaks immediately after glycol ethers are introduced therein.
- When a leak is found, it shall be repaired promptly. Work shall resume normally only after necessary repair or replacement has been completed and the area has been well ventilated.

1.7.3 Confined or Enclosed Spaces

- A permit system shall be used to control entry into confined or enclosed spaces holding containers of glycol ethers (e.g., tanks, pits, tank cars, and process vessels) where egress is limited. Permits shall be signed by an authorized representative of the employer and shall certify that preparation of the confined space, precautionary measures, and personal protective equipment are adequate and that precautions have been taken to ensure that prescribed procedures will be followed.
- Confined spaces that hold containers of EGME, EGEE, and their acetates shall be thoroughly ventilated, inspected, and tested for oxygen deficiency and for airborne concentrations of these glycol ethers. Every effort shall be made to prevent the

inadvertent release of hazardous amounts of these glycol ethers into confined spaces in which work is in progress. Glycol ether supply lines shall be disconnected or blocked off before such work begins.

- No worker shall enter a confined space holding containers of glycol ethers without an entry large enough to admit a worker wearing a safety harness, lifeline, and appropriate personal protective equipment as specified in Section 1.5.
- Confined spaces shall be ventilated while work is in progress to keep the concentration of glycol ethers below the RELs, to keep the concentration of other contaminants below toxic or dangerous levels, and to prevent oxygen deficiency.
- If the concentrations of these glycol ethers in the confined space exceed the RELs, respiratory protective equipment is required for entry.
- Anyone entering a confined space shall be observed from the outside by another properly trained and protected worker. An additional supplied-air or self-contained breathing apparatus with safety harness and lifeline shall be located outside the confined space for emergency use. The person entering the confined space shall maintain continuous communication with the standby worker.

1.7.4 Emergency Procedures

Emergency plans and procedures shall be developed for all work areas where there is a potential for exposure to EGME, EGEE, and their acetates. These plans and procedures shall include those specified below and any others considered appropriate for a specific operation or process. Workers shall be instructed in the effective implementation of these plans and procedures.

- The following steps shall be taken in the event of a leak or spill of these glycol ethers:
  - — All nonessential personnel shall be evacuated from the leak or spill area.
  - — Persons not wearing the appropriate protective equipment and clothing shall be restricted from the leak or spill area until cleanup has been completed.
  - — All ignition sources shall be removed.
  - — The area where the leak or spill occurs shall be adequately ventilated to prevent the accumulation of vapor.
  - — EGME, EGEE, EGMEA and EGEEA shall be contained and absorbed with vermiculite, sand, paper towels, or equivalent materials.
  - — Small quantities of absorbed material shall be placed under a fume hood and sufficient time shall be allowed for the liquid to evaporate and for the vapors to clear the ductwork in the hood.

— Large quantities of absorbed material shall be burned in a suitable combustion chamber.

— Absorbed materials shall be disposed of as hazardous waste.

— The spill area shall be cleaned with water.

- Only personnel trained in the emergency procedures and protected against the attendant glycol ether hazards shall clean up spills and control and repair leaks.
- Personnel entering the spill or leak area shall be furnished with appropriate personal protective clothing and equipment. Other personnel shall be prohibited from entering the area.
- Safety showers, eyewash fountains, and washroom facilities shall be provided, maintained in working condition, and made readily accessible to workers in all areas where skin or eye contact with EGME, EGEE, EGMEA, or EGEEA is likely. If one of these glycol ethers is splashed or spilled on a worker, contaminated clothing shall be removed promptly, and the skin shall be washed thoroughly with soap and water. Eyes splashed by these glycol ethers shall be irrigated immediately with a copious flow of water for 15 min. If irritation persists, the worker should seek medical attention.

1.7.5 Storage

EGME, EGEE, and their acetates shall be stored in cool, well-ventilated areas and kept away from acids, bases, and oxidizing agents.

1.7.6 Waste Disposal

All waste material shall be securely packaged in double bags, labeled, and incinerated. The incinerator residue shall be disposed of in a manner consistent with Federal (EPA), State, and local regulations, or it shall be disposed of in a licensed hazardous waste landfill.

1.8 SANITATION AND HYGIENE

1.8.1 Food, Cosmetics, and Tobacco

The following shall be prohibited in areas where EGME, EGEE, EGMEA, or EGEEA is produced or used: the storage, preparation, dispensing, or consumption of food or beverages; the storage or application of cosmetics; and the storage or use of all tobacco products.

1.8.2 Handwashing

The employer shall provide handwashing facilities and encourage workers to use them before eating, smoking, using the toilet, or leaving the worksite.

1.8.3 Laundering

- Protective clothing, equipment, and tools shall be cleaned periodically.
- The employer shall provide for the cleaning, laundering, or disposal of contaminated work clothing and equipment.
- Any person who cleans or launders this work clothing or equipment must be informed by the employer that it may be contaminated with EGME, EGEE, EGMEA, or EGEEA—chemicals that may cause adverse reproductive, developmental, hematologic (blood), and central nervous system (CNS) effects.

1.8.4 Cleanup of Work Area

The work area shall be cleaned at the end of each shift (or more frequently if needed) using vacuum pickup. Collected wastes shall be placed in sealed containers with labels that indicate the contents. Cleanup and disposal shall be conducted in a manner that prevents worker contact with wastes and complies with all applicable Federal, State, and local regulations.

1.8.5 Showering and Changing Facilities

Workers shall be provided with quick-drench shower facilities and with facilities for showering and changing clothes at the end of each workshift.

1.9 RECORDKEEPING

1.9.1 Exposure Monitoring

The employer shall establish and maintain an accurate record of all exposure measurements required in Section 1.2. These records shall include the name of the worker being monitored, social security number, duties performed and job locations, dates and times of measurements, sampling and analytical methods used, type of personal protection used (if any), and number, duration, and results of samples taken.

1.9.2 Medical Monitoring

The employer shall establish and maintain an accurate record for each worker subject to the medical monitoring specified in Section 1.3. Pertinent medical records (i.e., the physician's written statement, the results of medical examinations and tests, medical complaints, reports of skin exposure, etc.) shall be retained in the medical files of all workers subject to airborne concentrations of EGME, EGEE, EGMEA, or EGEEA in the workplace at or above one-half the REL. Copies of applicable environmental monitoring data shall also be included in the worker's medical file.

1.9.3 Record Retention

In accordance with the requirements of 29 CFR 1910.20(d) (Preservation of Records), the employer shall retain the records described in Sections 1.2, 1.3, and 1.6 for at least the following periods:

- 30 years for exposure monitoring records, and
- the duration of employment plus 30 years for medical surveillance records

1.9.4 Availability of Records

- In accordance with 29 CFR 1910.20 (Access to Employee Exposure and Medical Records), the employer shall allow examination and copying of exposure monitoring records by the subject worker, the former worker, or anyone having the specific written consent of the subject or former worker.
- Any medical records required by this recommended standard shall be provided upon request for examination and copying to the subject worker, the former worker, or anyone having the specific written consent of the subject or former worker.

1.9.5 Transfer of Records

If the employer ceases to do business and no successor is available to receive and retain the records for the prescribed period, the employer shall notify the Director of NIOSH at least 3 months before record disposal and transmit them to the Director if instructed to do so [29 CFR 1910.1028].

2 INTRODUCTION

2.1 PURPOSE

This document presents the criteria and recommended standards necessary to prevent health impairment from exposure to ethylene glycol monomethyl ether (EGME), ethylene glycol monomethyl ether acetate (EGMEA), ethylene glycol monoethyl ether (EGEE), and ethylene glycol monoethyl ether acetate (EGEEA). The document was developed in accordance with Section 20(a)(3) of the Occupational Safety and Health (OSH) Act of 1970. In this Act, the National Institute for Occupational Safety and Health (NIOSH) is charged with developing criteria for toxic materials and harmful physical agents, and describing exposure concentrations at which no worker will suffer impaired health or functional capacities or diminished life expectancy as a result of work experience. This document also responds to Section 2.2(c)(1) of the OSH Act, which authorizes NIOSH to develop and establish recommended occupational safety and health standards.

NIOSH has formalized a system for developing criteria on which to base standards for ensuring the health and safety of workers exposed to hazardous chemical and physical agents. Simple compliance with these standards is not the only goal. The criteria and recommended standards are intended to help management and labor develop better engineering controls and more healthful work practices.

Recommended standards for EGEE, EGME, EGEEA, and EGMEA apply only to workplace exposures arising from the processing, manufacturing, handling, and use of these glycol ethers. The recommendations are not designed for the population at large, and any extrapolation beyond the occupational environment may not be warranted. The recommended standards are intended to protect workers from the acute and chronic effects of EGEE, EGME, EGEEA, and EGMEA. Exposure concentrations are measurable by techniques that are valid, reproducible, and available to industry and government agencies.

2.2 SCOPE

The information in this document assessed the hazards associated with occupational exposure to EGEE, EGME, EGEEA, and EGMEA. Chapter 1 presents the recommended standards and describes their requirements. Chapter 3 gives information about the chemical and physical properties of EGEE, EGME, EGEEA, and EGMEA, production methods, uses, and the extent of worker exposure. Chapter 4 discusses and summarizes the effects of exposure to these glycol ethers on humans and animals. Subsequent chapters describe environmental sampling and analytical methods, medical monitoring, biological monitor-

ing, existing occupational health standards, and a correlation of exposure and effect. In addition, methods for worker protection are discussed, including suggested work practices, engineering controls, personal protective clothing and equipment, and exposure monitoring and recordkeeping.

3 PROPERTIES, PRODUCTION, AND POTENTIAL FOR EXPOSURE

3.1 CHEMICAL AND PHYSICAL PROPERTIES

EGME, EGMEA, EGEE, and EGEEA are part of a family of ethylene glycol monoalkyl ethers represented by the general formula $R_1OCH_2CH_2OR_2$ where R_1 represents the alkyl moiety and R_2 either H or acetate. In this document, unless otherwise specified, the term "glycol ethers" will refer to EGME, EGEE, and their acetates.

EGME (ethylene glycol monomethyl ether), also known as methyl Cellosolve®, 2-methoxyethanol (2-ME), or Jeffersol EM® [NIOSH 1987c], is an organic compound with the chemical formula $CH_3OCH_2CH_2OH$. It is a colorless liquid with a mild, nonresidual odor; the odor threshold is 2.3 ppm [Amoore and Hautala 1983]. EGME is miscible with water and many organic solvents.

EGMEA (ethylene glycol monomethyl ether acetate), also known as methyl Cellosolve® acetate or 2-methoxyethyl acetate (2-MEA), is the acetate ester of EGME with the chemical formula $CH_3OCH_2CH_2OCOCH_3$ and is prepared by esterifying EGME with acetic acid. It is a colorless liquid with a mild, ether-like odor; no data are available on the odor threshold of EGMEA. It is miscible in water and with many organic solvents.

EGEE (ethylene glycol monoethyl ether), also known as Cellosolve®, 2-ethoxyethanol (2-EE), or Jeffersol EE® [NIOSH 1987c], is an organic compound with the chemical formula $C_2H_5OCH_2CH_2OH$. It is a colorless liquid with a sweetish odor; the odor threshold is 2.7 ppm [Amoore and Hautala 1983]. EGEE is miscible with water and many organic solvents.

EGEEA (ethylene glycol monoethyl ether acetate), the acetate ester of EGEE, is also known as Cellosolve® acetate, 2-ethoxyethyl acetate (2-EEA), and has the chemical formula $C_2H_5OCH_2CH_2OCOCH_3$. It is a colorless liquid with a mild, nonresidual odor; the odor threshold is 0.056 ppm [Amoore and Hautala 1983]. EGEEA has a low solubility in water, but is miscible with many organic solvents.

Other chemical and physical properties are listed in Table 3-1.

3.2 PRODUCTION METHODS AND USES

The ethylene glycol monoalkyl ethers EGME and EGEE are usually produced by a reaction of ethylene oxide with methyl or ethyl alcohol, but may also be made by the direct alkylation

Table 3-1.—Chemical and physical properties of EGME, EGEE, and their acetates*

Property	EGME	EGMEA	EGEE	EGEEA
RTECS† number	KL5775000	KL5950000	KK8050000	KK8225000
CAS‡ number	109-86-4	110-49-6	110-80-5	111-15-9
Molecular formula	$C_3H_8O_2$	$C_5H_{10}O_3$	$C_4H_{10}O_2$	$C_6H_{12}O_3$
Molecular weight	76.1	118.1	90.1	132.2
Specific gravity 25°/4°C	0.962	1.007	0.926	0.975
Evaporation rate (butyl acetate = 1.00)	0.62	0.30	0.41	0.2
Boiling point (°C)	124.2	144.5	135.0	156.3
Freezing point (°C)	−85	−65.1	−100	−61.7
Vapor pressure (mm Hg 25°C)	9.7	2.0-3.7	5.75	2.8
Refractive index	1.400	1.402	1.406	1.406
Flash point (°C), closed cup	39	49	43	52
Autoignition temperature (°C)	285	392	235	379
Flammability limits (vol. % in air)	1.8-14.0	1.5-12.3	1.70-15.6	1.7
Water solubility (% by weight)	Miscible	Miscible	Miscible	23
Vapor density (air = 1)	2.6	4.1	3.1	4.6
ppm in saturated air (25°C)	12,800	2,600-4,900	7,600	3,700
mg/m^3 at 25°C, 760 mm Hg = 1 ppm	3.11	4.83	3.69	5.41
ppm at 25°C, 760 mm Hg = 1 mg/m^3	0.32	0.21	0.27	0.19

*Adapted from Rowe and Wolf [1982], UCC [1983], NFPA [1987].
†Registry of Toxic Effects of Chemical Substances [NIOSH 1987c].
‡Chemical Abstract Services.

of ethylene glycol with an alkylating agent such as dimethyl or diethyl sulfate [Rowe and Wolf 1982]. Temperature, pressure, reactant molar ratios, and catalysts are selected to give the product mix desired. Ethylene glycol monoalkyl ethers are not formed as pure compounds, but must be separated from the diethers of diethylene glycol, triethylene glycol, and the higher glycols. Ethylene glycol monoalkyl ether acetates are prepared by esterifying the particular glycol ether with acetic acid, acetic acid anhydride, or acetic acid chloride.

Glycol ethers and their acetates are widely distributed and have been used commercially for more than 50 years. Table 3-2 presents production figures for these glycol ethers. The most important single use of EGME is as a jet fuel deicer [Meridian Research, Inc. 1987]. Because military jets lack the inline deicers found on commercial jets, all JP-4 jet fuel contains 0.1% to 0.2% EGME as a deicing agent. JP-5, a new jet fuel, uses 0.15% diethylene glycol monomethyl ether (DEGME) in place of EGME as a deicer [Meridian Research, Inc. 1987]. EGME is also used in the manufacture of printed circuit boards, as an intermediate in the manufacture of plasticizers, in inks and coatings, and in photography and dyeing applications. EGMEA is a low production chemical that is used as an intermediate for plasticizers and also in specialty solvent applications. Approximately 50% of EGEE produced is utilized as a chemical intermediate for EGEEA production; it is also used as a solvent for surface coatings (especially those based on epoxy resins) and as a solvent in cleaning and printing ink formulations. EGEEA is used as a solvent in coating applications for automobiles, coils, machinery and equipment, and metal furniture and appliances.

3.3 PROCESS AND WORKER JOB DESCRIPTIONS

The usefulness of glycol ethers and their acetate derivatives can be attributed to their physical properties, particularly their miscibility or high solubility in water and other organic solvents, and their low vapor pressures. These properties allow them to serve a number of functions in a variety of products. The following information was obtained during surveys conducted in various industries to determine occupational exposures to glycol ethers [Cal OSHA 1983; Meridian Research, Inc. 1987].

3.3.1 Paints and Coatings

Although frequently comprising less than 10% of the final product, glycol ethers serve a variety of important functions in paints and coatings. One function is as a solvent to keep

Table 3-2.—U.S. production of EGME, EGEE, and their acetates*

Compound	Production (lb)
EGME	79,849,000
EGMEA	1,000,000
EGEE	121,808,000
EGEEA	84,028,000

*Sources: TSCAPP [1977], Industrial Economics, Inc. [1985], and USITC [1986].

the various paint components in solution. Latex coatings contain glycol ethers or their acetate derivatives to enhance the coalescing properties of the product when applied. By slowing the evaporation rate, glycol ethers reduce moisture condensation or "blush." They also improve the penetration and bonding qualities of paints and coatings. Specialty products, such as aircraft or electrostatic paints, may contain 18% to 35% glycol ethers [Cal OSHA 1983].

The manufacture of paints and coatings is a batch process. Components are added manually or through a closed piping system to the mixing tank. Because glycol ethers generally constitute a small percentage of the total formulation, they are often added manually. After mixing, the product is packaged according to customer specifications. Maximum exposures occur during weighing, mixing, and filling operations. During the compounding and mixing of a batch, exposures to the glycol ethers are low, mainly due to low vapor pressures and short exposure times. If ventilation is required to control other more volatile components, glycol ether exposures will be coincidentally reduced. During filling operations, exposures depend on whether the process is manual or automated and vary with the size of the containers [Cal OSHA 1983].

A variety of industries use paints and coatings, but as previously noted, these products usually contain a small percentage of glycol ethers (i.e., less than 10%). Lacquer containing less than 1% glycol ethers is used to coat wood products. However, electrostatic paints used in a spraying process for metal parts may contain 20% to 30% glycol ethers. Glycol ethers are also used in the manufacture of coated fabrics. These fabrics pass through a dip pan to pick up the coating and then rise through a ventilated drying tower [Cal OSHA 1983].

The use of EGEE and EGME in protective coatings declined by more than 80% and 50%, respectively, between 1980 and 1984. Reformulation has virtually eliminated the use of EGEE, EGME, EGEEA, and EGMEA in consumer paints [Meridian Research, Inc. 1987].

3.3.2 Inks

Printing inks and solutions are formulated in batch-type operations and hence exposures are similar to those found in the manufacture of paints and coatings. Glycol ethers modify the drying rate, viscosity, fluidity, and penetrative ability of inks. Flexographic inks, such as alcohol-dilutable inks, acrylic inks, and water-based inks, contain glycol ethers in low concentrations, usually 5% to 10%. Ballpoint and marker inks may contain as much as 40% glycol ethers. Glycol ethers are also found in printing chemicals (e.g., "fountain solutions").

Printing press operators can receive exposure to glycol ethers through inhalation as well as skin contact because of their intimate contact with printing materials and machinery. Glycol ethers are used in several phases of printing and silkscreening operations. A few ounces used as a retarding agent may be added directly to the ink tray or pan, which is often left uncovered. Press and plate cleaning solvents may also contain glycol ethers. The most extensive dermal contact occurs when trays and other parts of the press are cleaned [Cal OSHA 1983].

In recent years, ink companies have reformulated away from glycol ethers. The use of EGEE in printing inks declined by 60% between 1977 and 1984 [Meridian Research, Inc. 1987].

3.3.3 Cleaners and Cleaning Solvents

Cleaning agents that contain glycol ethers are spot removers, carburetor cleaners, metal cleaners, and glass cleaners. In these products, glycol ethers function as surface active agents, enhancing the penetration of the product, clarifying the appearance, and in glass cleaners, increasing the viscosity. The percentage of glycol ethers in these products is less than 5% [Cal OSHA 1983].

3.4 NUMBER OF WORKERS POTENTIALLY EXPOSED

Based on information from the National Occupational Exposure Survey (NOES) [NIOSH 1983c], the estimated number of workers potentially exposed to glycol ethers in the workplace during the period 1981 to 1983 is as shown in Table 3-3. Among industries labeled by the 4-digit Standard Industrial Code (SIC), 34 were identified as having workers potentially exposed to EGEE, 26 to EGEEA, 24 to EGME, and 10 to EGMEA. NOES identified 102 occupations in which workers were potentially exposed to EGEE, 99 to EGEEA, 80 to EGME, and 27 to EGMEA. Table 3-4 presents the six industries and six occupations with the most workers potentially exposed to EGEE, EGME, and their acetates.

Appendix C presents representative information about the occurrence of airborne EGEE, EGME, and their acetates in the workplace.

Table 3-3.—Estimated number of U.S. workers potentially exposed to EGME, EGEE, and their acetates*

Compound	Number of workers
EGME	130,608
EGMEA	9,892
EGEE	247,691
EGEEA	244,639

*Source: NIOSH [1983c].

Table 3–4.—Six industries and six occupations with the most workers potentially exposed to EGEE, EGME, and their acetates*

Compound and industry	Workers exposed: Number	Workers exposed: % of total
EGEE:†		
Health services	40,893	16.5
Business services	26,476	10.7
Printing and publishing	23,634	9.5
Instruments and related products	19,419	7.8
Rubber and miscellaneous plastic products	16,781	6.8
Chemicals and allied products	14,251	5.8
EGEEA:‡		
Printing and publishing	37,431	15.3
Transportation equipment	30,256	12.4
Transportation by air	16,143	6.6
Special trade contractors	11,934	4.9
Electric and electronic equipment	11,892	4.8
Machinery, except electrical	11,702	4.7
EGME:§		
Chemicals and allied products	29,014	22.2
Business services	22,537	17.3
Printing and publishing	16,619	12.7
Machinery, except electrical	11,047	8.5
Fabricated metal products	10,697	8.2
Paper and allied products	6,934	5.3

Compound and occupation	Workers exposed: Number	Workers exposed: % of total
EGEE:†		
Janitors and cleaners	40,086	16.2
Printing machine operators	19,321	7.8
Assemblers	15,747	6.4
Miscellaneous machine operators, N.E.C.	11,513	4.6
Registered nurses	10,988	4.4
Engineers, N.E.C.	8,805	3.6
EGEEA:‡		
Painting and paint spraying machine operator	27,924	11.4
Printing machine operators	23,191	9.5
Assemblers	17,412	7.1
Laborers, except construction	9,823	4.1
Machine operators, not specified	9,783	4.0
Hand packers and packagers	9,190	3.8
EGME:§		
Assemblers	21,844	16.7
Janitors and cleaners	20,379	15.9
Printing machine operators	10,874	8.3
Machinists	7,325	5.6
Typesetters and compositors	5,416	4.1
Chemists, except biochemists	5,267	4.0

(Continued)

See footnotes at end of table.

Table 3–4 (Continued).—Six industries and six occupations with the most workers potentially exposed to EGEE, EGME, and their acetates

Compound and industry	Workers exposed	
	Number	% of total
EGMEA:**		
Fabricated metal products	3,142	31.8
Electric and electronic equipment	1,743	17.6
Miscellaneous manufacturing industries	1,605	16.2
Chemicals and allied products	1,276	12.9
Machinery, except electrical	938	9.5
Rubber and miscellaneous plastics products	465	4.7

Compound and occupation	Workers exposed	
	Number	% of total
EGMEA:**		
Assemblers	2,775	28.1
Janitors and cleaners	1,160	11.7
Packaging and filling machine operators	783	7.9
Metal plating machine operators	638	6.4
Miscellaneous machine operators, N.E.C.	592	6.0
Hand engraving and printing	526	5.3

*Source: NIOSH [1983b].
†Total workers exposed to EGEE = 247,691.
‡Total workers exposed to EGEEA = 244,639.
§Total workers exposed to EGME = 130,608.
**Total workers exposed to EGMEA = 9,892.

4 EFFECTS OF EXPOSURE

4.1 EFFECTS ON HUMANS

4.1.1 Case Studies and Miscellaneous Reports

The first known case study involving occupational exposure to EGME was reported in 1936 [Donley 1936]. A female worker was employed in a shirt factory where she "fused" collars by dipping them into a solvent mixture, followed by application of pressure to dry and stiffen them. The solvent mixture used in the collar fusing contained EGME (<3%), dimethyl phthalate (<3%), isopropyl alcohol (74%), and water (20%). The patient had worked at this job for six months without ventilation or respiratory protection when she was admitted to the hospital with symptoms of encephalopathy (i.e., headache, drowsiness, forgetfulness, and general apathy), signs of respiratory infection with coughing and sneezing, and blurred vision. Blood tests for erythrocytes, leukocytes, and hemoglobin were within normal ranges. Her diagnosis included psychosis, encephalopathy, acute rhinitis (inflammation of the nasal mucosa), bronchitis, and phlegmasia alba dolens (extreme edematous swelling of the leg) caused by occupational exposure to vapors from the solvent. An inquiry three months after the patient's discharge from the hospital revealed that she had fully recovered.

Parsons and Parsons [1938] reported case studies of two brothers, ages 22 and 20, who fused collars in the "dipping room" of a New York shirt factory. Rubber gloves were worn during this operation. The dipping fluid at the shirt factory contained two substances, EGME and "Solox" which contained ethyl alcohol (90%), methyl alcohol (4.4%), ethyl acetate (4.7%), and petroleum naphtha (0.9%). Both men were admitted to the hospital with symptoms of toxic encephalopathy (including personality change, dizziness, sleepiness, and apathy), nausea, weakness, burning eyes, and headache. An examination in the hospital revealed moderately severe anemia with leukopenia and lymphocytosis. A neurologic examination revealed general hypertonicity of all skeletal muscles, transitory right ankle clonus, moderate ataxia, and persistent dilation of pupils. The patients completely recovered one month after they were removed from exposure and treated for anemia. When followup blood tests were conducted about one year later the older brother, who was exposed to the dipping fluid for about one year, had an abnormal differential count (i.e., a relative lymphocytosis). The younger brother, who was exposed for only three months, had a normal differential count.

All ten workers in a small printing shop in Germany experienced discomfort when a printing press that used aniline-dye-based inks containing EGME was placed in operation [Groetschel and Schuermann 1959]. After one month of exposure, the workers experienced vomiting, intoxication, and deterioration of vision, hearing, and sense of taste. Attending physicians

also reported exhaustion, slowed reactions, irritability, vertigo, and disturbance of sleep patterns in the workers. Anemia and lymphopenia were found in the one individual whose blood was tested.

Zavon [1963] described case histories for five workers exposed to EGME in the printing department of a plant where plastic materials were made. EGME was used as a cleaning agent for the printing machines and the floor, and as a solvent in the printing ink, which also contained diethylene glycol monomethyl ether (DEGME). Few of the workers wore gloves while working and they were not required to wear clean work clothes or wash their hands before leaving work. Each worker saw a different private physician when symptoms developed and Zavon [1963] summarized the case reports. All five workers had worked in the printing department for the five months that EGME had been in use. The signs and symptoms reported were consistent with those reported previously in workers exposed to EGME, including drowsiness, personality change, memory loss, ataxic gait, tremors, slurred speech, hearing loss, loss of appetite, and apathy. All workers had low erythrocyte (RBC) counts and low hemoglobin (Hb) values. White blood cell (WBC) counts ranged from low to high. Two workers had abnormal differential counts and a third worker's differential count was slightly outside normal limits, but his bone marrow smear showed a hypocellular marrow with a decrease in the percentage of erythroid elements. Breathing zone samples taken under simulated conditions using EGME to clean the floor and equipment ranged from 61 to 3,960 ppm. Process changes and safe-handling requirements resulted in a reduction of EGME concentrations to below 40 ppm and the elimination of any reported health effects.

Nitter-Hauge [1970] reported the accidental poisoning of two men who each ingested about 0.1 liter of pure EGME that they believed was ethyl alcohol. They were admitted to the hospital with general weakness, disorientation, muscular restlessness, nausea, and vomiting. Clinical signs and symptoms appeared from 8 to 18 hr after ingestion and included cerebral confusion, pronounced hyperventilation, and profound metabolic acidosis (reduced alkali reserve in the blood and body fluids). Moderate renal failure developed in the older of the patients, along with a marked oxaluria (abnormally large amounts of oxalates in the urine). Both patients were treated intravenously with sodium bicarbonate and ethyl alcohol, and fully recovered over a period of approximately 4 weeks. The author [Nitter-Hauge 1970] concluded from this information that EGME hydrolyzed to methanol and ethylene glycol, which are metabolized to formic acid and oxalic acid, respectively.

Dermal absorption of EGME has caused a range of adverse health effects similar to those produced by the inhalation or ingestion of it [Ohi and Wegman 1978]. Two male workers were employed in an electroplating operation where they washed equipment by hand without protective gloves. EGME was substituted for acetone in the solvent bath. Air samples collected during the washing operation averaged 8 ppm; no estimate was made of the magnitude of skin absorption. The first worker, who was 48 years old, was hospitalized following 6 months exposure to EGME in the workplace. His symptoms included confusion, lethargy, sleepiness, impaired hearing, anorexia, weight loss, and personality change. On admission to the hospital, he had tremors of both upper extremities and reduced RBC and WBC counts. Bone marrow aspiration showed marrow depression consistent with a marrow toxin. His condition was diagnosed as metabolic encephalopathy and pancytopenia

(a reduction in the numbers of all formed elements of blood). Recovery was slow but uncomplicated, and within several weeks his blood count returned to normal. The second worker was a 45-year-old man who was admitted with similar symptoms following one month of using EGME on the job. His neurologic examination revealed poor concentration, orientation, reasoning, and memory. In addition, he had bone marrow depression. His symptoms disappeared within one week [Ohi and Wegman 1978].

Cohen [1984] described subacute hematopoietic effects in a male worker exposed to EGME in the microfilm production industry. The subject was a 32-year-old microfilm coating and mixing operator. His job entailed mixing chemicals and often standing directly over open 1,500-gallon kettles that contained 33% EGME. Methyl ethyl ketone (MEK) and propylene glycol monomethyl ether (PGME) were also present in small quantities. EGME was also used as a solvent in the manual cleaning of the kettles, usually done without gloves. Breathing zone samples revealed time-weighted average (TWA) concentrations of 18 to 58 ppm EGME (average, 35 ppm), 1 to 5 ppm MEK, and 4 to 13 ppm PGME. The worker had been employed for less than one year when signs and symptoms of EGME exposure appeared. His WBC and RBC counts, Hb, hematocrit (Hct), and platelets dropped to abnormally low levels. He also slept more, gained weight, had a decrease in appetite, felt fatigued, and was apathetic. The worker was removed from skin and inhalation exposure to EGME after 20 months on the job. Blood counts 1 and 3 months later revealed a return to normal limits. This case illustrates the development of reversible macrocytic anemia and subjective central nervous system (CNS) complaints (i.e., increased sleep needs, decreased appetite, fatigue, and apathy).

Bolt and Golka [1990] reported the occurrence of hypospadias at birth in two young boys whose mother had been occupationally exposed to EGMEA during her pregnancies. The woman had worked since 1974 in an industrial laboratory that produced lacquers and enameled wire. During her first pregnancy in 1980 to 1981, she cleaned the glassware 4 hrs a day using EGMEA as a solvent. Gloves were usually, but not always, worn. She cleaned the surfaces of laboratory desks by spreading EGMEA on a cloth and rubbing the desk surfaces with it. This was frequently done without the use of gloves. During her second pregnancy in 1983 to 1984, she cleaned the glassware for about an hour a day, generally under a laboratory hood. As before, EGMEA was used to clean the surfaces in the laboratory.

In 1981, the woman delivered a boy of normal birth weight with the following malformations: perineal hypospadia, micropenis, and pronounced bifid type of scrotum. The sex could not be determined without chromosomal analysis. Analysis of the chromosomes did reveal a normal male karyotype. Clinical examinations showed no further malformations. In 1984, the woman delivered a boy of normal birth weight with penile hypospadia and a bifid type of scrotum. Chromosomal analysis revealed a normal male karyotype.

Both children underwent surgery in the following years. The perineal and the penile hypospadias were corrected, chordee was removed in both children, and the undescended testes were removed to the scrotum. The older child was treated with chronic gonadotrophin, which led to normal-sized testes.

The authors stated that the risk of isolated hypospadia was between 1 in 300 and 1 in 1,800, while the risk for a boy whose brother has hypospadia was 1 in 24. They indicated that both the family history and medical examinations showed no overt risks other than the pronounced exposure of the mother to EGMEA during fetal development. The authors concluded that the hypospadias were actually caused by exposure to EGMEA.

There is only one case report that describes the effects of EGEE [Fucik 1969]. A 44-year-old woman who mistakenly ingested 40 ml of EGEE experienced adverse effects on the CNS, liver, and kidneys. After ingesting the EGEE, she suffered chest pains and vertigo, and lost consciousness. Upon hospitalization, signs and symptoms of EGEE exposure included restlessness, tachycardia, cyanosis, swelling of the lungs, tonoclonic spasms, and breath that smelled like acetone. Oxygen and chemical therapy were administered; 6 hr later the woman regained consciousness but was confused and markedly agitated. Her urine was positive for protein, acetone, and RBCs; liver enlargement and jaundice developed. After 44 days her condition improved. However, insomnia, fatigue, and paresthesia of the extremities persisted for one year.

4.1.2 Clinical and Industrial Hygiene Studies

4.1.2.1 Greenburg et al. [1938]

Greenburg et al. [1938] described a cross-sectional study of 19 workers exposed to EGME during the manufacture of fused shirt collars at the same factory studied by Parsons and Parsons [1938]. Greenburg et al. undertook this study following reports to the U.S. Department of Labor that two brothers employed in a collar fusing plant were hospitalized with aplastic anemia [Parsons and Parsons 1938]. The Greenburg et al. study included (1) a clinical examination with occupational history and (2) an environmental assessment of the loft area where EGME exposure took place during the collar fusing process. In the fused collar processing area, workers wearing rubber gloves rinsed shirts by hand in large open vats of the solvent containing EGME.

Air sampling was done after improvements were made to the exhaust and ventilation systems. EGME concentrations were 25 ppm with the windows open and 76 ppm with the windows partially closed. The authors stated that previous worker exposures were undoubtedly higher than the concentrations they measured. The occupational histories showed that the duration of exposure for the 19 workers ranged from 1 to 112 weeks prior to the examinations. Four of the 19 were exposed longer than 75 weeks; the other 15 workers were exposed fewer than 15 weeks. Sixteen of the 19 workers were employed in the collar fusing area when the medical examination was conducted.

Two clinical examinations of the exposed workers were conducted about 2 months apart. During the first exam, 11 exposed workers were examined. About 2 months later, 8 of the 11 original workers were reexamined and 8 additional workers were examined for the first time. Social, medical, and occupational histories were taken. Then the workers were given a complete medical examination with special attention to funduscopic tests, capillary

fragility tests, detailed hematologic studies, and neurologic findings. The results were normal for the funduscopic tests, capillary fragility tests, blood pressures, temperatures, pulse rates, and general physical status.

All 19 workers had abnormal hematology results, including low blood platelet counts. Nine of the workers' blood tests showed disturbed production of RBCs (erythropoiesis) including six subnormal RBC counts. The anemias were thought to be caused by a bone marrow toxin rather than hemolysis or peripheral toxicity. All 19 blood tests showed immature neutrophilic granulocytes indicative of bone marrow toxicity. Other results were normal, including Hct, bleeding time, coagulation time, erythrocyte sedimentation rate, and erythrocyte fragility.

Physical examinations of the workers revealed severe neurologic abnormalities. Two workers who were hospitalized for severe anemia and one who filed workman's compensation for multiple neuritis were not included in the physical findings. Four of the remaining 16 workers had symptoms of drowsiness or fatigue and the following neurologic abnormalities: clonus (rapid muscular contractions and relaxations) in one worker, mental retardation in two workers, exaggerated reflexes in four workers, and tremors of the hands in four workers. Four other workers did not complain of any symptoms; however, at examination two of these workers had abnormal reflexes, one had exaggerated knee and ankle reflexes, one had decreased knee jerks, and four had tremors of the hands. The remaining eight workers exhibited no abnormal symptoms.

4.1.2.2 Cook et al. [1982]

Cook et al. [1982] conducted a cross-sectional study of 65 male workers (40 with potential exposure to EGME during its manufacture and packaging) to determine if anemia, leukopenia, or infertility were present, and if these conditions were more prevalent among the exposed workers. The unrestricted, concurrent, nonexposed population consisted of 25 workers from plants where alkanolamines and salicylic acids were produced. In the EGME plant, the chemical was manufactured by a continuous enclosed process along with related products such as EGEE, polyols, polyoxy propylene glycols, brake fluids, butylene oxide, and polyglycols. In a separate packaging and distribution facility, EGME was loaded into drums, tank trucks, or rail cars; although drums were filled automatically, they were capped manually. Because of the potential for skin contact and absorption, continued use of rubber gloves was recommended during sampling and maintenance. There was also potential for exposure to ethylene, propylene, and butylene oxides, chlorobenzenes, and other ethylene glycol ethers. The control population had the potential for exposure to phenol, sodium phenate, potassium hydroxide, ammonia, propylene ethers of ethylene glycol, ethylene oxide, and propylene oxide. Industrial hygiene measurements taken in the production area indicated personal 8-hr TWA exposures of 0.4 ppm EGME or less. TWA air samples collected in the packaging and distribution facility for EGME indicated personal exposures of 5 to 9 ppm EGME and area concentrations of 4 to 20 ppm.

The clinical measures included Hb, WBC, RBC, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCHb), mean cell hemoglobin concentration (MCHC), hormone levels [i.e., luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone] and

sperm counts. Semen samples were available from six EGME-exposed workers and nine controls. Hematology results revealed no anemia or leukopenia in the EGME-exposed workers. No statistically significant differences were found in hematology test results, hormone levels, or sperm counts between the exposed workers and the controls. The investigators suggested that testicular size may have been reduced; however, the decrease in size approached but did not reach statistical significance ($P<0.05$) in either length ($P=0.19$) or width ($P=0.08$).

4.1.2.3 Markel and Moody [1982]

In a Health Hazard Evaluation [Markel and Moody 1982], NIOSH investigators evaluated exposure of workers to surfactant and emulsifier products used in a wet scrubbing system of a newspaper pressroom and reel room. The nonionic surfactant used in the air washer/demisting system was nonylphenoxy polyethylene oxyethanol and contained ethylene oxide and EGME. Although the surfactant was not used per se in the demisting system, it could have been present in pressroom air as a result of aerosolization of the surfactant solutions. Twenty workers were interviewed; half of them were asymptomatic. Five workers reported intermittent runny nose, nasal congestion and/or eye irritation at work. Of these five workers, three had histories of allergies or "sinusitis"; one of the five workers attributed his episodes of burning eyes to exposure to the mist produced by the de-mist system. The remaining five all complained of a "peculiar taste" in the mouth following exposure to the mist system. During splashing or siphoning by mouth of the surfactant solution, two workers noted an anesthetic effect on their lips. One worker experienced progressive ill health over a 10-month period. His symptoms consisted of headaches, fatigue, sores in the mouth, chronic eye irritation, shortness of breath, nausea, vomiting, trembling, and staggering. However, he stated that following termination of his work with the de-mist system, these symptoms abated. Environmental monitoring (five breathing zone and three general area measurements) indicated that the concentrations of EGME ranged from 0.3 to 0.5 ppm for six of the samples and were below the lower limit of detection (0.003 ppm) of the analytical method for the remaining two. The authors concluded that there was no evidence of EGME concentrations exceeding recommended levels and no evidence of ethylene oxide exposure.

4.1.2.4 Boiano [1983]

NIOSH conducted a health hazard evaluation in 1983 to evaluate worker exposure to two solvent cleaners, an image remover, and the paint remover used in a silk screening process [Boiano 1983]. The silk screener using the image remover was monitored for exposure to EGEEA and cyclohexanone, while the worker using the paint remover was monitored for a variety of organic solvents, one of which was EGEEA. Although the workers were primarily exposed by inhalation, they may have also been exposed by skin absorption because personal protective clothing was not always worn. The workers complained of headaches, lethargy, sinus problems, nausea, and heartburn. When they were away from work, their symptoms improved. The silk screener using image remover had TWA exposures to EGEEA ranging from 1.3 to 3.3 ppm, with short-term excursions to 3.8 ppm. The silk screener using paint remover had TWA exposures to EGEEA ranging from 0.5 to 3.9 ppm, with a short-term excursion to 4.0 ppm. Measured airborne exposures thus were

below occupational standards, but absorption through the skin may have contributed to the workers' overall exposure [Boiano 1983].

4.1.2.5 Gunter [1985]

In 1985, NIOSH conducted a health hazard evaluation of production areas at a plant that manufactured solid-state electronic circuits [Gunter 1985]. Soldering, degreasing, and circuit-board coating areas were evaluated. Workers in these areas had previously complained of narcosis, burning eyes, and dermatitis. Personal and area air samples were collected on charcoal tubes and analyzed for EGEE, EGEEA, Freon 113, toluene, MEK, xylene, petroleum distillates, methyl isobutyl ketone (MIBK), and methyl chloroform. Samples were also collected and analyzed for lead, zinc, and toluene diisocyanate (TDI). Six personal air samples taken for EGEE averaged 1.7 ppm; 14 personal air samples for EGEEA averaged 0.15 ppm. Samples taken for lead, zinc, and TDI were found to contain concentrations below even the lowest of the established limits (the NIOSH REL, the OSHA PEL, or the ACGIH TLV®).

4.1.2.6 Ratcliffe et al. [1986]

NIOSH conducted an evaluation for possible adverse effects on testicular function in male workers potentially exposed to EGEE during the preparation of ceramic shells used to cast metal parts [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 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. The comparison group consisted of men who worked elsewhere in the plant and who were not exposed to EGEE. Air samples, most of which were from the breathing zone, were collected. Because the potential for skin exposure existed, spot urine samples were taken and sent frozen to a laboratory to analyze for the presence of ethoxyacetic acid (EAA); blood samples were also drawn and analyzed. An evaluation of semen quality (pH, sperm concentration, and viability, motility, velocity, and morphology) was conducted. Brief examinations of the urogenital tract were also done. In addition, questionnaires were administered to determine personal habits and medical and work histories.

The NIOSH survey showed full-shift, breathing-zone exposures of EGEE ranging from nondetectable to 24 ppm. Collection of general area air samples at two sites revealed higher concentrations of EGEE (10 to 17 ppm) in the investment rooms, which contained open tanks of slurry, than in the mixing and storage rooms (5 to 7 ppm). However, analysis of quality control samples indicated that the measured airborne concentrations could be underestimated; recovery of analyte from field samples was below 100%, and as low as 60%. Analysis of blood samples collected at the end of the work shift from nine EGEE-exposed and four nonexposed workers revealed no detectable levels of EGEE in any of the samples. The concentrations of EAA in the urine of EGEE-exposed workers ranged from 16 to

163 mg/g creatinine for individual voids. No statistical testing was attempted because of the few data points.

A cross-sectional evaluation of semen quality was conducted among 37 men exposed to EGEE and a group of 38 men who were not exposed to EGEE. The average sperm count of the EGEE-exposed group was considerably lower than that of the nonexposed group (113 vs. 154 million per ejaculate, $P<0.05$). The mean sperm concentration of the unexposed group (60 million/ml) and that of the exposed group (48 million/ml) did not differ statistically from each other. It should be noted however, that the average sperm concentration for both groups was considerably lower ($P<0.001$) than the 70 million/ml these investigators had observed in similar studies of other working populations. No differences were observed with respect to other characteristics of semen quality or testicular size. It was concluded from this study that there was a possible effect of EGEE on semen quality.

4.1.2.7 Welch et al. [1988], Sparer et al. [1988], and Welch and Cullen [1988]

The effect of combined EGME and EGEE exposure on the reproductive potential of men who worked in a large shipbuilding facility was recently studied [Welch et al. 1988]. This site was selected for study because of a previous health hazard evaluation [Love and Donohue 1983] in which evidence of glycol ether exposure had been obtained. The shipyard employed 900 painters, 600 of whom were men. The painters were divided into four crews that included the shop men who mixed the paint formulations, interior and exterior painters, and the tank crew that painted interiors of ballast tanks and other confined spaces. The interior painting crew members were involved in a variety of jobs, using spray and brush painting; half-face cartridge respirators were available to these men, but their use was at the discretion of the individual painters. The tank crew applied paint primarily in spray form and wore supplied-air respirators. Cotton gloves were available for use. In the course of a year, many painters rotated from crew to crew. At the completion of a boat's construction, exterior painting was done; often all the painters were assigned to this job for a brief period of time. Prior to painting, exterior painters wearing air-supplied respirators sandblasted the boats. The entire study population for the semen, hematologic, and male reproductive studies consisted of 94 painters and 55 nonexposed controls, but only 73 of the 94 painters and 40 of the 55 nonexposed controls participated in the semen study. Urine was collected for the determination of EAA and methoxyacetic acid (MAA), the principal metabolites of EGEE and EGME (Section 4.2), respectively. At the clinic site, participants filled out questionnaires revealing personal habits and medical and work histories; a medical examination was performed at the same time.

Personal air samples were collected over six workshifts for three consecutive days and analyzed for EGME and EGEE [Sparer et al. 1988]. Because no tanks were being painted at the time of the study, sampling was performed only for the interior work. The industrial hygiene survey revealed that the painters were exposed to EGME at a TWA concentration of 0 to 5.6 ppm with a mean of 0.8 ppm and a median of 0.44 ppm, and to EGEE at 0 to 21.5 ppm with a mean of 2.6 ppm and a median of 1.2 ppm. Urine samples were obtained from each participant during the medical examination and when the participant brought his semen sample. Measurement of the urinary metabolites MAA and EAA [Smallwood et al. 1988]

confirmed that the painters had been exposed to EGME and EGEE; none of the controls' specimens had detectable MAA or EAA. Two other reproductive toxins, lead and epichlorohydrin, were present in the work environment. Epichlorohydrin was not detected in the air sampling. Exposure to lead was limited to sandblasting operations. Although there were significant air lead levels during blasting, the painters wore air-supplied respirators during this operation. A review of the shipyard biological monitoring data revealed that most blood lead levels were below 20 microgram (μg)%, with the highest single level being 40 μg% [Welch et al. 1988].

Serum samples were analyzed for testosterone, FSH, and LH. It was concluded that there was no pituitary or hypothalamic dysfunction in the exposed group relative to controls. Semen samples were analyzed for pH, sperm density, viability, count, motility, and morphology. The authors reported that although the semen of the exposed group had a significantly lower pH, no significant differences were found in measures of sperm motility, viability, and morphology (no statistics presented). They compared mean sperm density and count using analysis of variance. Sperm counts per ejaculate and per cubic centimeter (cc) of semen were lower (but not statistically significant) in the painters. The proportion of men with a sperm density ≤20 million/ml was higher in the exposed group than in the unexposed group (13.5% vs. 5%, P=0.12). The authors also compared the proportion of each group with oligospermia (defined as a count per ejaculate ≤100 million). Eight of the controls (20%) and 24 of the painters (32%) had oligospermia (P=0.2). The authors concluded that exposure to EGME and EGEE caused functional impairment by lowering sperm counts in this group of painters. In addition, when the authors controlled the analysis for the effects of smoking, they concluded that there was an increased odds ratio for a lower sperm count per ejaculate [Welch et al. 1988].

The effect of combined EGME and EGEE exposure on hematologic parameters was also assessed in these 94 painters and 55 controls [Welch and Cullen 1988]. Mean values for Hb, Hct, total and differential WBC count, and platelet count were assessed for painters and controls. Statistical analysis revealed no difference between exposed and nonexposed groups in mean Hb and Hct levels, and polymorphonuclear leukocyte and platelet counts. However, nine painters, and no controls were anemic. Similarly, five painters and no controls had mild to moderate granulocytopenia. A review of company medical records indicated that these abnormalities were acquired during employment. Analysis of blood lead levels appeared to eliminate lead as the cause of the abnormalities. Exposure to EGME and EGEE was suspected as being the cause of the hematologic disorders. However, because of the authors' inability to establish an exposure-effect relationship, they concluded that further investigation was necessary.

4.2 METABOLISM, UPTAKE, AND ELIMINATION

4.2.1 Studies in Animals

Studies have been conducted in animals to determine the metabolites of EGME and EGEE. Investigations by Tsai [1968] and Blair and Vallee [1966] demonstrated that EGME is a

possible substrate for alcohol dehydrogenase (ADH). Miller et al. [1982, 1983b] concluded that EGME was oxidized via ADH to methoxyacetaldehyde and via aldehyde dehydrogenase to MAA. In studies using radio-labeled EGME, MAA was identified as the major metabolite, and the urine as the major route of elimination [Miller et al. 1983b; Moss et al. 1985].

The metabolism of EGME to MAA has been evaluated as a bioactivation mechanism for EGME [Miller et al. 1982, 1983b; Foster et al. 1983; Brown et al. 1984]. Oral administration of MAA caused testicular changes; increases in embryo-fetal death; decreased fetal weights; increases in structural malformations; and urogenital abnormalities; and heart, tail, and limb defects [Miller et al. 1982; Foster et al. 1983; Brown et al. 1984; Ritter et al. 1985]. The preceding effects were similar to those caused by corresponding EGME doses.

Pretreatment of rats with pyrazole, an ADH inhibitor, inhibited the metabolism of EGME to MAA; however, pretreatment of rats with disulfiram, an aldehyde dehydrogenase inhibitor, had no significant effect on plasma or urinary metabolic profiles [Moss et al. 1985]. Administration of EGME by i.p. injection demonstrated extensive degeneration and necrosis of rat primary spermatocytes in the early and late pachytene stages of development. Pretreatment of rats with pyrazole appeared to protect against spermatocyte damage, while pretreatment with disulfiram had no effect on the degree of spermatocyte damage.

The role of EGME metabolism in the induction of paw malformations was also examined [Sleet et al. 1988]. Single oral exposures of mice to EGME or MAA produced comparable digit anomalies. The incidence of digit malformations was lower in i.v.-treated mice than in gavage-treated mice. When orally administered 1 hr before EGME, 4-methylpyrazole (4-MP), a potent ADH inhibitor, reduced the incidence of paw malformations in a dose-dependent manner. Oral administration of ethanol with and after EGME also caused reduced incidences of digit anomalies [Sleet et al. 1988]. These data are compatible with those of Romer et al. [1985], which demonstrated that ADH has a higher affinity for ethanol than for the glycol ethers [Sleet et al. 1988].

Administration of EGEE by gastric intubation or inhalation resulted in two major urinary metabolites in rats, EAA and N-ethoxyacetyl glycine [Jonsson et al. 1982; Cheever et al. 1984]. In rats, the metabolism of EGEE proceeded chiefly through oxidation via ADH to EAA, with some subsequent conjugation of the acid metabolite with glycine [Jonsson et al. 1982; Cheever et al. 1984]. EAA was found in rat testes 2 hr after oral administration of EGEE. The data suggested that adverse testicular effects exerted by EGEE may be caused by its active metabolite EAA [Cheever et al. 1984].

Foster et al. [1987] examined the toxicity of MAA and EAA. Oral administration of equimolar doses of MAA or EAA in rats determined the initial target for testicular toxicity. Histologic examination of testes revealed testicular damage in all MAA-treatment groups, while EAA exerted testicular damage only at the highest dose. Pachytene spermatocytes were targets for reversible MAA and EAA toxicity. The addition of MAA or EAA to in vitro Sertoli cell and germ cell cultures caused depletion of pachytene spermatocytes within 24 hr [Foster et al. 1987].

An in vitro culture system utilizing rat embryos was used to assess potential adverse effects of MAA and EAA on fetal development [Rawlings et al. 1985]. At the highest dose used, both metabolites exerted adverse effects on fetal development in vitro. These effects included significant reductions in crown-rump length, head length, yolk sac diameter, and protein content of the embryo.

4.2.2 Studies in Humans

Recently EAA has been identified in the urine of workers exposed to EGEE vapor during physical exercise and at rest [Groeseneken et al. 1986a; Groeseneken et al. 1986c]. These findings are consistent with the previously described biotransformation studies in animals which identified EAA as the major metabolite of EGEE [Jonsson et al. 1982; Cheever et al. 1984]. The total amount of urinary EAA was related to the EGEE concentration in inspired air, uptake rate, pulmonary ventilation rate, oxygen consumption during exposure, and heart rate during and after exposure [Groeseneken et al. 1986c]. After the end of a 4-hr EGEE exposure period, maximal EAA excretion was achieved within 3 to 4 hr. EAA excretion then declined slowly with a biological half-life of 21 to 24 hr [Groeseneken et al. 1986c]. On the average, 23% of the absorbed EGEE was recovered as EAA within 42 hr. Respiratory frequency was also a contributing factor in urinary EAA concentration. About 64% of inhaled EGEE vapor was retained at rest, and retention increased as physical exercise was performed during exposure. The rate of EGEE uptake increased as exposure concentration or pulmonary ventilation rate, or both, increased. Individual uptake of EGEE appeared to depend on pulmonary ventilation or cardiac output, or both and not on anthropometric factors [Groeseneken et al. 1986b].

Groeseneken et al. [1988] compared urinary EAA excretion in man and rats after EGEE exposure (oral in rats and by inhalation in man). The human data were taken from Groeseneken et al. [1986c]. In rats the mean elimination half-life was determined to be 7.2 ± 1.5 hr; in man the half-life mean was 42 ± 4.7 hr. (This half-life of 42 hr differs from 23 hr reported in Groeseneken et al. [1986c].) The authors [Groeseneken et al. 1988] attributed the difference in half-lives to the averaging effect of pooling urine collections [Groeseneken et al. 1986c], especially during the first 12 hr.

EAA has also been identified in man as a metabolite of EGEEA [Groeseneken et al. 1987b]. EGEEA is believed to pass through the same metabolic pathway as EGEE after hydrolysis of the ester moiety. EAA excretion in workers exposed to EGEEA vapor was similar to EAA excretion in workers exposed to EGEE [Groeseneken et al. 1986c]. The maximal EAA excretion rate was achieved 3 to 4 hr after the end of the EGEEA exposure period; however, unlike EGEE exposure, a second peak EAA excretion appeared 3 hr later. On average, within 42 hr, 22.2% of absorbed EGEEA was metabolized and excreted as EAA [Groeseneken et al. 1987b]. In beagle dogs exposed to 50 ppm EGEEA for 5 hr, 80% of EGEEA was absorbed in 10 min and reached a plateau in 3 hr [Guest et al. 1984]. The pharmacokinetics of respiratory uptake were more complicated for EGEEA than for EGEE. Individual uptake of EGEEA was determined by pulmonary ventilation, cardiac output, height, and body fat. During exposure to EGEEA vapor, partial respiratory elimination of EGEE was observed.

This finding confirmed the hypothesis that EGEEA is first converted to EGEE by esterases [Groeseneken et al. 1987a].

MAA was detected in the urine of seven male volunteers exposed at rest to 5 ppm EGME [Groeseneken et al. 1989a]. MAA was present in the urine during and up to 120 hr after the beginning of exposure. The elimination half-life of MAA was estimated to be 77 hr. By extrapolation the total amount of MAA was estimated to be 85.5% of inhaled EGME.

No studies are available on the metabolism of EGMEA. However, based on the metabolism of EGEEA to EAA [Groeseneken et al. 1987a,b], EGMEA would be expected to act similarly and be metabolized to MAA.

A detailed description of the preceding studies may be found in Appendix B.

4.3 EFFECTS ON ANIMALS

Although kidney and liver damage, hematologic, CNS, reproductive, and teratogenic effects have been observed in experimental animals exposed to glycol ethers and their acetates, the type and severity of the response induced by each glycol ether are not identical. Therefore, each glycol ether and its corresponding acetate will be discussed separately following Section 4.3.1.

4.3.1 Acute Toxicity

Many experiments investigating the acute toxicity of glycol ethers to animals have been performed. These investigations led to the establishment of a lethal concentration or lethal dose for 50% of the exposed animals (LC_{50} or LD_{50}) in a variety of species by a variety of routes (inhalation, oral, dermal, injection). A summary of the available data by animal species is presented in Table 4-1.

4.3.1.1 Oral Administration

The toxicity of glycol ethers has been studied more extensively by oral administration than by any other route. Hematuria, narcosis, and digestive tract irritation were reported after oral administration of near-lethal or lethal concentrations of EGEE, EGEEA, EGME, or EGMEA in rats, mice, rabbits, and guinea pigs [Laug et al. 1939; Smyth et al. 1941]. However, the principal effect exerted by these glycol ethers in animals that did not die immediately was damage to the kidneys. Pathological examination revealed extreme tubular degeneration along with almost complete necrosis of the cortical tubules.

4.3.1.2 Inhalation Exposure

Waite et al. [1930] examined the effect on guinea pigs of a single inhalation exposure to EGEE vapor. The EGEE concentrations and periods of exposure ranged from those that produced death to those that caused no apparent effect after 24 hr of exposure. EGEE

Table 4-1.-Lethal doses or concentrations of glycol ethers

Species and sex	LD_{50}* oral (mg/kg)		LD_{50} oral (mg/kg)		LD_{50} i.p. (mg/kg)		LD_{50} i.v. (mg/kg)	LD_{50} dermal (mg/kg)		LC_{50} inhalation (ppm)	
	EGME	EGMEA	EGEE	EGEEA	EGME	EGEE	EGEE	EGME	EGEEA	EGME	EGEE
Rat:											
Male	2,460	3,930	3,000	3,900	----	----	----	----	----	----	----
	3,250	----	5,000	5,100	----	----	----	----	----	----	----
Female	3,400	----	2,300	2,900	----	----	----	----	----	----	----
	----	----	5,400	----	----	----	----	----	----	----	----
Not stated	----	----	3,204	----	----	----	2,691	----	----	----	----
Rabbit:											
Male	890	----	3,100	----	----	----	----	1,300	----	----	----
Not stated	----	----	----	----	----	----	840	----	10,500	----	----
Guinea pig:											
Male and Female	950	1,250	1,400	1,910	----	----	----	----	----	----	----
Not stated	----	----	2,584	----	----	----	----	----	----	----	----
Mouse:											
Female	----	----	----	----	2,150	1,709	----	----	----	1,480	1,820 (7 hr)
Not stated	----	----	3,991	----	----	----	3,600	3,600	----	----	----

*Abbreviations: i.p. = intraperitoneal; i.v. = intravenous; LD_{50} = median lethal dose; LC_{50} = median lethal concentration.

concentrations ranged from 500 to 6,000 ppm and were administered over a period of 1 to 24 hr. Guinea pigs exposed to 6,000 ppm for 24 hr exhibited inactivity, weakness, and dyspnea, and died by the end of the exposure; 3,000 ppm for 24 hr caused death within 24 hr following exposure; and exposure to 6,000 ppm for 10 hr, and 3,000 ppm or 1,000 ppm for 18 hr, caused death 1 to 8 days following exposure. Exposure to 6,000 ppm for 1 hr, 3,000 ppm for 4 hr, and 500 ppm for 14 hr caused no apparent harm. Gross pathological examinations of animals that died during and up to two days after exposure revealed congestion and edema of the lungs, distended and hemorrhagic stomachs, and congested kidneys.

Werner et al. [1943c] demonstrated an adverse effect of EGME and EGEE on the hematopoietic system. Groups of 14 or 16 white Swiss mice were subjected to single, 7-hr, inhalation exposures to EGME (930 to 6,800 ppm) and to EGEE (1,130 to 6,000 ppm). Although these vapors produced no typical narcotic action in mice, there was marked dyspnea. Histopathological examinations revealed slight damage to the lungs. The spleen consistently showed marked follicular phagocytosis, which indicated toxic action on the WBC [Werner et al. 1943c].

Groups of female rats developed increased osmotic fragility of erythrocytes when exposed by inhalation to EGEE, EGEEA, EGME, or EGMEA for 4-hr periods [Carpenter et al. 1956]. Of the four compounds, EGMEA (32 ppm) was the most toxic in terms of erythrocyte fragility, followed by EGEEA (62 ppm), and EGEE (125 ppm); EGME at 2,000 ppm only slightly affected erythrocyte fragility.

Ten male and ten female rats and two male and two female rabbits were exposed to 2,000 ppm EGEEA for 4 hr [Truhaut et al. 1979]. Only in rabbits was there a slight and transient hemoglobinuria or hematuria; no gross pathological lesions were noted in either species.

4.3.1.3 Dermal Exposure

A modified Draize "sleeve" technique was used to study the acute dermal toxicity of EGEEA in rabbits [Truhaut et al. 1979]. Death generally occurred 24 to 48 hr after the application of 10,500 mg EGEEA/kg. Although hemoglobinuria and/or hematuria were observed, there was little variation in Hb concentration and the number of RBCs (less than 15% to 20%) in blood; however, there was a considerable decrease in the number of WBCs (50% to 70%). In surviving animals, the WBC counts gradually returned to normal. Necropsy revealed bloody kidneys and blood in the bladder. When survivors were examined after the 2-week observation period, no gross lesions were noted.

4.3.1.4 Intraperitoneal, Intravenous, and Subcutaneous Administration

Karel et al. [1947] conducted the first toxicity study of the glycol ethers administered by intraperitoneal (i.p.) injection. Female albino Carsworth Farms mice (9 to 10 animals/dose) were injected intraperitoneally with varying doses of either EGEE or EGME and were observed for 7 days following injection. Gross and microscopic pathological studies were

conducted on animals that died during the first 7 days after injection or were sacrificed at the end of the 7-day observation period. The LD_{50} for EGME was 2,150 mg/kg and the LD_{50} for EGEE was 1,709 mg/kg. During the first 72 hr after injection of either EGME or EGEE, toxic reactions in the lymph nodes and spleen (lymphocyte degeneration followed by reticulum cell proliferation and phagocytosis of cellular debris) and mild renal glomerular and tubular degeneration were noted. During the fifth through seventh day, lymphoid regeneration occurred while renal tubular damage continued. Pulmonary congestion and atelectasis (collapse of the alveoli or a portion of the lung) were also observed in EGEE-treated mice.

Dogs and rabbits were given three 7.1-g injections (unspecified as to type or site) of EGME [Wiley et al. 1938]. At necropsy (2 to 3 days after last injection) histological examination of the dogs' organs revealed damage to the kidney, bladder, liver, and spleen. Multiple organs of the rabbits also demonstrated tissue damage—the lungs showed multiple hemorrhages, the spleen and liver were damaged, and the kidneys had various degrees of tubular degeneration.

Another group of investigators [Stenger et al. 1971] determined the acute LD_{50} for EGEE in the mouse, rat, and rabbit by intravenous (i.v.) administration of 3,600, 2,691, or 840 mg/kg, respectively. The following symptoms were observed: dyspnea, somnolence, ataxia, stomach distending to the side, and convulsions.

The acute toxic effects of EGME, EGMEA, EGEE, and EGEEA are summarized in Table 4-2.

4.3.1.5 Summary of Acute Toxicity

The acute toxicity of EGEE, EGEEA, EGME, and EGMEA has been investigated in a number of experiments with a variety of species and routes of exposure. Animals exhibited inactivity, weakness, and dyspnea. Necropsies revealed congested lungs, hemorrhagic stomachs, congested kidneys, and damage to the bladder, liver, and spleen [Waite et al. 1930; Wiley et al. 1938; Karel et al. 1946; Carpenter et al. 1956; Truhaut et al. 1979]. The principal toxic effect of these compounds was damage to the kidneys [Waite et al. 1930; Laug et al. 1939; Smyth et al. 1941; Gross 1943], which included extreme tubular necrosis and degeneration. Additional adverse effects included increased erythrocyte osmotic fragility and damaged spleens [Werner et al. 1943c; Carpenter et al. 1956; Truhaut et al. 1979].

4.3.2 Male Reproductive Effects

A number of experimental animal studies have demonstrated the adverse effects of glycol ethers on the male reproductive system. These effects include testicular atrophy, decrease in fertility, germ cell depletion, decrease in sperm motility, and an increase in the number of abnormal sperm cells. Although a brief summary of these studies follows, a detailed description of them may be found in Appendix B.

Table 4-2.—Acute toxicity of EGEE, EGEEA, EGME, and EGMEA

Compound	Species	Route of administration and dose	Observed effects	Reference
EGEE	Mouse	i.p.: LD_{50}* 1,709 mg/kg	Damage to lymph nodes and spleen, renal glomerular and tubular degeneration, pulmonary congestion	Karel et al. 1947
	Mouse	i.v.: LD_{50} 3,600 mg/kg	Dyspnea, somnolence, ataxia, distended stomach	Stenger et al. 1971
	Mouse	Oral: LD_{50} 3,991 mg/kg	Hematuria, renal tubular degeneration and cortical necrosis	Laug et al. 1939
	Mouse	Inhalation: 1,130–6,000 ppm for 7 hr	Dyspnea, damaged lung, toxic effect on white blood cells	Werner et al. 1943c
	Mouse (F)	Inhalation: LC_{50}* 1,820 ppm for 7 hr	Death	Werner et al. 1943a
	Rat	i.v.: LD_{50} 2,691 mg/kg	Dyspnea, somnolence, ataxia, distended stomach	Stenger et al. 1971
	Rat	Oral: LD_{50} 3,204 mg/kg	Hematuria, renal tubular degeneration and cortical necrosis	Laug et al. 1939
	Rat (M)	Oral: LD_{50} 3,000 mg/kg	Narcosis, digestive tract irritation, kidney damage	Smyth et al. 1941
	Rat (M)	Oral: LD_{50} 5,000 mg/kg	Narcosis, lung and kidney damage	Carpenter et al. 1956
	Rat (F)	Oral: LD_{50} 5,400 mg/kg	Narcosis, lung and kidney damage	Carpenter et al. 1956
	Rat (M)	Oral: LD_{50} 2,300 mg/kg	Death	Cheever et al. 1984
	Rat (F)	Inhalation: 125 ppm for 4 hr	Increase in osmotic fragility	Carpenter et al. 1956
	Rabbit	i.v.: LD_{50} 840 mg/kg	Dyspnea, somnolence, ataxia, distended stomach	Stenger et al. 1971
	Rabbit (M)	Oral: LD_{50} 3,100 mg/kg	Narcosis, lung and kidney damage	Carpenter et al. 1956
	Rabbit (M)	Dermal: LD_{50} 3,296 mg/kg	Death	Carpenter et al. 1956
	Guinea pig	Oral: LD_{50} 2,584 mg/kg	Hematuria, renal tubular degeneration and cortical necrosis	Laug et al. 1939

EGEE	Guinea pig (M,F)	Oral: LD_{50} 1,400 mg/kg
	Guinea pig (M,F)	Oral: LD_{50} 1,400 mg/kg
	Guinea pig	Inhalation: 0.05%, 0.3%, for 1–24 hr or 0.06%
EGEEA	Rat (M)	Oral: LD_{50} 5,100 mg/kg
	Rat (F)	Oral: LD_{50} 2,900 mg/kg
	Rat (M)	Oral: LD_{50} 3,900 mg/kg
	Rat (F)	Inhalation: 62 ppm for 4 hr
	Rat (M,F)	Inhalation: 2,000 ppm for 4 hr
	Rabbit (M,F)	Inhalation: 2,000 ppm for 4 hr
	Rabbit (M,F)	Dermal: LD_{50} 10,500 mg/kg
	Guinea pig (M,F)	Oral: LD_{50} 1,910 mg/kg
EGME	Mouse (F)	i.p.: LD_{50} 2,150 mg/kg
	Mouse	Inhalation: 930 to 6,800 ppm for 7 hr

*Abbreviations: LC_{50} = median lethal concentration; LD_{50}

Narcosis, digestive tract irritation, kidney damage	Smyth et al. 1941
Narcosis, lung and kidney damage.	Carpenter et al. 1956
No effect (0.05% for 14 hr; 0.3% for 4 hr; 0.6% for 1 hr); death (0.6% for 24 hr; 0.3% for 24 hr); inactivity, weakness, dyspnea (0.6% for 18–24 hr); congestion and edema of the lungs, hemorrhagic and distended stomachs, congested kidneys (0.6% for 18–24 hr; 0.3% for 18–24 hr)	Waite et al. 1930
Narcosis, digestive tract irritation, damaged kidneys	Smyth et al. 1941
Hemoglobinuria, hematuria, renal lesions	Truhaut et al. 1979
Hemoglobinuria, hematuria, renal lesions	Truhaut et al. 1979
Increased osmotic fragility	Carpenter et al. 1956
No effect	Truhaut et al. 1979
Slight, transient hemoglobinuria and/or hematuria	Truhaut et al. 1979
Hemoglobinuria, hematuria, decreased white blood cell count, blood in kidneys and bladder	Truhaut et al. 1979
Narcosis, digestive tract irritation, damaged kidneys	Smyth et al. 1941
Damage to lymph nodes and spleen, renal glomerular and tubular degeneration	Karel et al. 1947
Dyspnea, damage to lungs and white blood cells	Werner et al. 1943c

(Continued)

= median lethal dose.

Table 4-2 (Continued).—Acute toxicity of EGEE, EGEEA, EGME, and EGMEA

Compound	Species	Route of administration and dose	Observed effects	Reference
EGME	Mouse (F)	Inhalation: LC_{50} to 1,480 ppm	Death	Werner et al. 1943c
	Rat (M)	Oral: LD_{50} 246 mg/kg	Digestive tract irritation, damaged kidneys	Smyth et al. 1941
	Rat (M)	Oral: LD_{50} 3,250 mg/kg	Narcosis, lung and kidney damage	Carpenter et al. 1956
	Rat (F)	Oral: LD_{50} 3,400 mg/kg	Narcosis, lung and kidney damage	Carpenter et al. 1956
	Rat (F)	Inhalation: 2,000 ppm for 7 hr	Slight increase in osmotic fragility	Carpenter et al. 1956
	Rabbit	Injection: 2,130 mg	Damage to tissues of kidney, bladder, liver, and spleen degeneration of testes	Wiley et al. 1938
	Rabbit (M)	Oral: LD_{50} 890 mg/kg	Narcosis, lung and kidney damage	Carpenter et al. 1956
	Rabbit (M)	Dermal: LD_{50} 1,289 mg/kg	Death	Carpenter et al. 1956
	Guinea pig (M,F)	Oral: LD_{50} 950 mg/kg	Digestive tract irritation, damaged kidneys	Smyth et al. 1941
	Guinea pig (M,F)	Oral: LD_{50} 950 mg/kg	Narcosis, lung and kidney damage	Carpenter et al. 1956
	Dog	Injection: 2,130 mg	Damage to tissues of kidney, bladder, liver, and spleen	Wiley et al. 1938
EGMEA	Rat (M)	Oral: LD_{50} 3,930 mg/kg	Narcosis, digestive tract irritation, damaged kidneys	Smyth et al. 1941
	Rat (F)	Inhalation: 32 ppm for 4 hr	Increased osmotic fragility	Carpenter et al. 1956
	Guinea pig (M,F)	Oral: LD_{50} 1,250 mg/kg	Narcosis, digestive tract irritation, damaged kidneys	Smyth et al. 1941

4.3.2.1 EGEE and EGEEA

EGEE administered by a variety of routes (subcutaneous, intravenous, oral, and inhalation) produced a marked toxic effect on the testes of many animal species. The testicular effects included edema [Morris et al. 1942; Stenger et al. 1971], an absence of testicular germ cells [Stenger et al. 1971; Nagano et al. 1979], and testicular atrophy [Morris et al. 1942; Nagano et al. 1979; Barbee et al. 1984; Terrill and Daly 1983a; Melnick 1984]. EGEEA has also caused testicular atrophy and depletion of spermatocytes in mice [Nagano et al. 1979]. Testicular degeneration in rats treated orally with EGEE or EGEEA was restricted to the later stages of primary spermatocyte development and secondary spermatocytes [Foster et al. 1983]. In detailed toxicologic studies, Creasy and Foster [1984] and Oudiz and Zenick [1986] concluded that primary spermatocytes in the pachytene stage of meiosis were the initial and major sites of morphologic damage from EGEE. Exposure of rats to EGEE has also resulted in reversible impairment of testicular function that was reflected in significantly decreased sperm counts ($P \leq 0.01$) and increased abnormal forms ($P \leq 0.05$) in the semen [Oudiz et al. 1984]. EGEE treatment has also resulted in lowered epididymal weights [Oudiz et al. 1984]. Oral treatment of rats with single doses of EAA affected diplotene, diakinetic, and secondary and early pachytene spermatocytes [Foster et al. 1987].

4.3.2.2 EGME and EGMEA

The testicular toxicity of EGME has been demonstrated in a number of species by a variety of routes. Adverse effects on the testes included the degeneration of germinal epithelium [Wiley et al. 1938; Miller et al. 1981; Foster et al. 1983; Chapin and Lamb 1984; Hobson et al. 1986], testicular atrophy [Nagano et al. 1979; Miller et al. 1981; Chapin and Lamb 1984; Hobson et al. 1986; Anderson et al. 1987; Exon et al. 1991; Smialowicz et al. 1991], and depletion of germ cells [Nagano et al. 1979; Miller et al. 1981; Foster et al. 1983; Hobson et al. 1986; Anderson et al. 1987]. In one inhalation study, microscopic testicular lesions were observed in rats only at the highest exposure level (300 ppm), but concentration-related testicular lesions were observed in rabbits at 30, 100, and 300 ppm [Miller et al. 1983a]. Miller et al. [1983a] concluded from this study that male rabbits were more sensitive than male rats to EGME vapor. A single 4-hr inhalation exposure to 625 ppm EGME damaged spermatids [Samuels et al. 1984].

Oral administration of 500 mg EGME/kg/day for 4 days caused maturation depletion of middle and late stage spermatids and maturation arrest of pachytene spermatocytes; partial recovery occurred four weeks after treatment and full recovery was achieved at 8 weeks [Foster et al. 1983]. A definite order of spermatocyte sensitivity to EGME has been demonstrated: dividing spermatocytes > early pachytene spermatocytes > late pachytene spermatocytes > midpachytene spermatocytes > leptotene/zygotene spermatocytes [Creasy and Foster 1984]. Anderson et al. [1987] concluded that testicular degeneration was restricted to later stages of primary spermatocyte development and secondary spermatocytes.

A partially reversible decrease in fertility was observed in male rats exposed to EGME by inhalation [Rao et al. 1983] or ingestion [Chapin et al. 1985a; Anderson et al. 1987]. Changes in fertility were correlated with changes in testicular histology and sperm morphology [Chapin et al. 1985b].

Nagano et al. [1979] demonstrated testicular toxicity of EGMEA administered orally to mice. Adverse effects included decreased testes weights and varying dose-related degrees of testicular seminiferous tubule atrophy.

The effects of EGEE, EGME, and their acetates on the male reproductive system are summarized in Tables 4-3 and 4-4.

4.3.3 Effects on the Female Reproductive System and the Developing Embryo

A number of experimental animal studies have investigated the effects of the glycol ethers on the female reproductive system and the developing embryo. Adverse maternal effects include prolonged gestation, reduced body weight, and reduced body weight gain. Adverse developmental effects include lethality, skeletal and visceral malformations, cardiovascular defects, and altered behavioral test responses.

4.3.3.1 EGEE and EGEEA

Treating pregnant females of various species with EGEE has caused adverse maternal and developmental effects. Effects on the dams included death [Schuler et al. 1984], reduced food consumption [Andrew et al. 1981; Hardin et al. 1981], reduced body weight and body weight gain [Andrew et al. 1981; Hardin et al. 1981], and prolonged gestation periods [Nelson et al. 1981]. Effects on the offspring included embryolethality [Stenger et al. 1971; Tinston 1983]; fetal skeletal, renal, cardiovascular, and ventral body wall defects [Stenger et al. 1971; Andrew et al. 1981; Hardin et al. 1981; Doe 1984a]; and reduced body weights [Andrew et al. 1981; Hardin et al. 1981; Hardin et al. 1982]. Altered behavioral test responses and altered neurochemical concentrations in the brain were also observed in the offspring of dams exposed by inhalation to EGEE [Nelson et al. 1982a].

Pregnant rabbits exposed by inhalation to EGEEA exhibited reduced body weight gain and food consumption and an increase in fetal resorptions [Doe 1984a; Tyl et al. 1988]. Embryolethality, visceral and skeletal abnormalities, and reduced fetal weights were observed in the offspring of dams treated with EGEEA [Doe 1984a; Nelson et al. 1984a; Hardin et al. 1984; Tyl et al. 1988].

4.3.3.2 EGME and EGMEA

Treating pregnant females of various animal species with EGME by various routes has caused adverse maternal and developmental effects. Effects on the dams included lethality, increased gestation period, decreased food consumption, and decreased body weight gain [Doe et al. 1983; Hanley et al. 1984a; Wickramaratne 1986]. Effects on the offspring included lethality, decreased fetal weights, decreased litter sizes, skeletal and visceral malformations, digit anomalies, and cardiovascular defects [Nagano et al. 1981; Doe et al. 1983; Hanley et al. 1984a; Horton et al. 1985; Toraason et al. 1985; Wickramaratne 1986; Greene et al. 1987; Hardin and Eisenmann 1987; Scott et al. 1989]. Although rabbits

Table 4-3.—Reproductive effects of EGEE and EGEEA

Compound	Species	Route of administration and dose	Observed effects	Reference
EGEE	Mouse (M)*	Oral: 500, 1,000, 2,000, or 4,000 mg/kg per day, 5 days/wk for 5 wk	Testicular atrophy (1,000 and 2,000 mg/kg per day); death (4,000 mg/kg per day)	Nagano et al. 1979
	Mouse (M)	Oral: 0.5, 1, or 2 g/kg per day for 2 yr	High mortality rate (2 gm/kg); testicular atrophy at 1 or 2 g/kg	Melnick 1984
	Rat (M)	s.c.: 93, 186, 372, or 744 mg/kg per day for 4 wk	Microscopic testicular changes (372 and 744 mg/kg per day)	Stenger et al. 1971
	Rat (M)	Oral: 1.45% in diet for 2 yr	Testicular enlargement, edema, and tubular atrophy	Morris et al. 1942
	Rat (M)	Oral: 46.5, 93, 186, 372 or 744 mg/kg per day for 13 wk	Microscopic testicular changes (186 and 744 mg/kg per day)	Stenger et al. 1971
	Rat (M)	Oral: 250, 500, or 1,000 mg/kg per day for 11 days	Decreased testes weights, spermatocyte depletion and degeneration (500, 1,000 mg/kg per day)	Foster et al. 1983
	Rat (M)	Oral: 250, 500, or 1,000 mg/kg per day for 11 days	Microscopic testicular lesions (500 and 1,000 mg/kg per day)	Creasy and Foster 1984
	Rat (M)	Oral: 0.5, 1, or 2 g/kg per day for 2 yr	High mortality rate (2 gm/kg); testicular atrophy at all doses	Melnick 1984

(Continued)

*Abbreviations: M = male; F = female.

Table 4-3 (Continued).—Reproductive effects of EGEE and EGEEA

Compound	Species	Route of administration and dose	Observed effects	Reference
EGEE (cont'd)	Rat (M)	Oral: 936, 1,972, or 2,808 mg/kg per day for 5 days	Increased abnormal forms of sperms and decreased sperm count (936 mg/kg); azoospermia and oligozoospermia, decreased epididymal wts (1,972, 2,808 mg/kg per day)	Oudiz et al. 1984
	Rat (M)	Oral: 0 or 936 mg/kg per day 5 days/wk for 6 wk	Decreased sperm count and percent normal morphology at weeks 5 and 6; decreased sperm motility at week 6 (pachytene spermatocyte the most sensitive target)	Oudiz and Zenick 1986
	Rat (F,M)	Inhalation: 25, 100, or 400 ppm, 6 hr/day, 5 days/wk for 13 wk	No biologically significant effects.	Terrill and Daly 1983b; Barbee et al. 1984
	Rabbit (F,M)	Inhalation: 25, 100, or 400 ppm, 6 hr/day, 5 days/wk for 13 wk	Testes weight was decreased (400 ppm) and microscopic testicular changes (males)	Terrill and Daly 1983a; Barbee et al. 1984
	Dog (M)	Oral: 46.5, 93, or 186 mg/kg per day for 13 wk	Microscopic testicular changes (186 mg/kg per day)	Stenger et al. 1971
EGEEA	Mouse (M)	Oral: 500, 1,000, 2,000, or 4,000 mg/kg per day, 5 days/wk for 5 wk	Testicular atrophy, depletion of spermatocytes (1,000, 2,000, or 4,000 mg/kg per day)	Nagano et al. 1979
	Rat (M)	Oral: 726 mg/kg per day for 11 days	Testicular atrophy, spermatocyte depletion and degeneration	Foster et al. 1984

Table 4–4.—Reproductive effects of EGME and EGMEA

Compound	Species	Route of administration and dose	Observed effects	Reference
EGME	Mouse (M)*	Oral: 62.5, 125, 250, 500, 1,000, or 2,000 mg/kg per day, 5 days/wk for 5 wk	Testicular atrophy (250–2,000 mg/kg per day); no germ cells (1,000–2,000 mg/kg per day)	Nagano et al. 1979
	Mouse (M)	Oral: 500, 750, 1,000, or 1,500 mg/kg	Reduced testes weight at wk 2–5 (500–1,500 mg/kg); increased abnormal sperm morphology (500–1,500 mg/kg); degeneration of late spermatocytes and spermatids (1,000–1,500 mg/kg)	Anderson et al. 1987
	Mouse (F)	Inhalation: 10 or 50 ppm on g.d. 6–15; sacrifice on g.d. 18	Decreased maternal body weight gain	Hanley et al. 1984a
	Rat (M)	Oral: 50, 100, 250, or 500 mg/kg per day for 11 days	Decreased testicular weight at days 2, 4, 7, and 11 (500 mg/kg per day group); decreased testicular weight at days 7 and 11 (250 mg/kg per day group)	Foster et al. 1983
	Rat (M)	Oral: 50, 100, 250, or 500 mg/kg per day for 11 days	Degeneration of pachytene spermatocytes at 24 hr (100, 250, 500 mg/kg per day); no testicular effects (50 mg/kg for 11 days); degeneration in spermatid population (500 mg/kg per day for 4 days; 250 mg/kg per day for 7 days); absence of spermatid and late spermatocyte populations after 11 days of 250 and 500 mg/kg per day; partial depletion and degeneration of spermatids and spermatocytes with 100 mg/kg per day for 11 days	Foster et al. 1983
	Rat (M)	Oral: 500 mg/kg per day for 4 days, then sacrificed at 2-wk intervals	Maturation depletion of middle and late stage spermatids, maturation arrest of pachytene spermatocytes (2 wk); partial recovery (4 wk); full spermatogenesis in majority of tubules from all animals (8 wk)	Foster et al. 1983

(Continued)

*Abbreviations: M = male; F = female.

Table 4–4 (Continued).—Reproductive effects of EGME and EGMEA

Compound	Species	Route of administration and dose	Observed effects	Reference
EGME (cont'd)	Rat (M)	Oral: 500 mg/kg per day for 4 days; animals sacrificed at 0, 2, 4, and 8 wk post-exposure	Decreased testicular weights at 0, 2, and 4 wk; return to normal size in 8th wk; increased seminal vesicle weights at wk 8	Foster et al. 1983
	Rat (M)	Oral: 150 mg/kg per day for 5 days; animals sacrificed on g.d. 1, 2, 4, 7, and 10 after initial dosing	Spermatocyte degeneration at day 1; no significant increase in production of testis fluid and androgen-binding protein at day 2, 4, 7, and 10; reduced testes weight at day 2 and after	Chapin and Lamb 1984
	Rat (M)	Oral: 50, 100, or 200 mg/kg per day for 5 days then mated with 2 female rats/wk for 8 wk. After 8-wk interval, mated again for 5 days	Decreased pregnancies at wk 4 (200 mg/kg per day); reduced fertility at wk 5 (100 mg/kg per day); decreased number of live fetuses at wk 4–16 (200 mg/kg per day); fewer pups/litter at wk 5 (100 mg/kg per day); increased numbers of resorptions at wk 5 and 6, and at wk 3–16 increase in pre-implantation loss (200 mg/kg per day); increase in pre-implantation loss at wk 2 and 5 (100 mg/kg per day)	Chapin et al. 1985a
	Rat (M)	Oral: 50, 100, or 200 mg/kg per day for 5 days at weekly intervals, for 8 wk, efferent duct ligations, and following day animal was sacrified	Decreased sperm/g cauda epididymis at wk 2 and remained low for 8 wk (100, 200 mg/kg per day); lower counts only at wk 5 (50 mg/kg per day); decreased sperm motility at wk 3–8 (200 mg/kg per day) and wk 4–8 (100 mg/kg per day); recovery began at wk 6. Increased abnormal sperm morphology at wk 3 (200 mg/kg per day) and wk 5 (100 mg/kg per day) and remained so	Chapin et al. 1985a
	Rat (M)	Oral: 50, 100 or 200 mg/kg per day for 5 days at weekly intervals, for 8 wk, efferent duct ligations, and animals sacrificed 16 hr later	Abnormal sperm morphology at wk 4 with recovery by wk 8 (50 mg/kg per day); abnormal sperm morphology at wk 1 with 50% recovery by wk 8 (100 mg/kg per day); severe testicular effects at wk 1, with 50% recovery by wk 7 (200 mg/kg per day) At wk 2 decreased numbers of sperm and increased numbers of immature germ cells (100, 200 mg/kg per day); transient mild increase in numbers of immature germ cells and decreased sperm density; elevated amount of protein in rete testis fluid at wk 2–5 (200 mg/kg per day) and wk 4–6 (100 mg/kg per day)	Chapin et al. 1985b

EGME (cont'd)	Rat (M)	Oral: 500, 750, 1,000, or 1,500 mg/kg	Reduced testes weight (500–1,500 mg/kg) at wks 3, 4, and 5; reduced sperm counts at wks 4, 5, 6, 7 (500–1,500 mg/kg); increased abnormal sperm morphology (500–1,500 mg/kg); 100% sterility (750–1,500 mg/kg); depletion of early pachytene spermatocytes (1,000–1,500 mg/kg)	Anderson et al. 1987
	Rat (M)	Oral: 2,000 or 6,000 ppm in drinking water for 10 days	Reduction in testes weights (6,000 ppm)	Exon et al. 1991
	Rat (M)	Oral: 50, 100, or 200 mg/kg per day for 10 days	Reduction in testes weights and elevated serum testosterone levels (200 mg/kg per day)	Smialowicz et al. 1991
	Rat (M)	Inhalation: 100, 300, or 1,000 ppm, 6 hr/day for 9 days	Microscopic testicular changes (1,000 ppm)	Miller et al. 1981
	Rat (M,F)	Inhalation: 30, 100, or 300 ppm, 6 hr/day, 5 days/wk for 13 wk	Reduced testicular weight and microscopic lesions (300 ppm) in males. Reduced body and thymus weights at 300 ppm in males and females	Miller et al. 1983a
	Rat (M)	Inhalation: 30, 100, or 300 ppm, 6 hr/day, 5 days/wk for 13 wk, then paired with unexposed females for breeding	Decreased male fertility (300 ppm), partially reversed when bred 13 and 19 wk after last exposure	Rao et al. 1983
	Rat (F)	Inhalation: 30, 100, or 300 ppm, 6 hr/day, 5 days/wk for 13 wk, then paired with unexposed males for breeding	No effect on female fertility	Rao et al. 1983
	Rat (M)	Inhalation: 100 or 300 ppm, 6 hr/day for 10 days	No effect at 100 ppm; testicular atrophy at 300 ppm	Doe et al. 1983

(Continued)

Table 4–4 (Continued).—Reproductive effects of EGME and EGMEA

Compound	Species	Route of administration and dose	Observed effects	Reference
EGME (cont'd)	Rat (M)	Inhalation: 150, 300, 625, 1,250, 2,500, or 5,000 ppm for 4 hr; sacrificed on day 14	Microscopic testicular changes and atrophy (1,250, 2,500, 5,000 ppm); damaged spermatids (625 ppm)	Samuels et al. 1984
	Rat (M)	Inhalation: 1,000 or 2,500 ppm for 4 hr; sacrificed on day 1, 2, 3, 4, 5, 8, 10 15, and 19 post exposure	Reduced testes weight at 48 hr (1,000, 2,500 ppm) and testicular atrophy on days 1–19	Samuels et al. 1984
	Rabbit (M)	Injection: (route and dose not specified)	Microscopic testicular changes	Wiley et al. 1938
	Rabbit (M,F)	Inhalation: 30, 100, or 300 ppm, 6 hr/day, 5 days/wk for 13 wk	Reduced testicular weight and microscopic lesions (300 ppm); dose-related increase in incidence and severity of testicular lesions (30, 100, 300 ppm); reduced thymus and body weights at 300 ppm (M,F)	Miller et al. 1983a
	Guinea pig (M)	Dermal: 1 g/kg per day, 5 days/wk for 13 wk	Decreased testicular weights, severe testicular atrophy, degeneration of seminiferous tubules with complete loss of spermatogenic cells	Hobson et al. 1986
EGMEA	Mouse (M)	Oral: 62.5, 125, 250, 500, 1,000, or 2,000 mg/kg per day, 5 days/wk for 5 wk	Testicular atrophy (500–2,000 mg/kg per day); no germ cells (2,000 mg/kg per day)	Nagano et al. 1979

demonstrated a greater sensitivity to EGME vapor than rats or mice, the results established no-observed-effect levels of 10 ppm EGME in these three species [Hanley et al. 1984a]. Oral EGME treatment of mice on different days of gestation caused exencephaly and digit anomalies [Horton et al. 1985]. The authors concluded that 100 mg/kg of EGME was the no-observed-effect level for digit malformations after a single oral dose of EGME on g.d. 11. Oral EGME treatment of nonhuman primates during gestation resulted in a missing digit on each forelimb of one dead embryo [Scott et al. 1989]. An altered response in avoidance conditioning and altered neurochemical levels in the brain were observed in the offspring of dams treated with EGME vapor [Nelson et al. 1984a]. Feuston et al. [1990] demonstrated that treatment of pregnant rats with a single dermal application of EGME caused statistically significant increases ($P<0.05$) in both the mean number of resorptions and the mean percentage of resorptions, as well as in visceral, external, and skeletal malformations. In this study, the authors established a NOAEL of 250 mg/kg on g.d. 12 for developmental effects. No studies have been reported using EGMEA; it would, however, be expected to have the same effects as EGME (see Section 4.2).

The effects of EGEE, EGEEA, and EGME on the female reproductive system and the embryo are summarized in Tables 4-5, 4-6, and 4-7.

4.3.4 Hematology

EGEE, EGEEA, EGME, and EGMEA exert adverse hematologic effects. These effects include increased osmotic fragility and decreased levels of Hb, Hct, platelets, RBCs, WBCs, and MCV. The following studies, which show these effects, are described in detail in Appendix B.

4.3.4.1 EGEE and EGEEA

Adverse hematological effects were observed in a number of species following administration of EGEE or EGEEA by oral, inhalation, and dermal routes. These effects included hemolysis [von Oettingen and Jirouch 1931] and increased osmotic fragility [Carpenter et al. 1956]. Other investigations demonstrated that EGEE and EGEEA caused decreased Hb concentrations, decreased numbers of RBCs, WBCs, and platelets, reduced Hct levels, and decreased MCVs [Werner et al. 1943a,b; Stenger et al. 1971; Nagano et al. 1979; Truhaut et al. 1979; Terrill and Daly 1983a; Barbee et al. 1984; Doe 1984a; Tyl et al. 1988]. These effects were shown to be reversible in only one study [Werner et al. 1943b]. In another study [Tyl et al. 1988], EGEEA caused an increase in WBC levels.

4.3.4.2 EGME and EGMEA

The effect of EGME and EGMEA treatment on the blood and the hematopoietic system has been investigated in a variety of species by a variety of routes. Adverse effects of EGME and EGMEA include decreased Hb, Hct, RBC, and WBC levels, and altered MCVs [Werner et al. 1943a,b; Miller et al. 1981, 1983a; Nagano et al. 1979; Grant et al. 1985; Hobson et al. 1986]. Carpenter et al. [1956] showed that EGME (2,000 ppm) and EGMEA (32 ppm)

Table 4-5.—Developmental effects of EGEE

Species	Route of administration and dose	Observed effects	Reference
Mouse (F)*	s.c.: 46.5 or 93 mg/kg per day on g.d. 1-18	No embryotoxic or teratogenic effects	Stenger et al. 1971
Mouse (F)	Oral: 3.6 g/kg per day on g.d. 7-14	Maternal death (10%); embryonic death (100%)	Schuler et al. 1984
Rat (F)	s.c.: 23, 46.5, 93 mg/kg per day on g.d. 1-21	Fetal skeletal defects (93 mg/kg per day)	Stenger et al. 1971
Rat (F)	Oral: 11.5, 23, 46.5, 93, 186 or 372 mg/kg per day on g.d. 1-21	Complete resorption of all litters (372 mg/kg per day); embryonic death increased (46.5-186 mg/kg per day); fetal skeletal defects and lower body weight (93-186 mg/kg per day)	Stenger et al. 1971
Rat (F)	Inhalation: before pregnancy, 150 or 650 ppm 7 hr/day, 5 days/wk for 3 wk; then 200 or 765 ppm, 7 hr/day on g.d. 1-19	No effect on fertility; slight maternal toxicity (765 ppm); embryonic death (100% at 765 ppm); fetal cardiovascular and skeletal defects and reduction in growth (200 ppm)	Andrew et al. 1981 Hardin et al. 1981
Rat (F)	Inhalation: 900 ppm, 7 hr/day on g.d. 14-20;	Extended gestation duration by 48 hr	Nelson et al. 1981
Rat (F)	Inhalation: 100 ppm, 7 hr/day on g.d. 7-13 or 14-20	Prolonged gestation (0.7 day); altered behavioral test results; altered neurochemical concentrations in brain	Nelson et al. 1982a

Rat (F)	Inhalation: 200 ppm, 7 hr/day on g.d. 7–13
Rat (F)	Inhalation: 10, 50, or 250 ppm, 6 hr/day on g.d. 6–15
Rat (F)	Dermal: 1.0 or 2.0 ml/day on g.d. 7–16
Rat (F)	Dermal: 1.0 ml/day on g.d. 7–16
Rabbit (F)	s.c.: 23 mg/kg per day on g.d. 7–16
Rabbit (F)	Inhalation: 160 or 615 ppm, 7 hr/day on g.d. 1–18
Rabbit (F)	Inhalation: 10, 50, or 175 ppm, 6 hr/day on g.d. 6–18
Rabbit (F)	Inhalation: 50, 150, or 400 ppm on g.d. 6–18

*F = female.

Increased dopamine levels in cerebrum; increased norepinephrine levels in cerebrum and cerebellum	Nelson et al. 1982b
Fetotoxic, reduced ossification, skeletal variants (250 ppm)	Doe 1984a
Reduced maternal weight gain (2.0 ml/day); embryonic death (100% at 2.0 ml/day and 76% at 1.0 ml/day); fetal cardiovascular defects and skeletal variations and reduced fetal body weight (1.0 ml/day)	Hardin et al. 1982
Increase of visceral malformations	Hardin et al. 1984
No embryotoxic or teratogenic effects	Stenger et al. 1971
Embryonic death (100% at 615 ppm and 22% at 160 ppm); fetal renal, cardiovascular, and ventral body wall defects and skeletal variations (160 ppm); reduced maternal food consumption (160, 615 ppm); maternal death (615 ppm)	Andrew et al. 1981 Hardin et al. 1981
Skeletal variations in fetus (175 ppm)	Doe 1984a
Decreased number of live fetuses, gravid uterus weights and litter weights, increased post implantation loss, early and late fetal deaths (400 ppm)	Tinston 1983

Table 4-6.—Developmental effects of EGEEA

Species	Route of administration and dose	Observed effects	Reference
Rat (F)*	Inhalation: 130, 390, or 690 ppm, 7 hr/day on g.d. 7-15	Embryonic death (100% at 690 ppm and 56% at 390 ppm); reduced fetal weights and increased visceral malformations (130 and 390 ppm)	Nelson et al. 1984b
Rat (F)	Inhalation: 50, 100, 200, or 300 ppm, 6 hr/day on g.d. 6-15	Reduced weight gain and food consumption, elevated liver weight (100-300 ppm); embryo/fetotoxicity (100-300 ppm), external (300 ppm), visceral, and skeletal malformations (200-300 ppm)	Tyl et al. 1988
Rat (F)	Dermal: 1.4 ml/day on g.d. 7-16	Reduced maternal body weight; embryonic death (100%); reduced fetal body weights and visceral malformations and skeletal variations	Hardin et al. 1984
Rabbit (F)	Inhalation: 25, 100, or 400 ppm, 6 hr/day on g.d. 6-18	Reduced maternal body weight gain and food consumption (400 ppm); increased resorptions (400 ppm) and reduced fetal body wt (100 ppm); major vertebral column malformations (400 ppm)	Doe 1984a
Rabbit (F)	Inhalation: 50, 100, 200, or 300 ppm, 6 hr/day on g.d. 6-18	Decreased weight gain, reduced gravid uterine wt; elevated absolute liver wt (100-300 ppm); embryotoxicity (200-300 ppm); fetotoxicity (100-300 ppm); external, visceral, and skeletal malformations (200-300 ppm)	Tyl et al. 1988

*F = female.

Table

Species	Route of administration and dose
Mouse (F)*	Oral: 31.25, 62.5, 125, 250, 500 or 1,000 mg/kg per day on g.d. 7–14
Mouse (F)	Oral: 1,400 mg/kg per day on g.d. 7–14
Mouse (F)	Oral: 250 mg/kg on g.d. 7–14 Oral: 250 mg/kg per day on g.d. 7–9, 8–10, or 9–11; Oral: 250 mg/kg on g.d. 7–8, 9–10, or 10–11; Oral: 250 or 500 mg/kg per day on g.d. 10, 11, 12, or 13
	Oral: 100, 175, 250, 300, 350 400, or 450 mg/kg on g.d. 11
Mouse (F)	Oral: 250 mg/kg per day on g.d. 7–14; sacrificed on g.d 18
Mouse (F)	Oral: 25, 50, or 100 mg/kg per day on g.d. 7–13

*F = female.

4-7.—Developmental effects of EGME

Observed effects	Reference
Embryonic death (250–1,000 mg/kg per day); 100% dead (1,000 mg/kg per day), 1 alive (500 mg/kg per day); reduced fetal weights (125–250 mg/kg per day); gross anomalies and skeletal malformations (250 mg/kg per day); increased skeletal malformations (62.5–125 mg/kg per day); retarded fetal ossification (31.25–1,000 mg/kg per day); bifurcated or split cervical vertebrae	Nagano et al. 1981
100% embryonic death	Schuler et al. 1984
Exencephaly and paw lesions; reduced fetal weights, increased embryolethality in all dosage groups except single 500 mg/kg on g.d. 12 or 13; increased exencephalic fetuses (250 mg/kg on g.d. 7–9, or 8–10); increased digit malformations (250 mg/kg on g.d. 8-10, or 9–11, or 10 and 11); increased paw malformations (500 mg/kg on g.d. 9, 10, 11, or 12); forepaw anomalies (500 mg/kg on g.d. 9, 10, or 11); hindpaw syndactyly (500 mg/kg on g.d. 12)	Horton et al. 1985
Increased digit anomalies (250–450 mg/kg); present at 175 mg/kg, but not statistically significant; NOAEL = 100 mg/kg	Horton et al. 1985
Gross malformations (exencephaly and paw lesions)	Horton et al. 1985
100% resorption (100 mg/kg per day); increased cardiovascular defects (50 mg/kg per day); increased numbers of fetuses with aberrant QRS complexes (25–50 mg/kg per day)	Toraason et al. 1985

(Continued)

Table 4-7 (Continued).—Developmental effects of EGME

Species	Route of administration and dose	Observed effects	Reference
Mouse (F)	Oral: 100, 250, or 350 mg/kg on g.d. 11, then sacrificed 2, 6, 24, or 48 hr later and embryos removed	No maternal toxicity; forelimb bud cytotoxicity as early as 2 hr post EGME treatment, with maximum effect at 6 hr (350 mg/kg)	Greene et al. 1987
Mouse (F)	Oral: 100, 175, 250, 300, 350 400, 450, or 500 mg/kg on g.d. 11 and embryos removed 6 or 24 hr later	Paw malformations induced in dose-dependent manner (all dose levels except 100 mg/kg)	Greene et al. 1987
Mouse (F)	Oral: 304 mg/kg on g.d. 11, sacrificed on g.d. 18	No maternal toxicity; paw malformations	Hardin and Eisenmann 1987
Mouse (F)	Inhalation: 0, 10, or 50 ppm on g.d. 6-15; sacrificed on g.d. 18	Slight fetotoxicity (50 ppm): minor skeletal variations	Hanley et al. 1984a
Rat (F)	Inhalation: 100 or 300 ppm, 6 hr/day on g.d. 6-17, then litters delivered	Reduced maternal body weight gain and 100% embryonic death (300 ppm), prolonged gestation and reduced number of pups and live pups (100 ppm)	Doe et al. 1983
Rat (F)	Inhalation: 3, 10, or 50 ppm on g.d. 6-15	Minor skeletal variations (50 ppm)	Hanley et al. 1984a
Rat (F)	Inhalation: 25 ppm, 7hr/day on g.d. 7-13 or 14-20	Significant differences in avoidance conditioning of offspring from mothers exposed on g.d. 7-13; neurobehavioral deviations in offspring	Nelson et al. 1984a
Rat (F)	Dermal: 3%, 10%, 30%, or 100% solutions at 10 ml/kg, 6 hr/day on g.d. 6-17	100% maternal deaths (100% soln); 100% fetal death (30%); reduced litter sizes (10%)	Wickramaratne 1986

Rat (F)	Dermal: 250, 500, 1,000 or 2,000 mg EGME/kg on g.d. 12
	2,000 mg EGME/kg on g.d. 10, 11, 12, 13, or 14
Rabbit (F)	Inhalation: 3, 10, or 50 ppm on g.d. 6–18
Monkey (F)	Oral: 12, 24, or 36 mg/kg on g.d. 20–45

Reduced maternal body weight gain day after EGME application (all EGME exposures and times except for 250 mg on g.d. 12)	Feuston et al. 1990
Increase in mean number of resorptions, mean percentage resorptions (2,000 mg/kg on g.d. 10); decrease in fetal body weights (1,000 or 2,000 mg/kg on g.d. 10 and 12). Increases in external,visceral, or skeletal malformations (500, 1,000, or 2,000 mg/kg on g.d. 12)	
Reduced maternal body weight gain, increased absolute liver weight, increased resorption rate, reduced mean fetal body weights (50 ppm); increased incidence of skeletal and visceral malformations (50 ppm); 10 ppm = no effect level	Hanley et al. 1984a
Embryonic death — 3 of 13 or 23% at 12 mg/kg, 3 of 10 or 30% at 24 mg/kg, 8 of 8 or 100% at 36 mg/kg; 1 embryo (36 mg/kg group) was missing one digit on each forelimb	Scott et al. 1989

caused increased osmotic fragility of RBCs. Histopathology of EGME- and EGMEA-exposed animals revealed reduced bone marrow cellularity, lymphoid atrophy of the thymus and gut-associated lymphoid organs, decreased hepatocyte size, and reduced thymus weights [Miller et al. 1981, 1983a; House et al. 1985]. In addition, serum total protein, albumin, and globulin levels were reduced [Miller et al. 1981, 1983a], while serum creatinine kinase and lactate dehydrogenase activity were increased [Hobson et al. 1986].

The hematologic effects of EGEE, EGME, and their acetates are summarized in Tables 4-8 and 4-9.

4.3.5 Immunology of EGME and MAA

Houchens et al. [1984] examined the effect of EGME and EGEE on cell-mediated immunity using an allograft rejection assay. In this model, mice that are allogenic in relation to the leukemic cell tumor used survive when challenged with the tumor unless they have been immunosuppressed; the tumor will grow in syngeneic mice unless chemical treatment has a direct cytotoxic effect on the tumor cells. Day zero was the tumor implantation day. Allogeneic $B6C3F_1$ mice were given 600, 1,200, or 2,400 mg EGEE/kg or 300, 600, or 1,200 mg EGME/kg orally on days -12 to -0, or 100 mg/kg cyclophosphamide (Cy) i.p. on day -1. Sham-treated controls were given oral doses of water on days -12 to -0 and -5 to -1, respectively. The mice were then challenged with 100 (10^2), 3,000 (3×10^3), 300,000 (3×10^5), or 3,000,000 (3×10^6) L1210 cells i.p. on day zero. Syngeneic $CD2F_1$ mice were challenged with 100,000 (10^5) L1210 cells on day zero and were treated on days 1 to 5 and 8 to 12 with the same doses of EGME and EGEE used for the $B6C3F_1$ mice. Water-treated syngeneic mice died with a median survival time of 8 days. In the syngeneic mice there was no direct antitumor activity of EGME or EGEE against the L1210 tumor at the doses tested because there was no effect on the median survival time. Neither EGME nor EGEE were toxic to the syngeneic mice, as determined by weight loss or early death. The authors [Houchens et al. 1984] suggested that higher doses might be tolerated and have some direct cytotoxic effect on the tumor.

The results for the allogeneic mice were more complex. All allogeneic mice receiving either water or Cy and challenged with 3×10^6 tumor cells died with ascites. However, no more than one animal per group died when the mice were treated with EGME or EGEE and challenged with 3×10^6 tumor cells. Houchens et al. [1984] suggested that the compounds may in some way stimulate the immune system and provide a prophylactic action. Blood smears of allogeneic mice were made for differential counts the last day of dosing, the day of death when possible, and on survivors at day 43 after tumor implantation. In those mice not surviving until the day of sacrifice, differential counts showed evidence of monocytosis, which is indicative of monocytic leukemia. All surviving allogeneic mice were sacrificed and necropsied on day 43. Cholecystitis was present in 7% of the mice that had received EGEE and in 58% of the mice that had received EGME. The authors did not refer to the control group.

Exposure of laboratory animals to glycol ethers has been associated with thymus atrophy and leukopenia [Nagano et al. 1979; Truhaut et al. 1979; Miller et al. 1981, 1983a; Grant et al. 1985]. Because these effects could involve depletion of immunoresponsive cells,

Table 4-8.—Hematologic effects of EGEE and EGEEA

Compound	Species	Route of administration and dose	Observed effects	Reference
EGEE	Dog and beef blood	in vitro (1 cc)	Hemolysis	von Oettingen and Jirouch 1931
	Mouse	Oral: 0, 500, 1,000, or 2,000 mg/kg per day, 5 days/wk for 5 wk	Reduced WBC counts (2,000 ppm)	Nagano et al. 1979
	Rat	Inhalation: 370 ppm 7 hr/day, 5 days/wk for 5 wk	Increase in hemosiderin; fat replacement in bone marrow; decrease in myeloid cells	Werner et al. 1943a
	Rat	Inhalation: 125 ppm for 4 hr	Increased erythrocyte osmotic fragility	Carpenter et al. 1956
	Rat (M,F)*	Inhalation: 0, 25, 100 or 400 ppm, 6 hr/day, 5 days/wk for 13 wk	Decreased WBC in females (400 ppm)	Terrill and Daly 1983b; Barbee et al. 1984
	Rat (F)	Inhalation: 0, 10, 50 or 250 ppm on g.d. 6-15	Decreased Hb, Hct, and MCV (250 ppm)	Doe 1984a
	Rabbit	Oral: 186, 372, or 744 mg/kg per day, 7 hr/day for 13 wk	Decreased Hb and Hct; increased hemosiderin; hematopoietic foci in spleens	Stenger et al. 1971
	Rabbit (M,F)	Inhalation: 0, 25, 100, or 400 ppm, 6 hr/day, 5 days/wk for 13 wk	Decreased Hb, Hct, and RBC in males and females (400 ppm)	Terrill and Daly 1983a; Barbee et al. 1984
	Rabbit (F)	Inhalation: 0, 10, 50, or 175 ppm on g.d. 6-18	No effects	Doe 1984a
	Dog	Oral: 186 mg/kg per day, 7 hr/day for 13 wk	Decreased Hb and Hct; increased hemosiderin; hematopoietic foci in spleens	Stenger et al. 1971
	Dog	Inhalation: 840 ppm, 7 hr/day, 5 day/wk for 12 wk	Increased circulating immature granulocytes; increased hemosiderin	Werner et al. 1943b

(Continued)

*Abbreviations: M = male; F = female.

Table 4-8 (Continued).—Hematologic effects of EGEE and EGEEA

Compound	Species	Route of administration and dose	Observed effects	Reference
EGEEA	Dog and beef blood	in vitro (1 cc)	Hemolysis	von Oettingen and Jirouch 1931
	Mouse	Oral: 0, 500, 1,000, 2,000, or 4,000 mg/kg per day, 5 days/wk, for 5 wk	Reduced white blood cell counts (2,000 mg/kg per day); reduced packed erythrocyte volume (4,000 mg/kg per day)	Nagano et al. 1979
	Rat	Inhalation: 62 ppm for 4 hr	Increased erythrocyte osmotic fragility	Carpenter et al. 1956
	Rat	Inhalation: 2,000 ppm for 4 hr	No effect	Truhaut et al. 1979
	Rat (F)	Inhalation: 0, 50, 100, 200 or 300 ppm for 6 hr/day on g.d. 6-15	Increased WBC (200 and 300 ppm); reduced RBC, Hb, Hct, erythrocyte size (100, 200, and 300 ppm); reduced platelet counts (200 and 300 ppm)	Tyl et al. 1988
	Rabbit	Inhalation: 2,000 ppm for 4 hr	No effect	Truhaut et al. 1979
	Rabbit (F)	Inhalation: 0, 25, 100, or 400 ppm, 6 hr/day on g.d. 6-18	Reduced Hb; slight reduction in Hct, RBC, and MCV (400 ppm)	Doe 1984a
	Rabbit	Dermal: 10.5 g/kg	Decreased white blood cell count	Truhaut et al. 1979

Table 4-9.—Hematologic effects of EGME and EGMEA

Compound	Species	Route of administration and dose	Observed effects	Reference
EGME	Mouse (M)*	Oral: 500, 1,000, or 2,000 mg/kg, 5 times/wk for 5 wk	Decreased WBC counts (500 mg); decreased RBCs and Hb (1,000 mg)	Nagano et al. 1979
	Mouse (F)	Oral: 250, 500, or 1,000 μg/g, 10 times during 2 wk	Reduced thymus wts (500 and 1,000 μg/g)	House et al. 1985
	Mouse (M)	Oral: 500, 1,000, or 2,000 mg/kg, 5 times/wk for 5 wk	Decreased WBC and RBC counts (1,000 mg/kg); decreased Hb (2,000 mg/kg)	Nagano et al. 1979
	Mouse (M, F)	Inhalation: 100, 300, or 1,000 ppm 6 hr/day for 9 days	Decreased WBC counts, packed cell volume, and RBC counts (1,000 ppm); similar but less severe effects at 300 ppm	Miller et al. 1981
	Rat (M)	Oral: 100 or 500 mg/kg per day for 4 days; animals sacrificed on day 1, 4, 8, and 22 after last treatment	Day 1: (500 mg/kg per day) hemorrhagic bone marrow and sinus endothelial damage, return to normal on day 4; splenic medullary hemopoiesis abolished, partial recovery by day 4, return to normal on day 22; mild anemia; reduced Hct and Hb (day 4) and reduced RBC counts (day 8); reduced WBC counts and no return to normal; (100 mg/kg per day) reduced WBC on day 1	Grant et al. 1985
	Rat	Inhalation: 310 ppm, 7 hr/day, 5 days/wk for 5 wk	Increased levels of hemosiderin and immature granulocytes	Werner et al. 1943a
	Rat	Inhalation: 32 ppm for 4 hr	Increased osmotic fragility (hemolysis)	Carpenter et al. 1956
	Rat (F)	Inhalation: 2,000 ppm for 4 hr	Increased osmotic fragility	Carpenter et al. 1956
	Rat (M, F)	Inhalation: 100, 300, or 1,000 ppm 6 hr/day for 9 days	Decreased WBC counts, packed cell volume, and RBC counts (1,000 ppm); similar but less severe effects at 300 ppm; decreased Hb (300 ppm in F); reduced total serum protein, albumin, and globin (1,000 ppm in M)	Miller et al. 1981

(Continued)

*Abbreviations: M = male; F = female.

Table 4-9 (Continued).—Hematologic effects of EGME and EGMEA

Compound	Species	Route of administration and dose	Observed effects	Reference
EGME	Rat	Inhalation: 30, 100, or 300 ppm 6 hr/day, 5 days/wk for 13 wk	After 4 and 12 wks, decreased WBC counts, platelet counts, and HB, reduced total protein, albumin, and globin; thymic atrophy (300 ppm)	Miller et al. 1983a
	Rabbit	Inhalation: 30, 100, or 300 ppm 6 hr/day, 5 days/wk for 13 wk	After 4 and 12 wks, decreased WBC counts, platelet counts, Hb, and RBC counts; thymic atrophy (300 ppm)	Miller et al. 1983a
	Guinea pig(M)	Dermal: 1 g/kg per day, 5 days/wk for 13 wk	Decreased RBC counts, increased MCV, lymphopenia, neutrophilia, and increased serum creatinine kinase and lactate dehydrogenase activity	Hobson et al. 1986
	Dog	Inhalation: 750 ppm, 7 hr/day, 5 days/wk for 12 wk	Microcytic anemia; decreased Hb and Hct (at 4–6 wks); increased osmotic fragility (at 11–12 wks)	Werner et al. 1943b
EGMEA	Rat	Inhalation: 62 ppm for 4 hr	Increased osmotic fragility (hemolysis)	Carpenter et al. 1956

House et al. [1985] studied possible alterations in immune function and host resistance of mice following exposure to EGME or its metabolite MAA. Specific pathogen-free female $B6C3F_1$ mice were treated orally 10 times over a 2-week period with EGME or MAA to yield total doses of 0, 250, 500, or 1,000 mg/kg. A statistically significant reduction in thymus weights was seen in the 500 mg/kg groups of both compounds ($P<0.01$). However, no reduction was found in bone marrow cellularity or leukocyte counts. No significant alterations in immunopathology, humoral immunity, cell-mediated immunity, macrophage function, and host resistance to *Listeria monocytogenes* challenge were found in mice exposed to EGME or MAA. The authors concluded that care must be taken in interpreting thymus atrophy as evidence of functional immunotoxicity because EGME and MAA produced thymic atrophy without a concomitant decrease in immune function or host resistance [House et al. 1985].

Exon et al. [1991] investigated the effects of EGME on the immune function of male and female Sprague-Dawley rats. The animals (six per group) were exposed to EGME (2,000 or 6,000 ppm for males and 1,600 or 4,800 ppm for females) in deionized drinking water for 21 days; the unexposed group received only deionized drinking water. All rats were injected s.c. at the base of the tail vein with 1 mg of aqueous keyhole limpet hemocyanin (KLH) 7 days after beginning treatment with EGME; a second injection of KLH was administered on day 13 to initiate the production of immunoglobulin G (IgG) antibody. To determine the effect on delayed type hypersensitivity (DTH), the right footpad of each animal was injected with 100 µl of heat-aggregated KLH on day 20; the left footpad was injected with 100 µl of sterile saline.

On day 21, all animals were sacrificed by CO_2 asphyxiation. Serum was then collected by cardiac puncture, and the thymus, spleen, liver, right kidney, and right testis were removed. The mean dose of glycol ethers actually consumed was calculated on the basis of mean body weight and water consumed during the entire study. The actual exposure concentrations of EGME for male rats were determined to be 161 mg/kg per day (2,000 ppm) and 486 mg/kg per day (6,000 ppm). The actual exposure concentrations of EGME for female rats were determined to be 200 mg/kg per day (1,600 ppm) and 531 mg/kg per day (4,800 ppm).

The authors [Exon et al. 1991] reported the following results. The body and testis weights of male rats exposed to 6,000 ppm EGME were significantly reduced ($P\leq0.05$). Male and female rats exposed to either concentration of EGME had a dose-dependent reduction in thymus weights ($P\leq0.05$). Spleen weights were reduced ($P\leq0.05$) in female rats treated with 4,800 ppm EGME. Liver weights expressed as a percentage of body weight were significantly increased ($P\leq0.05$) in male rats treated with 2,000 ppm EGME; however, this effect was not apparent when the actual weights of the livers were compared. EGME exposure did not affect kidney weights in either sex.

Natural killer cytotoxic responses were enhanced ($P\leq0.05$) in male and female rats at either concentration of EGME, but specific IgG production to KLH was suppressed ($P\leq0.05$) in a dose-dependent manner in both sexes. Gamma interferon (γIF) production was decreased ($P\leq0.05$) in all EGME-treated male rats and in female rats exposed to 4,800 ppm EGME. Spleen cell numbers were reduced ($P\leq0.05$) in female rats exposed to both doses of EGME

and in male rats exposed to 6,000 ppm EGME. Interleukin-2 (IL2) production by spleen cells was decreased ($P \leq 0.05$) in female rats treated with 4,800 ppm EGME. No significant effects were observed on DTH reactions of either sex. EGME appears to exert immunomodulatory effects.

Smialowicz et al. [1991] studied the effects of EGME on the immune function of another strain of rat, the Fischer 344 (F344) rat. Adult male or female rats (six per group) were exposed by oral gavage to 25, 50, 100, or 200 mg/kg per day in a volume of 0.25 ml/100 g EGME in water for 2 or 10 consecutive days, depending on the experiments performed. Control rats were given 0.25 ml of water/100 g of body weight by oral gavage. Additional rats were treated by oral gavage with MAA (25 to 200 mg/kg per day) for 2 or 10 days. To generate an antibody response, the F344 rats were immunized in vivo on treatment day 9 or 4 hr before two treatments (separated by 24 hr) with either the sheep erythrocyte (SRBC) antigen or the trinitrophenyl-lipopolysaccharide (TNP-LPS) antigen. Forty-eight hours after the last treatment of EGME or MAA, the animals were sacrificed by asphyxiation with CO_2. Blood samples were obtained from the abdominal aorta, and the spleen, thymus, and mesenteric lymph nodes were removed.

Smialowicz et al. [1991] reported the following observations for male rats only (unless otherwise specified). EGME (50, 100, or 200 mg/kg per day for 10 days) caused a statistically significant ($P \leq 0.05$) dose-dependent decrease in thymus weights with no change in body or spleen weights. In rats immunized on day 9 of EGME treatment, the antibody response to SRBC antigen was enhanced ($P \leq 0.05$) at 50 mg EGME/kg per day; in contrast, the antibody response to TNP-LPS antigen was inhibited ($P \leq 0.05$) in a dose-dependent manner at 50, 100, or 200 mg EGME/kg per day.

When rats were immunized with either SRBC or TNP-LPS antigens and then treated with EGME 4 and 28 hr later (2 doses of EGME), the antibody response to both antigens was inhibited ($P < 0.01$). At 400 mg/kg per day, EGME inhibited the antibody response to SRBC; and at 100, 200, or 400 mg/kg per day inhibited the antibody response to TNP-LPS. The authors [Smialowicz et al. 1991] then compared the effect of 10 daily doses of EGME (25, 50, 100, or 200 mg/kg per day) on the antibody response to TNP-LPS in male and female rats immunized on day 9 of EGME treatment. The antibody response of both sexes was inhibited ($P < 0.05$), but male rats were more sensitive than female rats to the immunosuppressive effects of EGME. At concentrations of 50, 100, and 200 mg/kg per day, EGME inhibited the antibody response in the male rats. Although 50 mg EGME/kg per day had no effect on the antibody response in female rats, 100 and 200 mg EGME/kg per day inhibited the response in a dose-dependent manner.

No alterations were observed in natural killer cell activity, mixed lymphocyte reaction, or cytotoxic T lymphocyte responses. Lymphoproliferative responses to concanavalin A and phytohemagglutinin were reduced at 50 to 200 mg EGME/kg per day, and the mitogen responses of pokeweed and *Salmonella typhimurium* were reduced at 200 mg EGME/kg per day ($P < 0.05$). Interleukin-2 production was reduced ($P < 0.05$) in rats exposed to 50, 100, or 200 mg EGME/kg per day. Expulsion of adult *Trichinella spiralis* worms was reduced in rats treated with 200 mg EGME/kg per day and infected with *T. spiralis* larvae.

The authors then demonstrated that MAA (the metabolite of EGME) plays a role in EGME-induced immunosuppression. MAA administered by gavage (50, 100, or 200 mg EGME/kg per day) to male rats suppressed ($P<0.01$) the antibody response to TNP-LPS in animals immunized on day 9 of MAA treatment. Concomitant exposure of rats to EGME (100 or 200 mg/kg per day) and the alcohol dehydrogenase inhibitor 4-methylpyrazole (4-MP) blocked EGME-induced suppression of the TNP-LPS antibody response observed in rats treated with EGME only.

In this study [Smialowicz et al. 1991], the authors also examined the effect of EGME on male reproductive parameters. The results are presented in Section 4.3.2.2 and Table 4-4.

4.3.6 Carcinogenicity

The National Toxicology Program (NTP) of the U.S. Department of Health and Human Services tested EGEE for carcinogenicity in male and female rats and mice at 500, 1,000, and 2,000 mg/kg/day administered by gavage [Melnick 1982]. Because mortality was high in the 2,000 mg/kg/day groups, survivors were sacrificed after 16 weeks; males had testicular lesions. The final report of this study has not been published. Currently, prechronic carcinogenicity studies are in progress for EGEE and EGME [NTP 1988].

4.3.7 Mutagenicity

A limited number of studies of the potential mutagenicity of EGEE and EGME have been performed. Most of these were in vitro tests with microorganisms or mammalian cell cultures. EGME did not appear to be mutagenic, and EGEE was positive in one test system. No data are available concerning the mutagenicity of EGEEA and EGMEA.

4.3.7.1 EGEE

EGEE was not mutagenic in the Ames test using *S. typhimurium* TA1538, with or without metabolic activation [Kawalek and Andrews 1980], or *E. coli* scl-4-73 [Szybalski 1958]. EGEE was not mutagenic (up to 23 mg/plate) [Ong 1980] when tested in *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 with and without Aroclor-induced rat liver S9 supernatant. NTP reported that EGEE was not mutagenic at concentrations up to 10 mg/plate in the same four *Salmonella* strains with and without microsomal fractions prepared from Aroclor-induced rat and hamster livers [Melnick 1982].

EGEE was also tested in an NTP study at concentrations up to 9 mg/ml and was found to induce sister chromatid exchange in Chinese hamster ovary (CHO) cells in both the presence and absence of rat S9 mix. The response was weaker in the presence of rat S9 mix than in its absence. EGEE induced chromosomal aberrations in CHO cells in the absence of rat S9 mix, but failed to do so in its presence. EGEE was not mutagenic in the Drosophila, sex-linked, recessive lethal test [McGregor 1984].

4.3.7.2 EGME

Abbondandolo et al. [1980] assayed five organic solvents, including EGME, for their ability to induce forward mutations in the fission yeast, *Schizosaccharomyces pombe*, both with and without metabolic activation. An S10 post-mitochondrial fraction from phenobarbital-induced mouse liver was used for metabolic activation. EGME gave negative results in all forward mutation experiments.

EGME was not mutagenic (up to 200 mg/plate) to *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 with and without S9 mix [Ong 1980].

McGregor et al. [1983] tested EGME in various in vitro systems (i.e., bacterial and human embryonal intestinal fibroblasts) for mutagenic potential. In the bacterial mutation tests incubations were conducted both in the presence and absence of an adult male rat liver's post-mitochondrial supernatant fluid and NADPH-generating system (S9 mix). There was no evidence of mutagenicity in the Ames plate incorporation assay at levels up to 3 mg EGME/plate. In another experiment, alcohol metabolism was mediated by yeast B NAD+-dependent alcohol dehydrogenase, and no mutagenic effect was observed. Human embryonic intestinal fibroblasts in the presence of ^{3}H-thymidine were incubated with EGME both in the presence and absence of S9 mix. There was no indication of increased unscheduled DNA synthesis (UDS) in cells exposed to concentrations up to 10 mg EGME/ml. EGME had no effect on bone marrow cytogenetics and did not induce point mutations in the L5178Y mouse lymphoma TK^{+}/-cell assay in the presence of rat S9 mix [McGregor 1984]. In the sex-linked, recessive lethal test with *Drosophila*, results were inconsistent and reinvestigation was suggested. EGME was positive in both the mouse sperm abnormality test and the male rat dominant lethal test.

Mutagenic effects of EGEE and EGME are summarized in Table 4-10.

4.3.8 In Vitro Toxicity

The effects of EGME and MAA on lactate production and protein synthesis by cultured Sertoli cells were studied by Beattie et al. [1984], who suggested that alterations in Sertoli cell function induced by EGME or MAA could critically affect spermatocyte viability and maintenance of spermatogenesis. Sertoli cells were isolated from Sprague-Dawley CD rats and incubated with ^{3}H-labeled leucine. EGME or MAA was then added at 0-, 3-, or 10-mM concentrations, and spectrophotometric lactate determinations were made after 0, 1, 3, 6, 9, and 12 hr of incubation. EGME had no effect on lactate concentrations or rates of accumulation at any time point compared to controls. However, lactate concentration and rate of accumulation were both significantly decreased ($P<0.01$) by both 3 and 10 mM MAA at 6, 9, and 12 hr of incubation. No significant differences were seen between experimental and control plates in protein synthesis as measured by the incorporation of ^{3}H-labeled leucine into acid insoluble material at the end of 12 hr of incubation.

Table 4-10.—Mutagenic effects

Type of test	Compound	Test species and exposure	Results*	References
Bacterial, mutation	EGEE	S. typhimurium TA1538, with and without S9 mix	-	Kawalek and Andrews 1980
		S. typhimurium TA1535, TA1537, TA98, TA100, with and without rat S9 mix, a hamster S9 mix	-	Ong 1980; Melnick 1982
		E. coli scl-4-73	-	Szybalski 1958
	EGME	S. typhimurium TA1535, TA1537, TA98, and TA100, with and without S9 mix	-	Ong 1980
		S. typhimurium TA1535, TA1537, TA1538, TA98, TA100, with and without rat S9 mix and with alcohol dehydrogenase	-	McGregor et al. 1983
Yeast, mutation	EGME	Schizosaccharomyces pombe, with and without mouse S9 mix	-	Abbondandalo et al. 1980
Mammalian, in vitro, unscheduled DNA synthesis	EGME	Human embryonic intestinal fibroblast cells, with and without rat S9 mix	-	McGregor et al. 1983
Mammalian, in vitro, chromosomal aberrations	EGEE	CHO cells with S9 mix CHO cells without S9 mix	- +	McGregor 1984
Drosophila, sex-linked recessive lethal	EGEE EGME	3-day-old males 3-day-old males	- ?	McGregor et al. 1983 McGregor et al. 1983

(Continued)

*Abbreviations: - = no significant response; + = significant response; ? = unclear, further testing recommended.

Table 4-10 (Continued).—Mutagenic effects

Type of test	Compound	Test species and exposure	Results	References
Mammalian, in vitro, point mutations	EGME	L5178Y mouse lymphoma TK+/- cells with rat S9 mix	-	McGregor 1984
Rat bone marrow cytogenetics	EGME	Rats (M,F) exposed to 25 or 500 ppm 7 hr/day, for 1 or 5 days	-	McGregor et al. 1983
Mouse sperm abnormality	EGME	Mice exposed to 25 or 500 ppm, 7 hr/day for 5 days	+ (at 500 ppm)	McGregor et al. 1983
Male rat dominant lethal	EGME	Male rats exposed to 30, 100, or 300 ppm, 6 hr/day, 5 days/wk, for 13 wk	Male sterility at 300 ppm reversible	McGregor et al. 1983
		Male rats exposed to 30, 100, or 300 ppm, 7 hr/day, for 5 days, followed by 10 successive weekly matings	Male sterility at week 5 (500 ppm), reversible	McGregor et al. 1983

4.3.9 Cytotoxicity

The in vitro cytotoxicities of EGME, EGEE, and their corresponding alkoxyacetic acids (MAA and EAA) were studied using CHO cells [Jackh et al. 1985]. CHO cells were seeded into culture flasks, and after 4 to 5 hr test material was added to the medium. After 16 hr the medium was renewed and the cells were allowed to grow in colonies for 6 to 7 days prior to counting. Cloning efficiency was used as an indication of cytotoxicity. Concentrations that allowed approximately 50% of the seeded cells to form colonies (EC_{50}) were calculated. The EC_{50} for EGEE was 0.22 mmol/ml or 21.5 mg/ml and for EGME the EC_{50} was 0.49 mmol/ml or 37.5 mg/ml. EAA and MAA were more cytotoxic (EC_{50} = 0.04 to 0.05 mmol/ml or 4.6 mg/ml for both) than their parent compounds. The authors concluded that gross cytotoxicity to dividing cells is not the predominant mechanism for the reproductive, developmental, and myelotoxic effects of these glycol ethers [Jackh et al. 1985].

Chinese hamster V79 cells display a specific form of cell-to-cell communication called metabolic cooperation, which is characterized by the exchange of molecules between cells through permeable junctions formed at sites of cell contact [Hooper and Subak-Sharpe 1981]. Blockage of metabolic cooperation has been proposed as a mechanism of action of some teratogens [Trosko et al. 1982]. The effects of EGME and EGEE on cell-to-cell communication in Chinese hamster V79 cells were demonstrated in two separate studies [Welsch and Stedman 1984; Loch-Caruso et al. 1984]. In both studies, EGME and EGEE were able to block metabolic cooperation in vitro. The potencies were inversely related to the length of the aliphatic chain; in general, cytotoxicity increased with increasing aliphatic chain length. Loch-Caruso et al. [1984] concluded that because EGME was effective in blocking metabolic cooperation over a broad noncytotoxic range, blockage of intercellular communication may be its teratogenic mechanism. However, EGEE was more cytotoxic and interrupted cell communication over a narrower range of concentrations. The authors therefore concluded that interrupted intercellular communication may be mixed with cytotoxicity in the embryo and the dam, and thus is less specific as a mechanism of teratogenesis for EGEE.

Gray et al. [1985] also investigated the response of primary mixed cultures of Sertoli and germ cells prepared from testes of immature rats that had been exposed to EGEE and its alkoxyacetic acid metabolite, EAA. EGEE had no effect when added to the culture medium at concentrations up to 50 mM (4.505 mg) for up to 72 hr. In contrast, the following changes were induced when 2 to 10 mM of MAA, the major in vivo metabolite of EGME, was added for 24 to 72 hr. After 24 hr incubation of cultures with 5 mM MAA, pachytene spermatocytes were reduced in number and many of those remaining showed degenerative changes consisting of rounding up, increased cytoplasmic eosinophilia, and nuclear pyknosis. The number of pachytene spermatocytes was further reduced after 48 hr of incubation, and after 72 hr the cultures consisted of earlier spermatocytes, spermatogonia, and Sertoli cells with only occasional degenerate pachytene spermatocytes. At 10 mM MAA, pachytene spermatocytes were lost more rapidly, and cell debris in the Sertoli cells was observed more frequently. While no effect was observed at 1 mM MAA, 2 mM MAA caused a slightly increased frequency of pachytene spermatocyte degeneration. EAA, the major metabolite of EGEE in vivo, produced similar changes but was less potent than MAA. Although

cultures treated with 5 mM EAA showed some loss of pachytene spermatocytes, even after 72 hr frequent foci of these cells were still present and many appeared morphologically normal.

In view of the differences in the toxicity of MAA and EAA in cell culture, they were administered orally to rats at equimolar doses of 6.6 mM (592 mg MAA/kg and 684 mg EAA/kg, respectively) to characterize their relative testicular toxicity in vivo. Only MAA reduced testis weight. The effects of MAA were found mainly on the pachytene spermatocyte population; maturation depletion of the early round spermatid population was also evident, while leptotene and zygotene spermatocytes appeared unaffected. EAA had less severe effects, with only focal depletion of early pachytene spermatocytes and early round spermatids, while mid- and late-pachytene spermatocytes appeared normal. The authors concluded that the close correspondence between the testicular toxicity of MAA and EAA in vitro and in vivo suggests a similar mode of action in both cases.

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.

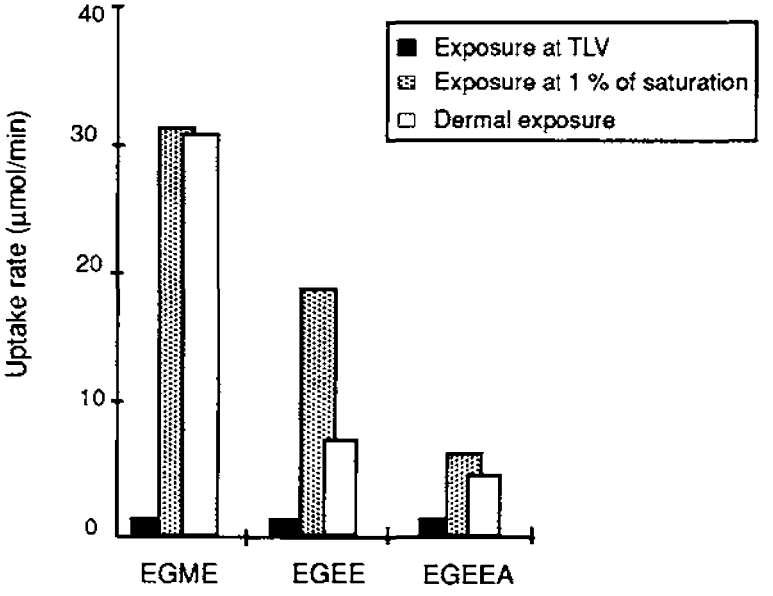

Figure 5-1. Relative uptake rates of glycol ethers under different exposure routes. Source: Johanson [1988].

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.

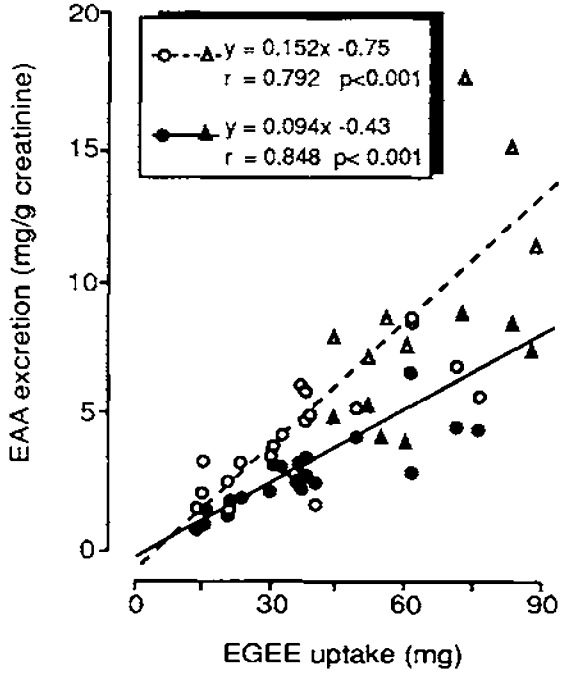

Figure 5-2. Relationship between uptake of EGEE and EAA excretion. Correlation between time-weighted individual uptake of EGEE at rest (o, •) and during physical exercise (Δ, ▲), and urinary excretion of ethoxyacetic acid at maximal excretion (open symbols) and next morning (closed symbols). Source: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

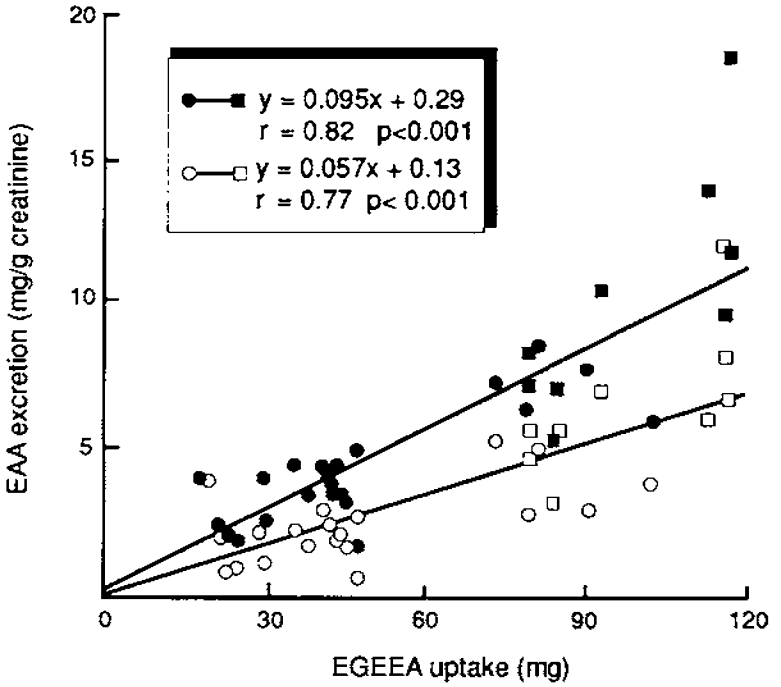

Figure 5–3. Relationship between EGEEA uptake and urinary excretion of EAA. Source: Groeseneken et al. [1987b].

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 ppm	EGME mg/m³	EGMEA ppm	EGMEA mg/m³	EGEE ppm	EGEE mg/m³	EGEEA ppm	EGEEA mg/m³
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.

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
	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
Developmental, Doe [1984a]	Female rats	Inhalation; 10, 50, or 250 ppm, 6 hr/day on g.d. 6–15	—	—	—
	Female rabbits	Inhalation; 10, 50, or 175 ppm, 6 hr/day on g.d. 6–18	—	—	—
Developmental, Nelson et al. [1981]	Female rats	Inhalation; 100 ppm on g.d. 7–13 and 14–20	—	—	100 ppm

—	160 ppm	—	Decreased maternal food consumption; 22% fetolethality and renal, cardiovascular, and ventral body wall defects
—	200 ppm	—	Slight maternal toxicity; retarded fetal growth and fetal cardiovascular and skeletal defects
—	250 ppm	50 ppm	Retarded fetal growth, decreased ossification, and increased skeletal variations
—	175 ppm	50 ppm	Fetal skeletal variations
—	—	—	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	–
	Male rabbits	Inhalation; 30, 100, or 300 ppm, 6 hr/day, 5 days/wk for 13 wk	100 ppm	—	–
			—	30 ppm	–
Reproductive, McGregor et al. [1983]	Male rats	Inhalation; 25 or 500 ppm, 7 hr/day for 5 days	500 ppm	25 ppm	–
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	—	—	–
Developmental, Toraason et al. [1985]	Female rats	Oral (gavage); 25 or 50 mg in 10 ml water/kg per day for 11 days	—	—	–

—	—	—	—	Microscopic testicular lesions and decreased testis weights
—	—	—	—	Slight microscopic changes in testicular tissue in 1 of 5 rabbits
—	—	—	—	Microscopic testicular lesions and decreased testis weights
—	—	—	—	Decreased fertility during weeks 3–8
—	—	31.25 mg/kg per day	—	Bifurcated or split cervical vertebrae
—	—	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
			—	—	—
Developmental, Nelson et al. [1984a]	Male rats	Inhalation; 25 ppm, 7 hr/day, 7 days/wk for 6 wk	—	—	—
	Female rats	Inhalation; 25 ppm, 7 hr/day on g.d. 7–13 or 14–20	—	—	—
Developmental, Wickramaratne [1986]	Female rats	Dermal; 3%, 10%, 30%, or 100% solutions	—	—	100%
			—	—	—
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
		2,000 mg/kg on g.d. 10, 11, 12, 13, or 14	—	—	—

10 ppm	—	—	Minimally decreased maternal body weight gains
—	50 ppm	10 ppm	Increased incidence of extra lumbar ribs and unilateral testicular hypoplasia
—	25 ppm	—	Neurochemical deviations in offspring
—	25 ppm	—	Significant differences in avoidance conditioning of offspring from mothers exposed on g.d. 7-13; neurochemical deviations in offspring
—	—	—	100% maternal death
—	10%	—	Reduced litter sizes
250 mg/kg	—	—	Decrease in mean body weight gain
—	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):

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

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:

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

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

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

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

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

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

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

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

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

8 METHODS FOR WORKER PROTECTION

8.1 INFORMING WORKERS OF HAZARDS

On November 21, 1983, OSHA promulgated an occupational safety and health standard entitled "Hazard Communication." Under the provisions of this standard (29 CFR 1910.1200), employers in the manufacturing sector (i.e., SIC Codes 20 through 39) must establish a comprehensive hazard communication program that includes, at a minimum, container labeling, material safety data sheets (MSDSs), and a worker training program. The hazard communication program is to be written and made available to workers and their designated representatives.

Chemical manufacturers, importers, and distributors are required to ensure that containers of hazardous chemicals leaving their workplaces are labeled, tagged, or marked to show the identity of the chemical, appropriate hazard warnings, and the name and address of the manufacturer or other responsible party. Employers must ensure that labels on incoming containers of hazardous chemicals are not removed or defaced unless they are immediately replaced with other labels containing the required information.

Each container in the workplace must be prominently labeled, tagged, or marked to show the identity of any hazardous chemical it contains and the hazard warnings appropriate for worker protection. If a work area has a number of stationary containers that have similar contents and hazards, the employer may post hazard signs or placards rather than label each container. Employers may use various types of standard operating procedures, process sheets, batch tickets, or other written materials as substitutes for individual container labels on stationary process equipment. However, these written materials must contain the same information that is required on the labels and must be readily accessible to workers in the work areas. Pipes or piping systems are exempted altogether from the OSHA labeling requirements, although NIOSH recommends that filler ports and outlets be labeled. In addition, NIOSH recommends that a system be set up to ensure that pipes containing hazardous materials are identified to avoid accidental cutting and discharge of their contents.

Employers are not required to label portable containers holding hazardous chemicals that have been transferred from labeled containers and that are intended only for the immediate use of the worker who performs the transfer. According to the OSHA definition of "immediate use," the container must be under the control of the worker performing the transfer and must be used only during the workshift in which the chemicals are transferred.

The OSHA Hazard Communication standard requires chemical manufacturers and importers to develop an MSDS for each hazardous chemical they produce or import. Employers in

the manufacturing sector (which includes paint and allied coating products) are required to obtain or develop an MSDS for each hazardous chemical used in the workplace. The MSDS is required to provide information such as the chemical and common names for the hazardous chemical. For hazardous chemical mixtures, the MSDS must list each hazardous component that constitutes 1% or more of the mixture. NIOSH suggests that any potential occupational carcinogen be listed. Ingredients present in concentrations of less than 1% must also be listed if there is evidence that the PEL may be exceeded or that the ingredients could present a health hazard in those concentrations. Additional information on the MSDS must include the physical and chemical characteristics of the hazardous chemical, known acute and chronic health effects, precautionary measures, and emergency and first aid procedures. The NIOSH publication entitled *A Recommended Standard—An Identification System for Occupationally Hazardous Materials* [NIOSH 1974] can be used as a guide when preparing the MSDS. Required information can be recorded on the MSDS shown in Appendix B or on a similar form.

Employers should establish a training program for all workers exposed to hazardous chemicals. Training should be provided whenever a new job is assigned and whenever a new chemical hazard is introduced into the work area. Workers should be informed about (1) any hazardous chemicals in their work areas, and (2) the availability of information about individual chemicals in the MSDS.

Workers should also be trained in methods for detecting the presence or release of hazardous chemicals (e.g., monitoring conducted by the employer, continuous monitoring devices, visual appearance or odor of hazardous chemicals when released, etc.). Training should include information about measures workers can take to protect themselves from exposure to hazardous chemicals (e.g., the use of appropriate work practices, emergency procedures, and personal protective equipment).

8.2 WORK PRACTICES

8.2.1 Worker Isolation

If feasible, workers should be isolated from direct contact with the work environment by the use of automated equipment operated from a closed control booth or room. The control room should be maintained at a positive pressure so that air flows out of rather than into the room. However, when workers must perform process checks, adjustments, maintenance, or other related operations in work areas where EGME, EGEE, or their acetates are present, personal protective clothing and equipment may be necessary, depending on exposure concentrations and the potential for dermal contact.

8.2.2 Storage and Handling

Containers of EGME, EGEE or their acetates should be stored in a cool, dry, well ventilated location away from any area containing a fire hazard. Outside or detached storage is preferred. These glycol ethers should be isolated from materials with which they are

incompatible; contact with strong oxidizing agents may cause fires and explosions. Containers of solvents, including those that contain EGME, EGEE, or their acetates, should be tightly covered at all times except when material is transferred. Working amounts of these solvents should be stored in containers that (1) hold no more than 5 gal, (2) have spring-closing lids and spout covers, and (3) are designed to safely relieve internal pressure in case of fire. Because small amounts of residue may remain and present a fire hazard, containers that have held solvents should be thoroughly cleaned with steam and then drained and dried before reuse. Fittings should not be struck with tools or other hard objects that may cause sparks. Special spark-resistant tools of nonferrous materials should be used where flammable gases, highly volatile liquids, or other explosive substances are used or stored [NSC 1980]. In addition, all sources of ignition such as smoking and open heaters should be prohibited except in specified areas. Fire hazards around tank trucks and cars can be reduced by keeping motors turned off during loading or unloading operations.

Specific OSHA requirements for the storage and handling of flammable and combustible liquids are given in 29 CFR 1910.106.

8.2.3 Sanitation and Hygiene

The preparation, storage, or consumption of food should not be permitted in areas where there is exposure to EGME, EGEE or their acetates. The employer should make handwashing facilities available and encourage the workers to use them before eating, smoking, using the toilet, or leaving the worksite. Tools and protective clothing and equipment should be cleaned as needed to maintain sanitary conditions. Toxic wastes should be collected and disposed of in a manner that is not hazardous to workers or the environment. Vacuum pickup or wet mopping should be used to clean the work area at the end of each workshift or more frequently if needed to maintain good housekeeping practices. Collected wastes should be placed in sealed containers that are labeled as to their contents. Cleanup and disposal should be conducted in a manner that enables workers to avoid contact with the waste.

Tobacco products should not be smoked, chewed, or carried uncovered in work areas. Workers should be provided with and advised to use facilities for showering and changing clothes at the end of each workshift. Work areas should be kept free of flammable debris. Flammable work materials (rags, solvents, etc.) should be stored in approved safety cans.

8.2.4 Spills and Waste Disposal

Procedures for decontamination and waste disposal should be established for materials or equipment contaminated with EGME, EGEE, or their acetates. The following procedures are recommended in the event of a spill of these glycol ethers [NIOSH 1981; DOT 1984; Canadian Center for Occupational Safety and Health 1988]:

- Exclude persons not wearing protective clothing and equipment from areas of spills or leaks until cleanup has been completed.
- Remove all ignition sources.

- Ventilate the area of a spill or leak.
- Absorb small spills on paper towels. Allow the vapors to evaporate in a suitable place such as a fume hood, allowing sufficient time for them to clear the hood ductwork. Burn the paper towels in a suitable location away from combustible materials.
- Absorb large quantities with sand or other noncombustible absorbent material and atomize the contaminated material in a suitable combustion chamber.
- Collect contaminated waste and place in sealed containers for disposal in accordance with existing regulations of the U.S. Environmental Protection Agency and the U.S. Department of Transportation. State and local regulations may supersede Federal regulations if they are more restrictive.

8.3 LABELING AND POSTING

In accordance with 29 CFR 1910.1200 (Hazard Communication), workers must be informed of chemical exposure hazards, of their potential adverse health effects, and of methods to protect themselves. Labels and signs also provide an initial warning to other workers who may not normally work near processes involving hazardous chemicals such as EGME, EGEE, or their acetates. Depending on the process, warning signs should state a need to wear eye protection or a respirator, or they may be used to limit entry to an area without protective equipment. For transient nonproduction work, it may be necessary to display warning signs at the worksite to inform other workers of the potential hazards.

All labels and warning signs should be printed in both English and the predominant language of workers who do not read English. Workers who cannot read labels or posted signs should be identified so that they may receive information about hazardous areas and be informed of the instructions printed on labels and signs.

8.4 EMERGENCIES

The employer should formulate a set of written procedures covering fire, explosion, asphyxiation, and any other foreseeable emergency that may arise during the use of materials that may contain EGME or EGEE, or their acetates. All potentially affected workers should receive training in evacuation procedures to be used in the event of fire or explosion. All workers who are using materials containing these glycol ethers should be thoroughly trained in proper work practices that reduce the potential for starting fires and causing explosions. Selected workers should be given specific training in first aid, cardiopulmonary resuscitation, and fire control. Procedures should include prearranged plans for transportation of injured workers and provision for emergency medical care. At least two trained persons in every work area should have received extensive emergency training. Necessary emergency

equipment, including appropriate respirators and other personal protective equipment, should be stored in readily accessible locations.

8.5 ENGINEERING CONTROLS

Engineering controls should be the principal method for minimizing exposure to airborne EGME, EGEE, or their acetates in the workplace. To achieve and maintain reduced airborne concentrations of these glycol ethers, adequate engineering controls are necessary (e.g., properly constructed and maintained closed-system operations and ventilation). Control technology applicable to spray painting is discussed in a NIOSH document [O'Brien and Hurley 1981].

Airborne concentrations of these glycol ethers can be most effectively controlled at the source of contamination by enclosure of the operation and use of local exhaust ventilation. Enclosures, exhaust hoods, and ductwork should be kept in good repair so that designed airflows are maintained. Measurements of variables such as capture velocity, duct velocity, or static pressure should be made at least semiannually, and preferably monthly, to demonstrate the effectiveness of the mechanical ventilation system. The use of continuous airflow indicators (such as water or oil manometers marked to indicate acceptable airflow) is recommended. The effectiveness of the system should also be made as soon as possible after any change in production, process, or control that may result in any increase in airborne contaminants.

It is essential that any scheme for exhausting air from a work area also provide a positive means of bringing in at least an equal volume of air from the outside, conditioning it, and evenly distributing it throughout the exhausted area. The ventilation system should be designed and operated to prevent the accumulation or recirculation of airborne contaminants in the workplace. Technical criteria to ensure this are discussed in the NIOSH publication, *The Recirculation of Industrial Exhaust Air* [NIOSH 1978].

Principles for design and operation of ventilation systems are presented in *Industrial Ventilation—A Manual of Recommended Practices*, published by the American Conference of Governmental Industrial Hygienists [ACGIH 1988a]; *American National Standard: Fundamentals Governing the Design and Operation of Local Exhaust Systems, Z9.2(1971)*, published by the American National Standards Institute [ANSI 1979]; and *Recommended Industrial Ventilation Guidelines*, published by NIOSH [Hagopian and Bastress 1976].

8.6 PERSONAL PROTECTIVE EQUIPMENT (PPE)

8.6.1 Protective Clothing and Equipment

Workers should use appropriate personal protective clothing and equipment that must be carefully selected, used, and maintained to be effective in preventing skin contact with EGME, EGEE or their acetates. The PPE ensemble is dictated by the worker's potential

exposure to these glycol ethers and ranges from gloves to encapsulating suits. The following materials have good but varied resistance to the chemicals indicated below [Forsberg and Mandorf 1989]:

Chemical	PPE material	Breakthrough time (hr)
EGEE	Butyl rubber, Saranex®	>8
	PE/EVAL laminate	>4
	Neoprene, nitrile	1-4
EGME	Butyl rubber	>8

To evaluate the use of these materials with EGMEA or EGEEA, users should consult the best available performance data and manufacturer's recommendations. Significant differences have been demonstrated in the chemical resistance of generically similar PPE materials (e.g., butyl) produced by different manufacturers [Mickelsen and Hall 1987]. In addition, the chemical resistance of a mixture may be significantly different from that of any of its neat components [Mickelsen et al. 1986]. Users should therefore test the candidate material with the chemicals to be used.

The worker should be trained in the proper use and care of the chemical protective clothing. After this clothing is in routine use, it should be examined along with the workplace to ensure that nothing has occurred to invalidate the effectiveness of these materials. The NIOSH publication *A Guide for Evaluating the Performance of Chemical Protective Clothing* [Roder 1990] may be helpful. Safety showers and eye wash stations should be located close to operations that involve EGME, EGEE, or their acetates.

Splash-proof chemical safety goggles or face shields (20 to 30 cm minimum) should be worn during any operation in which a solvent, caustic, or other toxic substance may be splashed into the eyes.

In addition to the possible need for wearing protective outer apparel (e.g., aprons, encapsulating suits), workers should wear work uniforms, coveralls, or similar full-body coverings that are laundered each day. Employers should provide lockers or other closed areas to store work and street clothing separately. Employers should collect work clothing at the end of each workshift and provide for its laundering. Laundry personnel should be informed about the potential hazards of handling contaminated clothing and instructed about measures to minimize their health risk.

Employers should ensure that protective clothing is inspected and maintained to preserve its effectiveness. Clothing should be kept reasonably free of oil or grease.

Workers and persons responsible for worker health and safety should be informed that protective clothing may interfere with the body's heat dissipation, especially during hot weather or in hot industries or work situations (e.g., confined spaces). Additional monitoring

is required to prevent heat-related illness when protective clothing is worn under these conditions.

8.6.2 Respiratory Protection

Engineering controls should be the primary method used to control exposure to airborne contaminants. Respiratory protection should be used by workers only in the following circumstances:

- During the development, installation, or testing of required engineering controls
- When engineering controls are not feasible to control exposure to airborne contaminants during short-duration operations such as maintenance and repair
- During emergencies

Respiratory protection is the least preferred method of controlling worker exposures and should not be used routinely to prevent or minimize exposures. When respirators are used, employers should institute a complete respiratory protection program that includes worker training at regular intervals in the use and limitations of respirators, routine air monitoring, and maintenance, inspection, cleaning, and evaluation of the respirator. Any respiratory protection program must, at a minimum, meet the requirements of 29 CFR 1910.134. Respirators should be used in accordance with the manufacturer's instructions. Each respirator user should be fit-tested and, if possible, receive a quantitative, on-the-job evaluation of his or her respiratory protection factor to confirm the protection factor assumed for that class of respirator. For additional information on the use of respiratory protection, refer to the *NIOSH Guide to Industrial Respiratory Protection* [NIOSH 1987a] and *NIOSH Respirator Decision Logic* [NIOSH 1987b].

Selection of the appropriate respirator depends on the types of glycol ethers and their concentrations in the worker's breathing zone. Before a respirator can be selected, an assessment of the work environment is necessary to determine the concentrations of EGME, EGEE, EGMEA, EGEEA and other contaminants that may be present. Respirator types should be selected in accordance with the most recent edition of the *NIOSH Respirator Decision Logic* [NIOSH 1987b].

The actual respirator selection should be made by a qualified individual, taking into account specific use conditions, including the interaction of contaminants with the filter medium, space restrictions caused by the work location, and the use of any required face and eye protective devices. Respirator selection tables are presented in Chapter 1.

8.7 CHEMICAL SUBSTITUTION

The substitution of less hazardous materials can be an important measure for reducing worker exposure to hazardous materials.

8.8 EXPOSURE MONITORING

An occupational health program designed to protect workers from adverse effects caused by exposure to EGME, EGEE, or their acetates should include the means for thoroughly identifying all potential hazards. Routine environmental sampling as an indicator of worker exposure is an important part of this program, as it provides a means of assessing the effectiveness of work practices, engineering controls, personal protective clothing and equipment, etc.

Prior knowledge of the presence of certain types of interfering compounds in the sampled environment will greatly help the analyst in the selection of 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 take place.

Initial and routine worker exposure surveys should be made by competent industrial hygiene and engineering personnel. These surveys are necessary to characterize worker exposures and to ensure that controls already in place are operational and effective. Each worker's exposure should be estimated, whether or not it is measured by a personal sampler. Therefore, the sampling strategy should allow reasonable estimates of each worker's exposure. The NIOSH publication *Occupational Exposure Sampling Strategy Manual* may be helpful in developing efficient programs to monitor worker exposure [Leidel et al. 1977].

In work areas where airborne exposures to EGME, EGEE or their acetates may occur, an initial survey should be done to determine the extent of worker exposure. In general, TWA exposures should be determined by collecting samples over a full shift. Measurements to determine worker exposure should be taken so that the average 8-hr exposure is based on a single 8-hr sample or on two 4-hr samples. Several short-term interval samples (up to 30 min) may also be used to determine the average exposure concentration.

When the potential for exposure to these glycol ethers is periodic, short-term samples may be needed to replace or supplement full-shift sampling. Personal sampling (i.e., samples collected in the worker's breathing zone) is preferred over area sampling. If personal sampling is not feasible, area sampling can be substituted only if the results can be used to approximate worker exposure. Sampling should be used to identify the sources of emissions so that effective engineering controls or work practices can be instituted.

If a worker is found to be exposed to EGME, EGEE, or their acetates at concentrations below the REL but at or above one-half the REL, the exposure of that worker should be monitored at least once every 6 months or as otherwise indicated by a professional industrial hygienist.

When the work environment contains concentrations exceeding the respective RELs for these glycol ethers, workers must wear respirators for protection until adequate engineering controls or work practices are instituted; exposure monitoring is recommended at 1-wk intervals. Such monitoring should continue until consecutive determinations at least 1 wk apart indicate that the workers' exposure no longer exceeds the REL.

When workers' exposures are greater than one-half the REL but less than the REL, sampling should be conducted after 6 months; if the concentrations of these glycol ethers are lower than one-half the REL after two consecutive biannual surveys, sampling can then be conducted annually. Exposure monitoring should be conducted whenever changes in production, process, controls, work practices, or weather conditions may result in a change in exposure conditions.

8.9 MEDICAL MONITORING

8.9.1 General Requirements

Workers exposed to EGME, EGEE, or their acetates are at risk of suffering adverse health effects. Medical monitoring as described below should be made available to all workers. The employer should provide the following information to the physician responsible for the medical monitoring program:

- Any requirements of the applicable OSHA standard or NIOSH recommended standard
- Identification of and extent of exposure to physical and chemical agents that may be encountered by the worker
- Any available workplace sampling results that characterize exposures for job categories previously and currently held by the worker
- A description of any protective devices or equipment the worker may be required to use
- The frequency and nature of any reported illness or injury of a worker
- The results of any monitoring of urinary MAA or EAA for any worker exposed to unknown concentrations of EGME or EGMEA during a spill or emergency (see Appendix G).

8.9.2. Medical Examinations

The objectives of a medical monitoring program are to augment the primary preventive measures, which include industrial hygiene monitoring of the workplace, the implementation of engineering controls, and the use of proper work practices and personal protective equipment. Medical monitoring data may also be used for epidemiologic analysis within large plants and on an industrywide basis; they should be compared with exposure data from industrial hygiene monitoring.

Medical examinations are conducted before job placement and periodically thereafter. The preplacement medical examination allows the physician to assess the applicant's functional

capacity and inform him or her of how it relates to the physical demands and risks of the job. Furthermore, such an examination provides baseline medical data that can be compared with subsequent health changes. The preplacement examination should also provide information about prior occupational exposures. Periodic medical examinations after job placement are intended to detect work-related changes in health at an early stage.

The following factors should be considered during the preplacement medical examination and any periodic medical examinations of the worker: (a) exposure to chemical and physical agents that may produce interdependent or interactive adverse effects on the worker's health (including exacerbation of pre-existing health problems and nonoccupational risk factors such as tobacco use), and (b) potentially hazardous characteristics of the worksite (e.g., confined spaces, heat, and proximity to hazards such as explosive atmospheres and toxic chemicals). The type of information that should be gathered is discussed in the following subsections.

8.9.2.1 Preplacement medical examination

8.9.2.1.1 Medical history

The medical history should contain information about occupational history, including the number of years worked in each job. Special attention should be given to any history of occupational exposure to hazardous chemical and physical agents [Guidotti et al. 1983].

8.9.2.1.2 Clinical examination

The preplacement clinical examination should determine the fitness of the worker to perform the intended job assignment. Appropriate pulmonary and musculoskeletal evaluation should be done for workers whose jobs may require extremes of physical exertion or stamina (e.g., heavy lifting), especially those who must wear personal respiratory protection. Because the standard 12-lead electrocardiogram is of little practical value in monitoring for asymptomatic cardiovascular disease, it is not recommended. More valuable diagnostic information is provided by physician interviews of workers that elicit reports of the occurrence and work-relatedness of angina, breathlessness, and other symptoms of chest illnesses. Special attention should also be given to workers who require the use of eyeglasses. These workers must be able to wear simultaneously any equipment needed for respiratory protection, eye protection, and visual acuity, and they must be able to maintain their concurrent use during work activities.

The worker's duties may be performed near unrelated operations that generate potentially harmful exposures (e.g., asbestos or cleaning or degreasing solvents). The physician must be aware of these potential exposures to evaluate possible hazards to the individual worker.

8.9.2.2 Periodic medical examination

A periodic medical examination should be conducted annually or more frequently, depending on age, health status at the time of a prior examination, and reported signs or symptoms

associated with exposure to EGME, EGEE, or their acetates. The physician should note any trends in health changes revealed by epidemiologic analyses of examination results. The occurrence of an occupationally related disease or other work-related adverse health effects should prompt an immediate evaluation of industrial hygiene control measures and an assessment of the workplace to determine the presence of a previously unrecognized hazard.

The physician's interview with the worker is an essential part of a periodic medical examination. The interview gives the physician the opportunity to learn of (1) changes in the work setting (e.g., confined spaces), and (2) potentially hazardous workplace exposures that are in the vicinity of the worker but are not related to the worker's job activities.

During the periodic medical examination, the physician should re-examine organ systems at risk to note changes from the previous examination.

8.10 BIOLOGICAL MONITORING

Urinary concentrations of the metabolites of EGME, EGEE, and their acetates may be useful biological indicators of worker exposure to these glycol ethers. Biological monitoring accounts not only for environmental concentrations and actual respiratory uptake, but also for absorption through the skin. Information about biological monitoring appears in Section 5.4 of this document and guidelines for biological monitoring are given in Appendix G.

Biological monitoring is suggested when the potential exists for (1) airborne exposure to EGME, EGEE, or their acetates at or above their respective RELs, or (2) skin contact as a result of accidental exposure or breakdown of chemical protective clothing (see Section 8.6.1). Monitoring of urinary MAA or EAA (see Appendix G) should be made available to any worker exposed to unknown concentrations of EGME, EGEE, or their acetates during a spill or other emergency. In the absence of skin exposure, a urinary MAA concentration of 0.8 mg/g creatinine or an EAA concentration of 5 mg/g creatinine approximates the concentration that would result from exposure to the REL for EGME (0.1 ppm) or EGEE (0.5 ppm) during an 8-hr workshift. If a worker's urinary MAA or EAA suggests exposure to EGME, EGEE, or their acetates above their respective RELs, an effort should be made to ascertain the cause (e.g., failure of engineering controls, poor work practices, or nonoccupational exposures).

8.11 RECORDKEEPING

Medical records as well as exposure and biological monitoring results must be maintained for workers as specified in Section 1.9 of this document. Such records must be kept for at least 30 years after termination of employment. Copies of environmental exposure records for each worker must be included with the medical records. These records must be made available to the past or present workers or to anyone having the specific written consent of a worker, as specified in Section 1.9.4 of this document.

9 RESEARCH NEEDS

The following research is needed to further reduce the risk of adverse developmental and reproductive effects from occupational exposure to EGME, EGEE, or their acetates:

- Investigations should be conducted in the workplace to relate glycol ether exposure to concentrations of metabolites in urine and toxic effects such as reduction in testis size, semen quality, etc.
- Additional studies are needed to define more accurately the human reproductive hazards posed by EGME, EGEE, and their acetates.
- Evaluations of exposed populations are needed to correlate dermal absorption of EGME, EGEE, and their acetates with concentrations of metabolites in urine.
- Additional data should be collected to quantify airborne and dermal exposures to EGME, EGEE, and their acetates under actual conditions of use in the workplace.
- Other glycol ethers should be evaluated to identify any that have effects similar to those of EGME, EGEE, and their acetates (see Appendix E for a list of glycol ethers).
- Physiologically based pharmacokinetic models for EGME, EGEE, and their acetates need to be developed and validated in both human beings and the animal species in which NOAELs were determined.
- Methods are needed for quantitative monitoring of dermal exposure.
- Epidemiologic studies are needed to determine the effects of occupational exposure to EGME, EGEE, and their acetates.
- The method of Groeseneken et al. [1989b] should be validated.

APPENDIX A

METHODS FOR SAMPLING AND ANALYSIS OF EGME, EGEE, EGMEA, AND EGEEA IN AIR*

A.1 General Requirements for Sampling

Air samples are collected that represent the air a worker breathes while performing each job or specific operation. It is advisable to maintain records of the date, time, rate, duration, volume, and location of sampling.

A.2 Collection and Shipping of Samples

1. Immediately before sampling, break the ends of the sampling tube to provide an opening at least one-half the internal diameter of the tube (2 mm).

2. Attach the sampling tube to the sampling pump with flexible tubing. The smaller section of charcoal is used as a backup and should be positioned nearest the sampling pump.

3. The charcoal tube should be placed in a vertical direction during sampling to minimize channeling through the charcoal.

4. Air being sampled should not be passed through any hose or tubing before entering the charcoal tube.

5. The flow rate of sampling should be known with an accuracy of at least ±5%. Calibrate each sampling pump with a representative charcoal tube in line.

6. The temperature, relative humidity, and pressure of the atmosphere being sampled should be recorded. If a pressure reading is not available, record the elevation.

7. The charcoal tubes should be capped with the supplied plastic caps immediately after sampling. Under no circumstances should rubber caps be used.

8. One tube should be handled in the same manner as the sample tube (break, seal, and transport), except that no air is sampled through this tube. This tube should be labeled as a blank.

*This appendix was reprinted from NIOSH [1984].

9. Capped charcoal tubes should be packed tightly and padded before they are shipped to minimize tube breakage during shipping.

10. A sample of the bulk material should be submitted to the laboratory in a glass container with a Teflon-lined cap. This sample should not be transported in the same container as the charcoal tubes.

OSHA METHOD NO. 79 FOR EGME, EGMEA, EGEE, AND EGEEA [OSHA 1990]*

2-METHOXYETHANOL (METHYL CELLOSOLVE, 2ME)
2-METHOXYETHYL ACETATE (METHYL CELLOSOLVE ACETATE, 2MEA)
2-ETHOXYETHANOL (CELLOSOLVE, 2EE)
2-ETHOXYETHYL ACETATE (CELLOSOLVE ACETATE, 2EEA)

Method no.: 79

Matrix: Air

Procedure: Samples are collected by drawing air through standard size coconut shell charcoal tubes. Samples are desorbed with 95/5 (v/v) methylene chloride/methanol and analyzed by gas chromatography using a flame ionization detector.

Recommended air volume and sampling rate: 48 liters at 0.1 liters/min for TWA samples
15 liters at 1.0 liters/min for STEL samples

	2ME	2MEA	2EE	2EEA
Target conc.: ppm (mg/m^3)	0.1 (0.3)	0.1 (0.5)	0.5 (1.8)	0.5 (2.7)
Reliable quantitation limit: ppb (μg/m^3)	6.7 (21)	1.7 (8.4)	2.1 (7.8)	1.2 (6.5)
Standard error of estimate at target concentration: (Section 4.7)	6.0%	5.7%	6.2%	5.7%

Special requirements: As indicated in OSHA Method 53 (Ref. 5.1), samples for 2MEA and 2EEA should be refrigerated upon receipt by the laboratory to minimize hydrolysis.

Status of method: Evaluated method. This method has been subjected to the established evaluation procedures of the Organic Methods Evaluation Branch.

Date: January, 1990 Chemist: Carl J. Elskamp

Organic Methods Evaluation Branch
OSHA Analytical Laboratory
Salt Lake City, Utah

*This method was reprinted from OSHA [1990].

1 General Discussion

1.1 Background

1.1.1 History of procedure

An air sampling and analytical procedure for 2ME, 2MEA, 2EE, and 2EEA (OSHA Method 53) was previously evaluated by the Organic Methods Evaluation Branch of the OSHA Analytical Laboratory (Ref. 5.1). The target concentration for all four analytes in that method was 5 ppm. OSHA is now in the process of 6(b) rulemaking to consider reducing occupational exposure to these glycol ethers. Because the proposed exposure limits may be significantly lower than the target concentrations in Method 53, the methodology was re-evaluated at lower levels.

A number of changes were made to Method 53 to accommodate the lower target concentrations.

(1) The recommended air volume for TWA samples was increased from 10 liters to 48 liters. This allows for lower detection limits and increases the TWA sampling time to a more convenient 480 min (8 hr) when sampling at 0.1 liter/min.

(2) A capillary GC column was substituted for a packed column to attain higher resolution. This was especially helpful in achieving better separation of 2ME and methylene chloride, a major component of the desorption solvent.

(3) It was found that the desorption efficiency from wet charcoal was significantly lower for 2ME, and to a lesser extent for 2EE, at these lower concentrations. This problem was overcome by adding about 125 mg of anhydrous magnesium sulfate to each desorption vial to remove the desorbed water. Because charcoal will always collect some water from sampled air, all 2ME and 2EE air samples must be treated in this manner.

Utilizing these three major modifications of Method 53, a successful evaluation was performed for these glycol ethers at the lower target concentrations. Also, a minor modification was made in the determination of desorption efficiencies. Aqueous instead of methanolic stock solutions were used to determine the desorption efficiencies for 2MEA and 2EEA. It was found that at these lower levels, when stock methanolic solutions are spiked on dry Lot 120 charcoal, part of the 2MEA and 2EEA react with the methanol to form methyl acetate and 2ME and 2EE, respectively. The reaction, which is analogous to hydrolysis, is called transesterification (alcoholysis) and is catalyzed by acid or base. The surface of dry Lot 120 charcoal is basic and the reaction was verified to occur by quantitatively

determining methyl acetate and the corresponding alcohol (2ME for 2MEA samples, 2EE for 2EEA samples) from spiked samples. Transesterification was not observed when methanolic stock solutions were spiked onto wet charcoal. Therefore, transesterification is not expected to occur for samples collected from workplace air containing methanol as well as 2MEA or 2EEA because workplace atmospheres are seldom completely dry.

Because of the number of modifications and the extensive amount of data generated in this evaluation, the findings are presented as a separate method instead of a revision of Method 53. This method supersedes Method 53, although Method 53 is still valid at the higher analyte concentrations. Although hydrolysis of 2MEA and 2EEA does not appear to be a problem at lower concentrations, as a precautionary measure, the special requirement that 2MEA and 2EEA samples should be refrigerated upon receipt by the laboratory was retained from Method 53.

1.1.2 Toxic effects (This section is for information only and should not be taken as the basis of OSHA policy.)

As reported in the Documentation of Threshold Limit Values (Refs. 5.2 to 5.5), all four analytes were investigated by Nagano et al. (Ref. 5.6) in terms of potency for testicular effects. They concluded that on an equimolar basis, the respective acetate esters were about as potent as 2ME and 2EE in producing testicular atrophy and leukopenia (an abnormally low number of white blood cells) in mice. Based on this study and because 2MEA and 2EEA hydrolyze to 2ME and 2EE respectively in the body, ACGIH suggests lowering the time-weighted TLVs for all four analytes to 5 ppm.

The following is quoted from NIOSH Current Intelligence Bulletin 39 (Ref. 5.7).

> The National Institute for Occupational Safety and Health (NIOSH) recommends that 2-methoxyethanol (2ME) and 2-ethoxyethanol (2EE) be regarded in the workplace as having the potential to cause adverse reproductive effects in male and female workers. These recommendations are based on the results of several recent studies that have demonstrated dose-related embryotoxicity and other reproductive effects in several species of animals exposed by different routes of administration. Of particular concern are those studies in which exposure of pregnant animals to concentrations of 2ME or 2EE at or below their respective Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs) led to increased incidences of embryonic death, teratogenesis, or growth retardation. Exposure of male animals resulted in

testicular atrophy and sterility. In each case the animals had been exposed to 2ME or 2EE at concentrations at or below their respective OSHA PELs. Therefore, appropriate controls should be instituted to minimize worker exposure to both compounds.

On May 20, 1986, EPA referred these four analytes to OSHA in accordance with the Toxic Substances Control Act (TSCA). On April 2, 1987, OSHA issued an Advanced Notice of Proposed Rulemaking (ANPR) which summarized the information currently available to OSHA concerning the uses, health effects, estimates of employee exposure and risk determinations for these glycol ethers. OSHA invited comments from interested parties and, based on the gathered information, will decide on appropriate action (Ref. 5.8).

1.1.3 Workplace exposure

2ME—It is used as a solvent for many purposes: cellulose esters, dyes, resins, lacquers, varnishes, and stains; and as a perfume fixative and jet fuel deicing additive (Ref. 5.2).

2MEA—It is used in photographic films, lacquers, textile printing, and as a solvent for waxes, oils, various gums and resins, cellulose acetate, and nitrocellulose (Ref. 5.3).

2EE—It is used as a solvent for nitrocellulose, natural and synthetic resins, and as a mutual solvent for the formulation of soluble oils. It is also used in lacquers, in the dyeing and printing of textiles, in varnish removers, in cleaning solutions, in products for the treatment of leather, and as an anti-icing additive for aviation fuels (Ref. 5.4).

2EEA—It is used as a blush retardant in lacquers; as a solvent for nitrocellulose, oils and resins; in wood stains, varnish removers; and in products for the treatment of textiles and leathers (Ref. 5.5).

1.1.4 Physical properties (Refs. 5.2-5.5)

Chemical formulae:

2ME- $CH_3OCH_2CH_2OH$ 2MEA- $CH_3OCH_2CH_2OOCCH_3$

2EE- $CH3CH2OCH_2CH_2OH$ 2EEA- $CH_3CH_2OCH_2CH_2OOCCH_3$

Synonyms: (Ref. 5.9)

2ME—Methyl Cellosolve; glycol monomethyl ether; ethylene glycol monomethyl ether; methyl oxitol; Ektasolve; Jeffersol EM

2MEA—Methyl Cellosolve acetate; glycol monomethyl ether acetate; ethylene glycol monomethyl ether acetate

2EE—Cellosolve solvent; ethylene glycol monoethyl ether

2EEA—Cellosolve acetate; glycol monoethyl ether acetate; ethylene glycol monoethyl ether acetate

Analyte	2ME	2MEA	2EE	2EEA
CAS no.	109-86-4	110-49-6	110-80-5	111-15-9
mol wt	76.09	118.13	90.11	132.16
bp (°C)	124.5	145	135.6	156.4
Color	all are colorless liquids			
sp gr	0.9663	1.005	0.931	0.975
vp [kPa (mm Hg) at 20°C]	0.8(6)	0.3(2)	0.49(3.7)	0.3(2)
Flash pt. (°C, closed cup)	43	49	40	49
Odor (Ref. 5.9)	mild, non-residual	mild, ether-like	sweetish	mild, non-residual
Explosive limits, % (Ref. 5.9):				
Lower	2.5	1.1	1.8	1.7
Upper	19.8	8.2	14	?

The analyte air concentrations throughout this method are based on the recommended TWA-sampling and analytical parameters. Air concentrations listed in ppm and ppb are referenced to 25°C and 101.3 kPa (760 mm Hg).

1.2 Limit-defining parameters

1.2.1 Detection limit of the analytical procedure

The detection limits of the analytical procedure are 0.10, 0.04, 0.04, and 0.03 ng per injection (1.0-μL injection with a 10:1 split) for 2ME, 2MEA, 2EE, and 2EEA respectively. These are the amounts of each analyte that will give peaks with heights approximately 5 times the height of baseline noise (Section 4.1).

1.2.2 Detection limit of the overall procedure

The detection limits of the overall procedure are 1.0, 0.40, 0.37, and 0.31 µg per sample for 2ME, 2MEA, 2EE, and 2EEA respectively. These are the amounts of each analyte spiked on the sampling device that allow recovery of amounts of each analyte equivalent to the detection limits of the analytical procedure. These detection limits correspond to air concentrations of 6.7 ppb (21 $\mu g/m^3$), 1.7 ppb (8.4 $\mu g/m^3$), 2.1 ppb (7.8 $\mu g/m^3$), and 1.2 ppb (6.5 $\mu g/m^3$) for 2ME, 2MEA, 2EE, and 2EEA respectively (Section 4.2).

1.2.3 Reliable quantitation limit

The reliable quantitation limits are the same as the detection limits of the overall procedure because the desorption efficiencies are essentially 100% at these levels. These are the smallest amounts of each analyte that can be quantitated within the requirements of recoveries of at least 75% and precisions (±1.96 SD) of ±25% or better (Section 4.3).

The reliable quantitation limits and detection limits reported in the method are based upon optimization of the GC for the smallest possible amounts of each analyte. When the target concentration of an analyte is exceptionally higher than these limits, they may not be attainable at the routine operating parameters unless one optimizes parameters of instruments.

1.2.4 Instrument response to the analyte

The instrument response over the concentration ranges of 0.5 to 2 times the target concentrations is linear for all four analytes (Section 4.4).

1.2.5 Recovery

The recovery of 2ME, 2MEA, 2EE, and 2EEA from samples used in a 15-day storage test remained above 84, 87, 84, and 85% respectively when the samples were stored at ambient temperatures. The recovery of analyte from the collection medium after storage must be 75% or greater. (Section 4.5, from regression lines shown in Figures 4.5.1.2, 4.5.2.2, 4.5.3.2, and 4.5.4.2)

1.2.6 Precision (analytical procedure)

The pooled coefficients of variation obtained from replicate determinations of analytical standards at 0.5, 1, and 2 times the target concentrations are 0.022, 0.004, 0.002, and 0.002 for 2ME, 2MEA, 2EE, and 2EEA respectively (Section 4.6).

1.2.7 Precision (overall procedure)

The precisions at the 95% confidence level for the ambient temperature 15-day storage tests are ±11.7, ±11.1, ±12.3, and ±11.2% for 2ME, 2MEA, 2EE, and 2EEA respectively. These include an additional ±5% for sampling error. The overall procedure must provide results at the target concentration that are ±25% or better at the 95% confidence level (Section 4.7).

1.2.8 Reproducibility

Six samples for each analyte collected from controlled test atmospheres and a draft copy of this procedure were given to a chemist unassociated with this evaluation. The samples were analyzed after 12 days of refrigerated storage. No individual sample result deviated from its theoretical value by more than the precision reported in Section 1.2.7 (Section 4.8).

1.3 Advantages

1.3.1 Charcoal tubes provide a convenient method for sampling.

1.3.2 The analysis is rapid, sensitive, and precise.

1.4 Disadvantage

It may not be possible to analyze co-collected solvents using this method. Most of the other common solvents which are collected on charcoal are analyzed after desorption with carbon disulfide.

2 Sampling Procedure

2.1 Apparatus

2.1.1 Samples are collected using a personal sampling pump calibrated to within ±5% of the recommended flow rate with a sampling tube in line.

2.1.2 Samples are collected with solid sorbent sampling tubes containing coconut shell charcoal. Each tube consists of two sections of charcoal separated by a urethane foam plug. The front section contains 100 mg of charcoal and the back section, 50 mg. The sections are held in place with glass wool plugs in a glass tube 4-mm i.d. × 70-mm length. For this evaluation, SKC Inc. charcoal tubes (catalog number 226-01, Lot 120) were used.

2.2 Reagents

None required

2.3 Technique

2.3.1 Immediately before sampling, break off the ends of the charcoal tube. All tubes should be from the same lot.

2.3.2 Connect the sampling tube to the sampling pump with flexible tubing. Position the tube so that sampled air first passes through the 100-mg section.

2.3.3 Air being sampled should not pass through any hose or tubing before entering the sampling tube.

2.3.4 Place the sampling tube vertically (to avoid channeling) in the employee's breathing zone.

2.3.5 After sampling, seal the tubes immediately with plastic caps and wrap lengthwise with OSHA Form 21.

2.3.6 Submit at least one blank sampling tube with each sample set. Blanks should be handled in the same manner as samples, except no air is drawn through them.

2.3.7 Record sample volumes (in liters of air) for each sample, along with any potential interferences.

2.3.8 Ship any bulk sample(s) in a container separate from the air samples.

2.4 Sampler capacity

2.4.1 Sampler capacity is determined by measuring how much air can be sampled before breakthrough of analyte occurs (i.e., the sampler capacity is exceeded). Individual breakthrough studies were performed on each of the four analytes by monitoring the effluent from sampling tubes containing only the 100-mg section of charcoal while sampling at 0.2 liters/min from atmospheres containing 10 ppm analyte. The atmospheres were at approximately 80% relative humidity and 20-25°C. No breakthrough was detected in any of the studies after sampling for at least 6 hr (>70 liters). (These data were collected in the evaluation of OSHA Method 53, Ref. 5.1.)

2.4.2 A similar study as in 2.4.1 was done while sampling an atmosphere containing 10 ppm of all four analytes. The atmosphere was sampled for more than 5 hr (>60 liters) with no breakthrough detected. (These data were collected in the evaluation of OSHA Method 53, Ref. 5.1.)

2.5 Desorption efficiency

2.5.1 The average desorption efficiencies of 2ME, 2MEA, 2EE, and 2EEA from Lot 120 charcoal are 95.8, 97.9, 96.5, and 98.3% respectively over the

range of 0.5 to 2 times the target concentrations. Desorption samples for 2MEA and 2EEA must not be determined by using methanolic stock solutions since a transesterification reaction can occur (Section 4.9).

2.5.2 Desorbed samples remain stable for at least 24 hr (Section 4.10).

2.6 Recommended air volume and sampling rate

2.6.1 For TWA samples, the recommended air volume is 48 liters collected at 0.1 liters/min (8-hr samples).

2.6.2 For short-term samples, the recommended air volume is 15 liters collected at 1.0 liter/min (15-min samples).

2.6.3 When short-term samples are required, the reliable quantitation limits become larger. For example, the reliable quantitation limit is 21 ppb (67 $\mu g/m^3$) for 2ME when 15 liters is sampled.

2.7 Interferences (sampling)

2.7.1 It is not known if any compound(s) will severely interfere with the collection of any of the four analytes on charcoal. In general, the presence of other contaminant vapors in the air will reduce the capacity of charcoal to collect the analytes.

2.7.2 Suspected interferences should be reported to the laboratory with submitted samples.

2.8 Safety precautions (sampling)

2.8.1 Attach the sampling equipment to the employee so that it will not interfere with work performance or safety.

2.8.2 Wear eye protection when breaking the ends of the charcoal tubes.

2.8.3 Follow all safety procedures that apply to the work area being sampled.

3 Analytical Procedure

3.1 Apparatus

3.1.1 A GC equipped with a flame ionization detector. For this evaluation, a Hewlett-Packard 5890 Series II Gas Chromatograph equipped with a 7673A Automatic Sampler was used.

3.1.2 A GC column capable of separating the analyte of interest from the desorption solvent, internal standard, and any interferences. A thick film, 60-m × 0.32-mm i.d., fused silica RTx-Volatiles column (Cat. no. 10904, Restek Corp., Bellefonte, PA) was used in this evaluation.

3.1.3 An electronic integrator or some other suitable means of measuring peak areas or heights. A Hewlett-Packard 18652A A/D converter interfaced to a Hewlett-Packard 3357 Lab Automation Data System was used in this evaluation.

3.1.4 Two-milliliter vials with Teflon-lined caps.

3.1.5 A dispenser capable of delivering 1.0 mL to prepare standards and samples. If a dispenser is not available, a 1.0-mL volumetric pipet may be used.

3.1.6 Syringes of various sizes for preparation of standards.

3.1.7 Volumetric flasks and pipets to dilute the pure analytes in preparation of standards.

3.2 Reagents

3.2.1 2-Methoxyethanol, 2-methoxyethyl acetate, 2-ethoxyethanol, and 2-ethoxyethyl acetate, reagent grade. Aldrich Lot HBO62777 2ME, Eastman Lot 701-2 2MEA, Aldrich Lot DB040177 2EE, and Aldrich Lot 04916HP 2EEA were used in this evaluation.

3.2.2 Anhydrous magnesium sulfate, reagent grade. Chempure Lot M172 KDHM was used in this evaluation.

3.2.3 Methylene chloride, chromatographic grade. American Burdick and Jackson Lot AQ098 was used in this evaluation.

3.2.4 Methanol, chromatographic grade. American Burdick and Jackson Lot AT015 was used in this evaluation.

3.2.5 A suitable internal standard, reagent grade. "Quant Grade" 3-methyl-3-pentanol from Polyscience Corporation was used in this evaluation.

3.2.6 The desorption solvent consists of methylene chloride/methanol, 95/5 (v/v) containing an internal standard at a concentration of 20 µL/liter.

3.2.7 GC grade nitrogen, air, and hydrogen.

3.3 Standard preparation

3.3.1 Prepare concentrated stock standards by diluting the pure analytes with methanol. Prepare working standards by injecting microliter amounts of concentrated stock standards into vials containing 1.0 mL of desorption solvent delivered from the same dispenser used to desorb samples. For example, to prepare a stock standard of 2ME, dilute 195 µL of pure 2ME (sp gr = 0.9663) to 50.0 mL with methanol. This stock solution would contain 3.769 µg/µL. A working standard of 15.08 µg/sample is prepared by injecting 4.0 µL of this stock into a vial containing 1.0 mL of desorption solvent.

3.3.2 Bracket sample concentrations with working standard concentrations. If samples fall outside of the concentration range of prepared standards, prepare and analyze additional standards to ascertain the linearity of response.

3.4 Sample preparation

3.4.1 Transfer each section of the samples to separate vials. Discard the glass tubes and plugs.

3.4.2 For 2ME and 2EE samples, add about 125 mg of magnesium sulfate to each vial.

3.4.3 Add 1.0 mL of desorption solvent to each vial using the same dispenser as used for preparation of standards.

3.4.4 Immediately cap the vials and shake them periodically for about 30 min.

3.5 Analysis

3.5.1 GC conditions

zone temperatures:	column—80°C for 4 min 10°C/min to 125°C 125°C for 4 min injector—150°C detector—200°C
gas flows (mL/min):	hydrogen (carrier)—2.5 (80 kPa head pressure) nitrogen (makeup)—20 hydrogen (flame)—65 air—400
injection volume:	1.0 µL (with a 10:1 split)
column:	60-m × 0.32-mm i.d. fused silica, RTx-Volatiles, thick film
retention times (min):	2ME-5.0 2MEA-10.0 2EE-6.7 2EEA-11.9 (3-methyl-3-pentanol-7.5)
chromatograms:	Section 4.11

3.5.2 Peak areas (or heights) are measured by an integrator or other suitable means.

3.5.3 An internal standard (ISTD) calibration method is used. Calibration curves are prepared by plotting micrograms of analyte per sample versus ISTD-corrected response of standard injections. Sample concentrations must be bracketed by standards.

3.6 Interferences (analytical)

3.6.1 Any compound that responds on a flame ionization detector and has the same general retention time of the analyte or internal standard is a potential interference. Possible interferences should be reported to the laboratory with submitted samples by the industrial hygienist. These interferences should be considered before samples are desorbed.

3.6.2 GC parameters (i.e., column and column temperature) may be changed to possibly circumvent interferences.

3.6.3 Retention time on a single column is not considered proof of chemical identity. Analyte identity should be confirmed by GC/mass spectrometer if possible.

3.7 Calculations

The analyte concentration for samples is obtained from the appropriate calibration curve in terms of micrograms per sample, uncorrected for desorption efficiency. The air concentration is calculated using the following formulae. The back (50-mg) section is analyzed primarily to determine if there was any breakthrough from the front (100-mg) section during sampling. If a significant amount of analyte is found on the back section (e.g., greater than 25% of the amount found on the front section), this fact should be reported with sample results. If any analyte is found on the back section, it is added to the amount found on the front section. This total amount is then corrected by subtracting the total amount (if any) found on the blank.

$$mg/m^3 = \frac{\text{(micrograms of analyte per sample)}}{\text{(liters of air sampled) (desorption efficiency)}}$$

where desorption efficiency = 0.958 for 2ME, 0.979 for 2MEA
0.965 for 2EE, 0.983 for 2EEA

$$ppm = \frac{(mg/m^3)\,(24.46)}{\text{(molecular weight of analyte)}}$$

where 24.46 = molar volume (liters) at 25°C and 101.3 kPa (760 mm Hg)
molecular weight = 76.09 for 2ME, 118.13 for 2MEA
90.11 for 2EE, 132.16 for 2EEA

3.8 Safety precautions (analytical)

3.8.1 Avoid skin contact and inhalation of all chemicals.

3.8.2 Restrict the use of all chemicals to a fume hood when possible.

3.8.3 Wear safety glasses and a lab coat at all times while in the lab area.

4 Backup Data

4.1 Detection limit of the analytical procedure

The injection size listed in the analytical procedure (1.0 µL with a 10:1 split) was used in the determination of the detection limits of the analytical procedure. The detection limits of 0.10, 0.04, 0.04, and 0.03 ng were determined by making injections of 1.00, 0.40, 0.37, and 0.31 ng/µL standards for 2ME, 2MEA, 2EE, and 2EEA respectively. These amounts were judged to produce peaks with heights approximately 5 times the baseline noise. Chromatograms of such injections are shown in Figures 4.1.1 and 4.1.2.

4.2 Detection limit of the overall procedure

Six samples for each analyte were prepared by injecting (from dilute aqueous standards) 1.00 µg of 2ME, 0.40 µg of 2MEA, 0.37 µg of 2EE, and 0.31 µg of 2EEA into the 100-mg section of charcoal tubes. The samples were stored at room temperature and analyzed the next day. The detection limits of the overall procedure correspond to air concentrations of 6.7 ppb (21 $\mu g/m^3$), 1.7 ppb (8.4 $\mu g/m^3$), 2.1 ppb (7.8 $\mu g/m^3$), and 1.2 ppb (6.5 $\mu g/m^3$) for 2ME, 2MEA, 2EE, and 2EEA respectively. The results are given in Tables 4.2.1 to 4.2.4.

Table 4.2.1
Detection Limit of Overall Procedure for 2ME

Sample no.	µg spiked	µg recovered
1	1.00	0.908
2	1.00	0.945
3	1.00	0.957
4	1.00	0.982
5	1.00	1.067
6	1.00	0.969

Table 4.2.2
Detection Limit of Overall Procedure for 2MEA

Sample no.	µg spiked	µg recovered
1	0.40	0.382
2	0.40	0.392
3	0.40	0.385
4	0.40	0.402
5	0.40	0.402
6	0.40	0.408

Table 4.2.3
Detection Limit of Overall Procedure for 2EE

Sample no.	µg spiked	µg recovered
1	0.37	0.347
2	0.37	0.352
3	0.37	0.347
4	0.37	0.388
5	0.37	0.370
6	0.37	0.361

Table 4.2.4
Detection Limit of Overall Procedure for 2EEA

Sample no.	µg spiked	µg recovered
1	0.31	0.301
2	0.31	0.319
3	0.31	0.304
4	0.31	0.322
5	0.31	0.328
6	0.31	0.328

4.3 Reliable quantitation limit

The reliable quantitation limits were determined by analyzing charcoal tubes spiked with loadings equivalent to the detection limits of the analytical procedure. Samples were prepared by injecting 1.0 µg of 2ME, 0.40 µg of 2MEA, 0.37 µg of

2EE, and 0.31 µg of 2EEA into the 100-mg section of charcoal tubes. These amounts correspond to air concentrations of 6.7 ppb (21 µg/m^3), 1.7 ppb (8.4 µg/m^3), 2.1 ppb (7.8 µg/m^3), and 1.2 ppb (6.5 µg/m^3) for 2ME, 2MEA, 2EE, and 2EEA respectively. The results are given in Tables 4.3.1 to 4.3.4.

Table 4.3.1
Reliable Quantitation Limit for 2ME
(Based on samples and data of Table 4.2.1)

Sample no.	Percent recovered	Statistics
1	90.8	$\bar{X}$ = 97.1
2	94.5	
3	95.7	
4	98.2	SD = 5.3
5	106.7	Precision = (1.96)(±5.3)
6	96.9	= ±10.4

Table 4.3.2
Reliable Quantitation Limit for 2MEA
(Based on samples and data of Table 4.2.2)

Sample no.	Percent recovered	Statistics
1	95.5	$\bar{X}$ = 98.8
2	98.0	
3	96.2	
4	100.5	SD = 2.6
5	100.5	Precision = (1.96)(±2.6)
6	102.0	= ±5.1

Table 4.3.3
Reliable Quantitation Limit for 2EE
(Based on samples and data of Table 4.2.3)

Sample no.	Percent recovered	Statistics
1	93.8	$\bar{X}$ = 97.5
2	95.1	
3	93.8	
4	104.9	SD = 4.3
5	100.0	Precision = (1.96)(±4.3)
6	97.6	= ±8.4

Table 4.3.4
Reliable Quantitation Limit for 2EEA
(Based on samples and data of Table 4.2.4)

Sample no.	Percent recovered	Statistics
1	97.1	$\bar{X}$ = 102.3
2	102.9	
3	98.1	
4	103.9	SD = 3.8
5	105.8	Precision = (1.96)(±3.8)
6	105.8	= ±7.4

4.4 Instrument response to the analyte

The instrument response to the analytes over the range of 0.5 to 2 times the target concentrations was determined from multiple injections of analytical standards. These data are given in Tables 4.4.1 to 4.4.4 and Figures 4.4.1 and 4.4.2. The response is linear for all four analytes with slopes (in ISTD-corrected area counts per micrograms of analyte per sample) of 980, 1040, 1300, and 1330 for 2ME, 2MEA, 2EE, and 2EEA respectively.

4.5 Storage test

Storage samples are normally generated by sampling the recommended air volume at the recommended sampling rate from test atmospheres at 80% relative humidity containing the analyte at the target concentration. Because this would require generation of 8-hr samples, in the interest of time, samples were generated by sampling from atmospheres containing the analytes at about 4 times the target concentrations for 60 min at 0.2 liters/min (12-liter samples). (Note: To test the performance of the sampler for 48-liter volumes and to show the validity of collecting 12-liter samples at 4 times the target concentrations instead of 48-liter samples at the target concentrations, a set of six 48-liter samples at the target concentration for each analyte was individually generated and compared to the corresponding Day 0 samples. All samples agreed within the precisions of the method.) 2ME and 2EE were generated in the same atmosphere, and 2MEA and 2EEA were generated together in another atmosphere. For each set of 36 samples, 6 samples were analyzed immediately after generation, 15 were stored in a refrigerator at 0°C and 15 were stored in a closed drawer at ambient temperatures of 20-25°C. Six samples, three from refrigerated and three from ambient storage, were analyzed in 3-day intervals over a period of 15 days. The results are given in Tables 4.5.1 to 4.5.4 and shown graphically in Figures 4.5.1.1, 4.5.1.2, 4.5.2.1, 4.5.2.2, 4.5.3.1, 4.5.3.2, 4.5.4.1, and 4.5.4.2.

Table 4.4.1
Instrument Response to 2ME

× target conc.	0.5×	1×	2×
µg/sample	7.537	15.07	30.15
ppm	0.050	0.101	0.202
area counts	6930.6	14033	29007
	6832.1	14219	28908
	6771.4	14139	28920
	6655.9	14133	28691
	6202.5	14165	28834
	6786.0	14176	28887
$\bar{X}$	6696.4	14144	28874

Table 4.4.2
Instrument Response to 2MEA

× target conc.	0.5×	1×	2×
mg/sample	11.66	23.32	46.63
ppm	0.050	0.101	0.201
area counts	11946	24182	48262
	11772	24108	48302
	11987	24124	48160
	12002	24230	48281
	11954	24168	48116
	11888	24111	48250
$\bar{X}$	11925	24154	48228

Table 4.4.3
Instrument Response to 2EE

× target conc.	0.5×	1×	2×
µg/sample	44.69	89.38	178.8
ppm	0.253	0.505	1.01
area counts	54351	112883	229836
	54263	113321	229797
	53870	113357	229284
	54239	113320	229292
	54102	113176	228496
	54292	113418	229250
$\bar{X}$	54186	113246	229326

Table 4.4.4
Instrument Response to 2EEA

× target conc.	0.5×	1×	2×
µg/sample	64.35	128.7	257.4
ppm	0.248	0.496	0.992
area counts	84793	171546	342651
	84896	171239	343419
	84718	171727	341665
	84795	171787	342505
	84446	171303	341122
	84612	171138	342812
$\overline{X}$	84710	171457	342362

Table 4.5.1
Storage Data for 2ME

Storage time (days)	% recovery (refrigerated)			% recovery (ambient)		
0	97.8	102.0	96.3	97.8	102.0	96.3
0	99.9	104.2	94.8	99.9	104.2	94.8
3	96.8	99.5	95.9	93.7	91.7	94.2
6	96.3	96.6	93.3	92.8	91.4	92.8
9	91.4	88.8	91.4	86.1	88.8	87.5
1	289.9	89.8	88.7	91.3	93.1	86.9
1	587.4	88.8	84.4	87.8	79.8	80.7

Table 4.5.2
Storage Data for 2ME

Storage time (days)	% recovery (refrigerated)			% recovery (ambient)		
0	101.2	103.5	101.8	101.2	103.5	101.8
0	102.0	105.0	103.8	102.0	105.0	103.8
3	96.8	99.2	99.4	94.1	95.0	93.7
6	94.2	93.1	95.9	92.6	93.3	92.0
9	96.9	99.7	98.7	92.0	90.8	90.2
12	95.1	96.2	95.5	88.6	90.5	87.1
15	94.0	95.9	96.1	89.3	89.4	89.8

Table 4.5.3
Storage Data for 2EE

Storage time (days)	% recovery (refrigerated)			% recovery (ambient)		
0	96.4	101.4	95.8	96.4	101.4	95.8
0	99.8	100.2	93.9	99.8	100.2	93.9
3	93.9	100.5	98.3	93.9	95.7	96.2
6	96.4	96.9	96.7	93.4	96.8	94.0
9	92.1	88.2	91.5	81.6	87.9	88.0
12	89.2	89.6	89.1	92.6	92.3	86.1
15	88.6	88.4	84.1	90.1	80.4	80.0

Table 4.5.4
Storage Data for 2EEA

Storage time (day)	% recovery (refrigerated)			% recovery (ambient)		
0	99.7	101.7	101.8	99.7	101.7	101.8
0	100.9	104.1	102.2	100.9	104.1	102.2
3	94.5	96.7	103.6	92.8	94.2	91.6
6	92.7	92.2	95.7	91.4	91.5	90.8
9	96.2	98.7	98.0	90.3	88.9	88.8
12	93.5	94.6	94.7	87.0	88.8	84.9
15	92.9	95.0	95.2	87.6	87.6	87.6

4.6 Precision (analytical procedure)

The precision of the analytical procedure for each analyte is the pooled coefficient of variation determined from replicate injections of standards.

The precision of the analytical procedure for each analyte is given in Tables 4.6.1 to 4.6.4. These tables are based on the data presented in Section 4.4.

Table 4.6.1
Precision of the Analytical Procedure for 2ME
(Based on Table 4.4.1)

× target conc.	**0.5×**	**1×**	**2×**
µg/sample	**44.69**	**89.38**	**178.8**
ppm	**0.253**	**0.505**	**1.01**
SD (area counts)	257.9	62.5	106.0
CV	0.0385	0.0044	0.0037

$\overline{CV}$ = 0.022

Table 4.6.2
Precision of the Analytical for 2MEA
(Based on Table 4.4.2)

× target conc.	0.5×	1×	2×
µg/sample	11.66	23.32	46.63
ppm	0.050	0.101	0.201
SD (area counts)	84.7	48.2	73.6
CV	0.0071	0.0020	0.0015

$\overline{CV}$ = 0.004

Table 4.6.3
Precision of the Analytical for 2EE
(Based on Table 4.4.3)

× target conc.	0.5×	1×	2×
µg/sample	44.69	89.38	178.8
ppm	0.253	0.505	1.01
SD (area counts)	175.6	194.8	485.7
CV	0.0032	0.0017	0.0021

$\overline{CV}$ = 0.002

Table 4.6.4
Precision of the Analytical for 2EEA
(Based on Table 4.4.4)

× target conc.	0.5×	1×	2×
µg/sample	64.35	128.7	257.4
ppm	0.248	0.496	0.992
SD (area counts)	160.0	269.3	830.3
CV	0.0019	0.0016	0.0024

$\overline{CV}$ = 0.002

4.7 Precision (overall procedure)

The precision of the overall procedure is determined from the storage data. The determination of the standard error of estimate (SEE) for a regression line plotted through the graphed storage data allows the inclusion of storage time as one of the factors affecting overall precision. The SEE is similar to the standard deviation,

except it is a measure of dispersion of data about a regression line instead of about a mean. It is determined with the following equation:

$$SEE = \left[\frac{\Sigma(Y_{obs} - Y_{est})^2}{n - k}\right]^{1/2}$$

where

n = total no. of data points
k = 2 for linear regression
k = 3 for quadratic regression
Yobs = observed % recovery at a given time
Yest = estimated % recovery from the regression line at the same given time

An additional 5% for pump error is added to the SEE by the addition of variances. The SEEs are 6.0%, 5.7%, 6.2%, and 5.7% for 2ME, 2MEA, 2EE, and 2EEA respectively. The precision of the overall procedure is the precision at the 95% confidence level, which is obtained by multiplying the SEE (with pump error included) by 1.96 (the z-statistic from the standard normal distribution at the 95% confidence level). The 95% confidence intervals are drawn about their respective regression lines in the storage graphs. The precisions of the overall procedure are ±11.7%, ±11.1%, ±12.3%, and ±11.2% for 2ME, 2MEA, 2EE, and 2EEA respectively. The SEE and precision of the overall procedure for each analyte were obtained from Figures 4.5.1.2, 4.5.2.2, 4.5.3.2, and 4.5.4.2 for 2ME, 2MEA, 2EE, and 2EEA respectively.

4.8 Reproducibility

Six samples for each analyte, collected from controlled test atmospheres (at about 80% R.H., 20-26°C, 86-88 kPa) containing the analytes at about 4 times the target concentrations, were analyzed by chemists unassociated with this evaluation. The samples were generated by drawing the test atmospheres through sampling tubes for 60 min at approximately 0.2 liters/min. The samples were stored in a refrigerator for 12 days before being analyzed. The results are presented in Tables 4.8.1 to 4.8.4.

Table 4.8.1
Reproducibility for 2ME

Sample no.	µg found	µg expected	% found	% deviation
1	14.90	14.59	102.1	+2.1
2	15.21	15.36	99.0	-1.0
3	15.06	14.93	100.9	+0.9
4	15.42	15.38	100.3	+0.3
5	15.41	15.07	102.3	+2.3
6	15.88	15.54	102.2	+2.2

Table 4.8.2
Reproducibility for 2MEA

Sample no.	µg found	µg expected	% found	% deviation
1	21.61	23.35	92.5	-7.5
2	20.33	22.77	89.3	-10.7
3	21.47	23.12	92.9	-7.1
4	21.51	22.84	94.2	-5.8
5	22.44	23.87	94.0	-6.0
6	22.48	24.01	93.6	-6.4

Table 4.8.3
Reproducibility for 2EE

Sample no.	µg found	µg expected	% found	% deviation
1	83.47	85.55	97.6	-2.4
2	88.22	90.07	97.9	-2.1
3	84.10	87.57	96.0	-4.0
4	86.57	90.20	96.0	-4.0
5	84.79	88.40	95.9	-4.1
6	88.90	91.16	97.5	-2.5

Table 4.8.4
Reproducibility for 2EEA

Sample no.	µg found	µg expected	% found	% deviation
1	117.3	129.9	90.3	-9.7
2	118.1	126.7	93.2	-6.8
3	117.5	128.6	91.4	-8.6
4	117.4	127.1	92.4	-7.6
5	122.8	132.8	92.5	-7.5
6	121.9	133.6	91.2	-8.8

4.9 Desorption efficiency

The desorption efficiency for each analyte was determined by injecting microliter amounts of aqueous stock standards onto the front section of charcoal tubes. Aqueous standards were used because it was found that when methanolic standards were injected onto dry charcoal, part of the 2MEA and 2EEA reacted with the methanol via transesterification (alcoholysis). The reaction was presumably catalyzed by the basic surface of the charcoal. Eighteen samples were prepared,

six samples for each concentration level listed in the following tables. The samples were stored in a refrigerator and analyzed the next day.

Table 4.9.1
Desorption Efficiency Data for 2ME and 2MEA

Analyte		2EE			2EEA	
× target conc.	0.5×	1×	2×	0.5×	1×	2×
µg/sample	7.537	15.07	30.15	11.66	23.32	46.63
ppm	0.050	0.101	0.202	0.050	0.101	0.201
Desorption efficiency, %	92.8	94.5	96.2	97.6	97.6	96.7
	96.8	97.7	97.0	98.8	98.0	98.3
	93.0	94.0	98.0	97.4	98.3	98.0
	97.1	96.4	97.6	97.5	99.6	96.9
	95.8	94.9	96.2	97.9	99.1	96.7
	90.7	97.9	97.3	98.1	98.4	96.9
$\bar{X}$	94.4	95.9	97.0	97.9	98.5	97.2
$\bar{\bar{X}}$		95.8			97.9	

Table 4.9.2
Desorption Efficiency Data for 2EE and 2EEA

Analyte		2EE			2EEA	
× target conc.	0.5×	1×	2×	0.5×	1×	2×
µg/sample	44.69	89.38	178.8	64.35	128.7	257.4
ppm	0.2530	0.505	1.01	0.248	0.496	0.992
Desorption efficiency, %	94.9	95.4	96.9	97.7	98.5	97.1
	95.3	97.3	97.7	99.1	98.8	98.4
	93.1	94.9	98.4	98.6	98.8	98.2
	97.3	97.2	98.3	98.3	100.2	97.5
	95.4	97.7	96.9	98.5	99.5	96.8
	93.0	98.8	98.1	97.9	98.9	97.3
$\bar{X}$	94.8	96.9	97.7	98.4	99.1	97.6
$\bar{\bar{X}}$		96.5			98.3	

4.10 Stability of desorbed samples

The stability of desorbed samples was checked by reanalyzing the target concentration samples from Section 4.9 one day later using fresh standards. The sample

vials were resealed with new septa after the original analyses and were allowed to stand at room temperature until reanalyzed. The results are given in Table 4.10.

Table 4.10
Stability of Desorbed Samples
at the Target Concentration

	% desorption after 24 h			
Sample no.	2ME	2MEA	2EE	2EEA
1	95.0	100.9	98.9	101.6
2	97.7	99.4	99.0	101.0
3	98.5	101.3	99.3	101.6
4	98.4	101.8	99.0	101.9
5	99.7	101.2	100.2	101.4
6	98.5	101.2	100.2	101.7
$\overline{X}$	98.0	101.0	99.4	101.5

4.11 Chromatograms

A chromatogram of the four analytes is shown in Figure 4.11. The chromatogram is from an injection of a standard equivalent to a 48-liter air sample at the target concentrations.

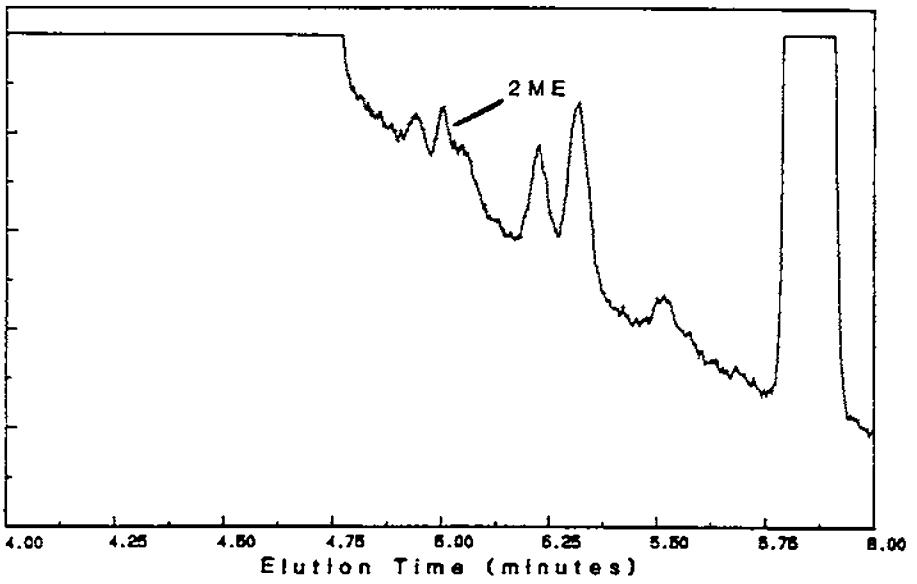

Figure 4.1.1 Detection limit chromatogram for 2ME.

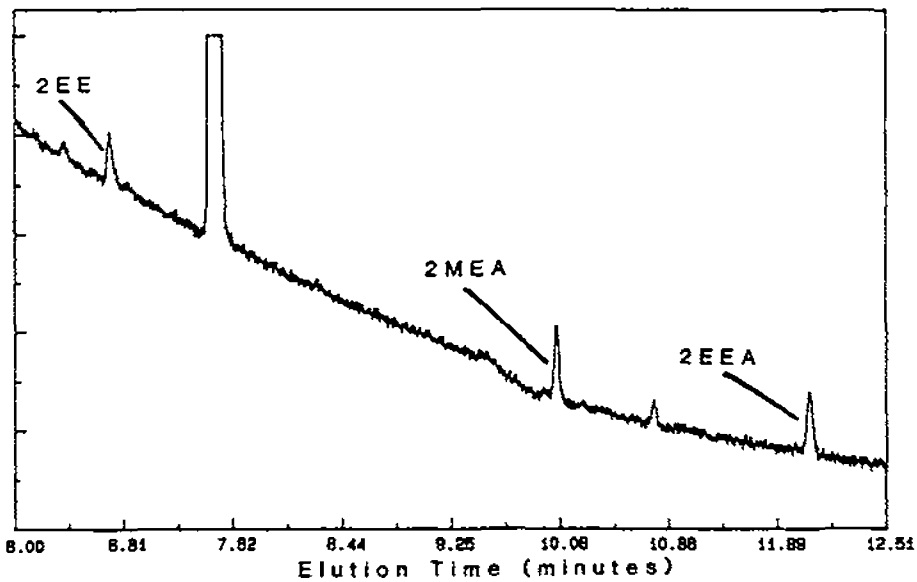

Figure 4.1.2 Detection limit chromatogram for 2MEA, 2EE, and 2EEA.

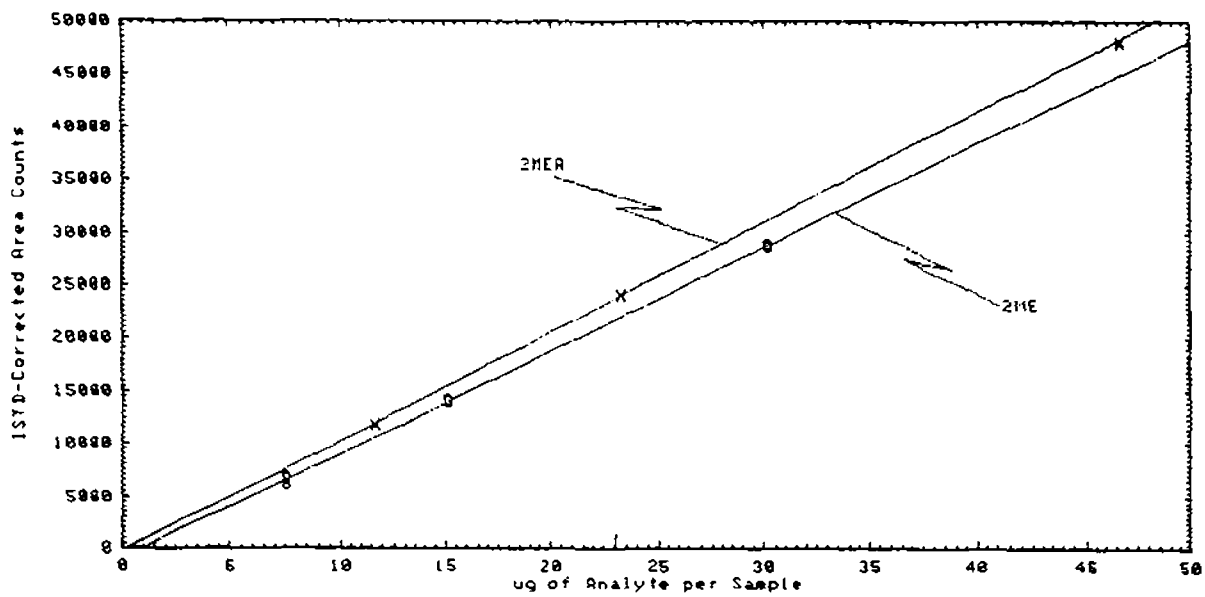

Figure 4.4.1 Instrument response to 2ME and 2MEA.

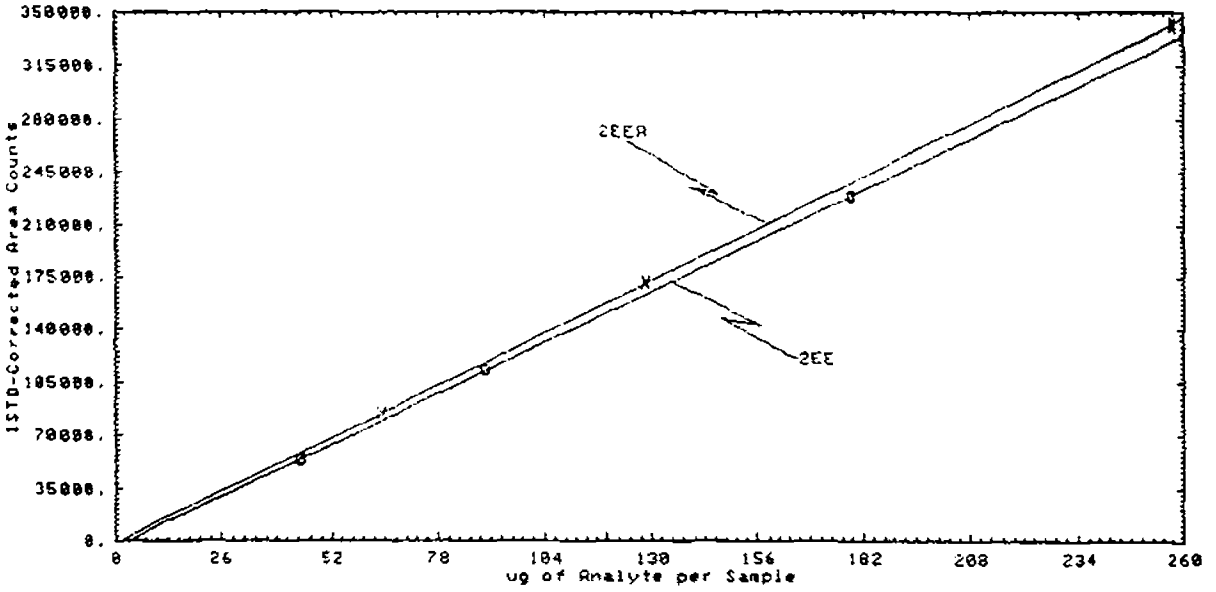

Figure 4.4.2 Instrument response to 2EE and 2EEA.

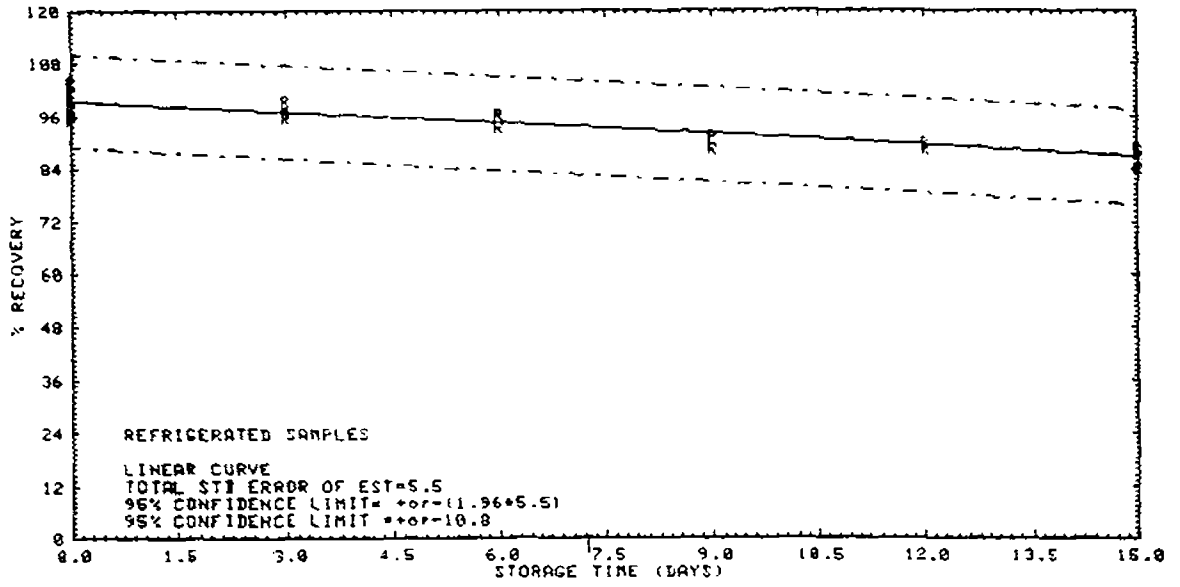

Figure 4.5.1.1 2ME refrigerated storage samples.

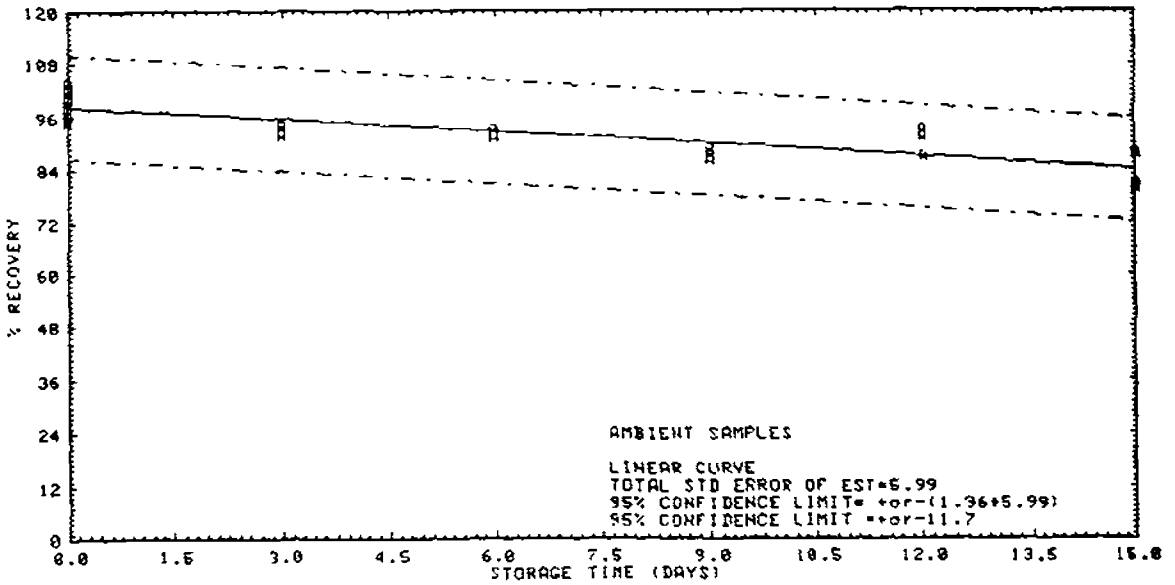

Figure 4.5.1.2 2ME ambient storage samples.

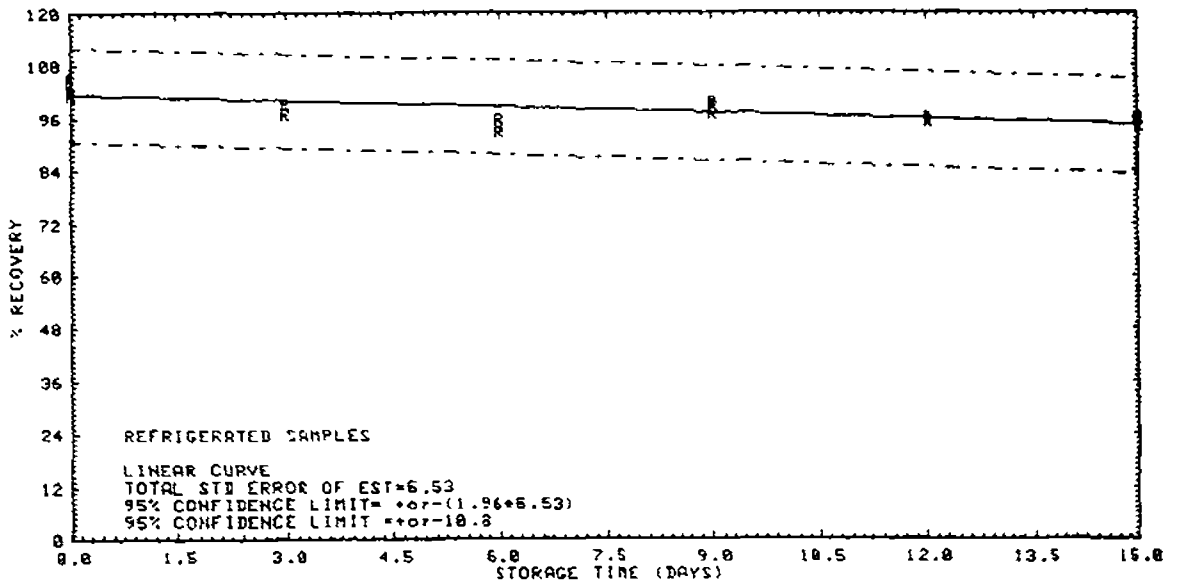

Figure 4.5.2.1 2MEA refrigerated storage samples.

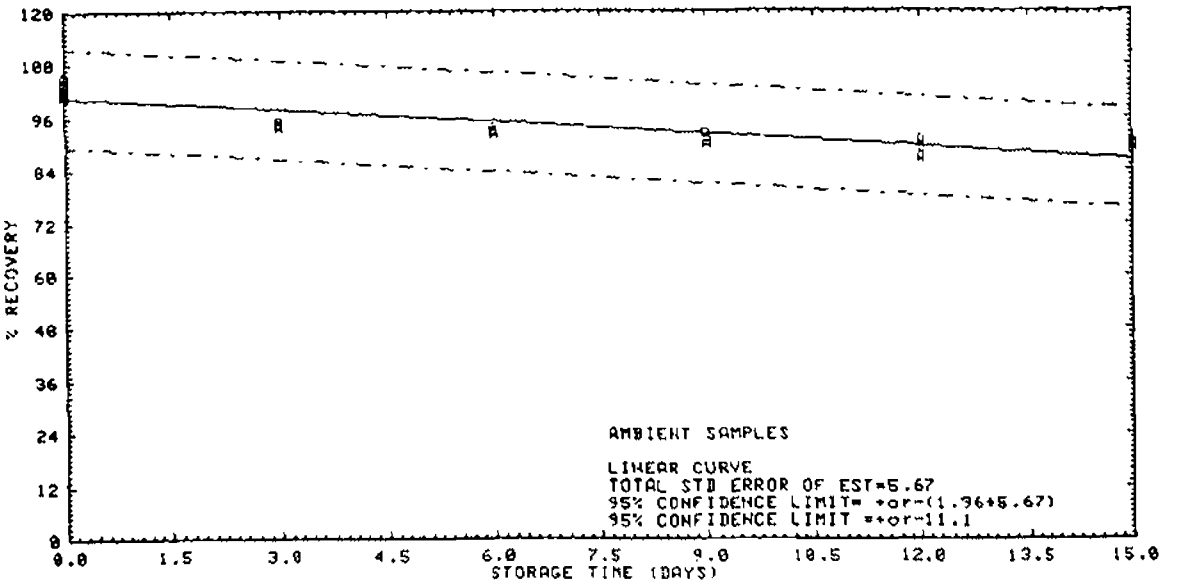

Figure 4.5.2.2 2MEA ambient storage samples.

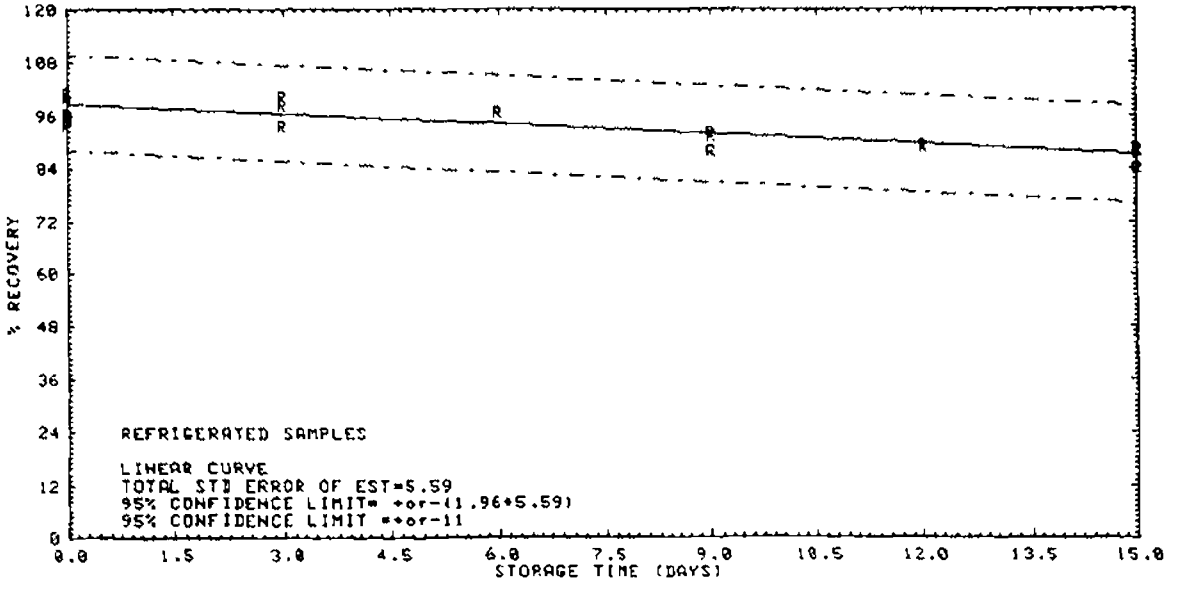

Figure 4.5.3.1 2EE refrigerated storage samples.

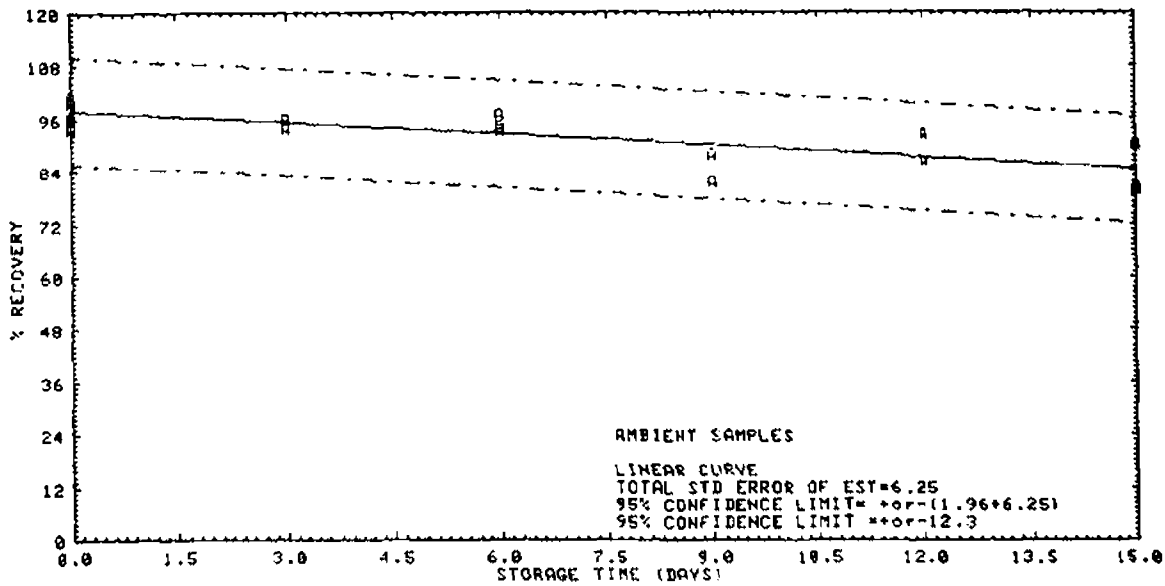

Figure 4.5.3.2 2EE ambient storage samples.

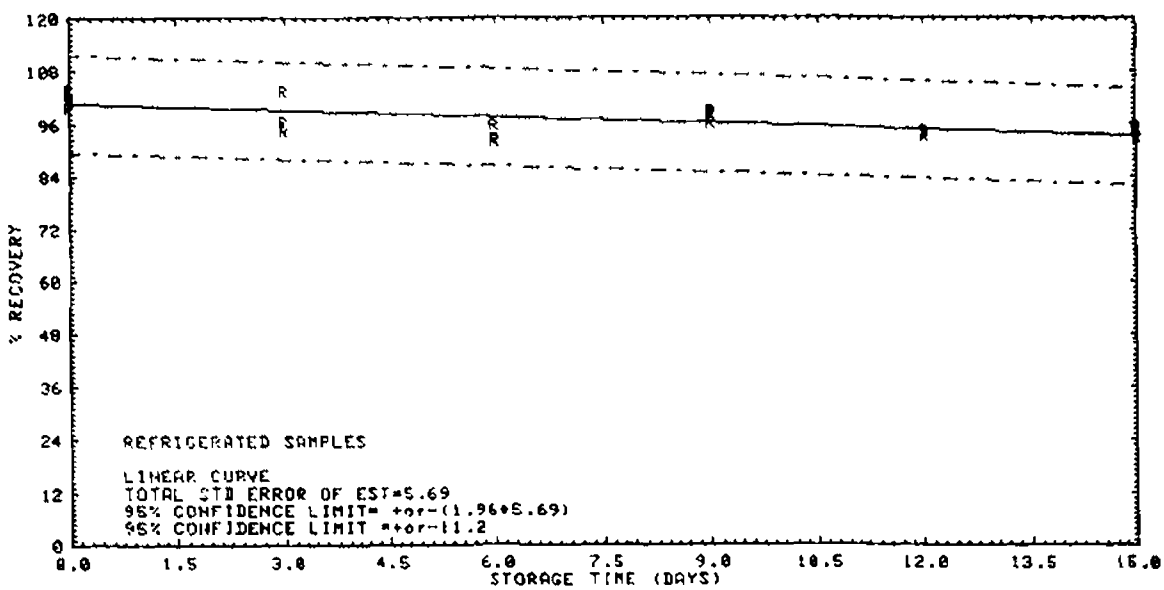

Figure 4.5.4.1 2EEA refrigerated storage samples.

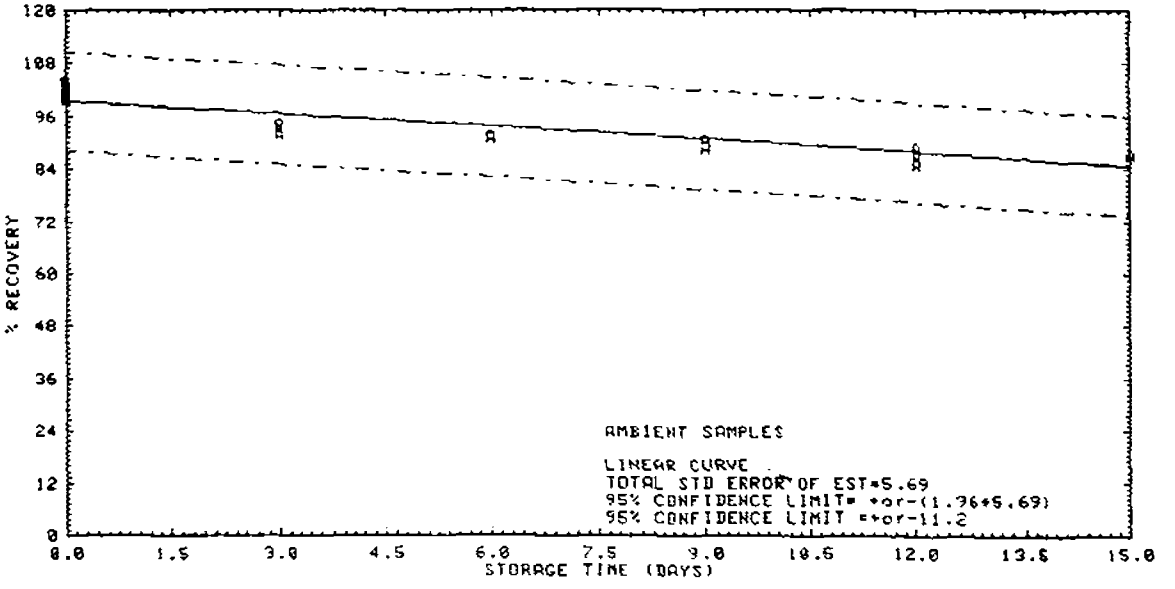

Figure 4.5.4.2 2EEA ambient storage samples.

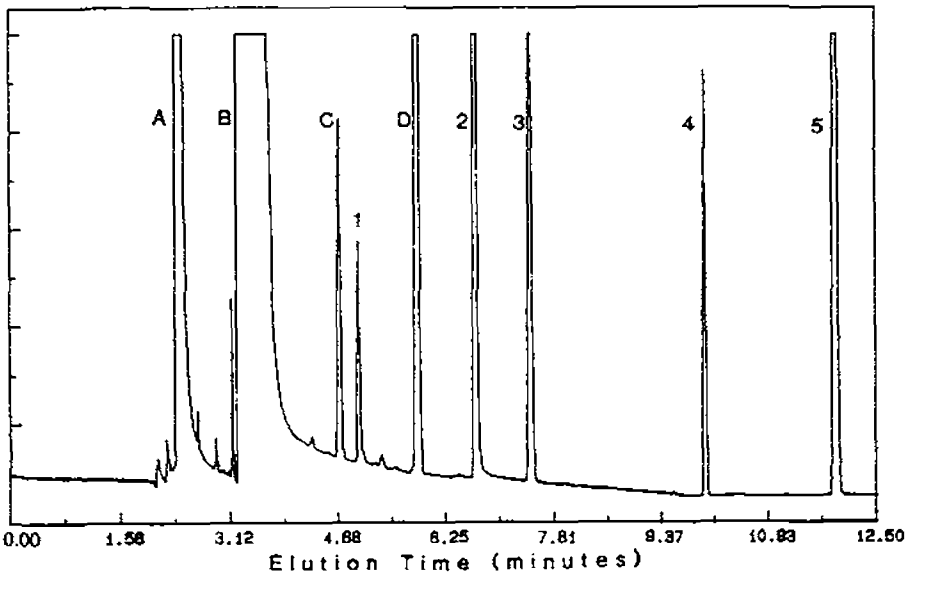

Figure 4.11 Chromatogram of a standard at the target concentrations. Key: (1) 2ME, (2) 2EE, (3) 3-methyl-3-pentanol, (4) 2MEA, (5) 2EEA. Other peaks: (A) methyl alcohol, (B) methylene chloride, (C) chloroform (impurity in methylene chloride), (D) cyclohexene (preservative in methylene chloride).

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UNION CARBIDE METHOD OF AIR MONITORING FOR GLYCOL ETHERS: DETERMINATION OF GLYCOL ETHERS IN AIR BY ADSORPTION ON ACTIVATED CHARCOAL AND PASSIVE DOSIMETERS WITH SUBSEQUENT ANALYSIS BY GAS CHROMATOGRAPHY[†]

INTRODUCTION

This bulletin details the air monitoring and analytical procedures used by Union Carbide Corporation in obtaining personal air samples to determine the degree of exposure, if any,

[†]Reprinted from an unpublished bulletin of the Union Carbide Corporation, Tarrytown, NY 10591.

of its employees to glycol ethers and glycol ether acetates. New information has been included in this booklet concerning the use of PASSIVE MONITORS as an alternate method to evaluate employee exposure. These PASSIVE MONITORS have become very popular recently because they are small, light-weight badges that are worn by the employee and do not require sampling pumps or other forms of calibration.

It is the intention of this bulletin to provide those who use glycol ethers or glycol ether acetates with all of the information available within Union Carbide in detecting and defining personal exposure to the chemicals. You are strongly urged to make use of this information to determine the degree of such exposure of your employees to these chemicals. This bulletin is designed as an aid to you in establishing and implementing your exposure limitation and reduction program.

METHOD

The method featured in this booklet can be used to measure several glycol ethers in the work environment. Union Carbide has confirmed the validity of the charcoal tube sampling method for:

Methyl CELLOSOLVE®
Methyl CELLOSOLVE® Acetate
CELLOSOLVE® Solvent
CELLOSOLVE® Acetate

while the Passive Dosimeter part of the method can be used for sampling:

Methyl CELLOSOLVE®
Methyl CELLOSOLVE® Acetate
CELLOSOLVE® Solvent

1. Principle

The sample is collected by drawing air through a glass tube containing activated charcoal (SKC-226-01) or by using a passive dosimeter (3M #3500 Organic Vapor Monitor) containing petroleum based carbon. The adsorbed glycol ethers and/or glycol ether acetates are then desorbed from the adsorbent with a 5% (v/v) methanol in methylene chloride solution and analyzed by gas chromatography with a flame ionization detector.

2. Range, Stability and Interference

This method has been validated for sampling air concentrations of the stated glycol ethers and their acetates from 2 to 25 ppm by volume in air. The method can be used for higher concentrations; however, the higher range has not been validated by Union Carbide.

Because some of the compounds may become hydrolyzed when sampled in high humidity atmospheres, the analysis of the charcoal tube samples must be completed within 24 hours

of the sampling. However, in the case of CELLOSOLVE® solvent, samples can be stored for up to 14 days in a refrigerator but should be analyzed within 90 minutes after desorption.

In the case of passive dosimeters, the sample may be refrigerated for up to five days prior to analysis without any significant loss.

The presence of other glycol ether vapor with similar molecular weights and vapor pressure may result in interference.

3. Instrument Parameters

Chromatograph	Hewlett-Packard 5830A or equivalent
Detector	Flame ionization
Column	3.05 m × 3.2 mm (10-ft × 1/8-inch) stainless steel packed with 5% FFAP on 80/100 mesh, acid washed DMCS Chromosorb W
Alternate column	Same as above except 10% FAPP loading
Temperatures	
Column	100°C
Detector	250°C
Injection Port	250°C
Carrier gas and flow rate	nitrogen at 30 cc per minute
Air flow rate	250 cc per minute
Hydrogen flow rate	20 cc per minute
Sample size	2 µL, solvent flush technique
Approximate retention time	Methyl CELLOSOLVE®: 2.45 min. Methyl CELLOSOLVE® acetate: 3.25 min. CELLOSOLVE® Solvent: 5.6 min. CELLOSOLVE® Acetate: 3.0 min.
Recorder	0-1 mV recorder or electronic integration

4. Apparatus

a) Personal sampling pump. MSA Model S, Sipin SP-2, SKC-222-3 or equivalent.

b) Charcoal tube. Coconut-Base, 150 mg. SKC Catalog, No. 226-01, SKC Inc. RDl, 395 Valley View Road, Eighty Four, PA 15330.

c) 3M Organic Vapor Monitor, #3500 3M Occupational Health and Safety Products Division, P.O. Box 33155, St. Paul, MN 55101.

d) Syringes, 10, 25, 100-µL Hamilton, or equivalent.

e) Pipets, 1 and 2-mL graduated, 1, 2, and 5-mL (Repipet' dispenser may be used to add desorption solvent to vials. Cat. No. 13-687-54, Fisher Scientific Co., or equivalent).

f) Balston DFU Grade B filter. Balston, Inc., P.O. Box C, 703 Massachusetts Ave., Lexington, MA 02173. The same filter is also available from DuPont Company, Applied Technology Division, Room B1275, Wilmington, DE 19898, Part No. P101.

g) Vials, 4.0-mL screw-capped septum, Cat., No. 2-2954, Supelco, Inc., Bellefonte, PA 16823 or equivalent.

h) Flasks, 10 and 100-mL, volumetric.

i) Rotameter, calibrated to measure flows in the 1000 cc per minute range or equivalent.

j) File, 3-corner for scoring sample tubes.

k) Wire, small diameter with hook formed at end to remove charcoal retainers from sample tube.

l) Sample tube holder, Size A, SKC Cat. No. 222-31, SKC, Inc., Eighty Four, PA or equivalent.

m) Soap film flow meter, 0-250 mL and 0-1000 mL to calibrate pumps and rotameter.

n) Developing vibrator, SKC Cat., No. 226-D-03-115, SKC, Inc., Eighty Four, PA or equivalent.

o) Sample tube opener. Tape a 4 × 6-inch piece of 1/2-inch plywood (or equivalent) to the top of a 6 × 6 × 6-inch cardboard box and drill a 7-mm hole through the plywood into the box.

p) 3M Organic Vapor Monitor Badge Sampling Chamber. Available from 3M, Occupational Health and Safety Division, P.O. Box 33155, St. Paul, MN 55101.

5. Reagents

a) Methanol, ACS Grade

b) Methylene Chloride ACS Grade

c) Methyl CELLOSOLVE®

d) Methyl CELLOSOLVE® Acetate

e) CELLOSOLVE® Solvent

f) CELLOSOLVE® Acetate

g) Nitrogen, high purity

h) Hydrogen, high purity

i) Compressed air-filtered

6. Sampling Procedure With Charcoal Tubes

a) Calibration of personal pumps: Each pump must be calibrated with a representative sample tube in line. This will minimize errors associated with uncertainties in the sample volume collected. Use soap film flowmeter to determine the sampling pump flow rate.

b) Immediately before sampling, break the tips of each tube to be used to provide openings of at least 2mm.

c) Attach the tube to a portable pump with the back-up section next to the pump by means of a piece of Tygon tubing of the desired length.

d) Long-term sampling: Set the air flow rate through the charcoal tube for 50 to 200 cc per minute. Collect 15 to 30 liters volume.

e) If a personal sample is to be taken, put the tube in an appropriate holder to protect the individual from the glass tube.

f) Record the stroke count, if using pump with counter, time, temperature, relative humidity, and barometric pressure when the air sampling is started.

g) At the end of the sample time stop the pump, seal the ends of the sample tube, record the stroke count, if required, and the time, temperature, relative humidity, and barometric pressure. Return the tube to the laboratory for analysis.

h) Short-term sampling. Flow rates of up to one liter per minute can be used to collect a sufficient quantity of the analyte to measure quantitatively. Use a MSA Model S personal pump or equivalent to obtain the flow rates.

i) Determine the actual flow rate through the charcoal tube by means of a soap film meter or a calibrated rotameter.

j) Record the flow rate, time, temperature, relative humidity and barometric pressure, when sampling is started.

k) At the end of the sampling period, recheck and record the flow rate, seal the ends of the tube, record the time, temperature, relative humidity, and barometric pressure and return the tube to the laboratory for analysis.

l) Sample tubes must be analyzed within 24 hours if stored at room temperature.

m) Break the tips from a tube at the same time the sample tubes are opened to be used as a blank. Cap, and return to the laboratory with the sample tubes.

7. Sampling Procedure with 3M Organic Vapor Monitors

a) Remove from protective pouch and clip monitor to lapel of worker near the breathing zone.

b) Record the time, temperature, relative humidity, and barometric pressure when the air sampling has started.

c) At the end of the sample time, remove the white face and retaining ring and snap on the elutriation cap. Firmly close both ports. Record the time, temperature, relative humidity, and barometric pressure.

d) Place monitor back in original package and seal.

e) Samples may be stored up to 5 days refrigerated before laboratory analysis.

f) Remove a monitor from the pouch at the same time the sample monitors are removed to be used as a blank. Reseal immediately and return to the laboratory with the sample monitors.

8. Analytical Procedure For Charcoal Adsorption Tubes

a) Wash all glassware with hot soapy water and rinse with distilled water followed by acetone. Air- or oven-dry to remove all traces of acetone.

b) Score the sample tube between the end and the primary section retainer and break off the end of the tube in the tube opener (care must be exercised to prevent loss of the bent wire retainer and possible loss of the glass wood and charcoal).

c) Make a small hook at the end of a piece of wire and remove the glass wool retainer plug and discard. Make sure no charcoal particles adhere to the glass wool plug.

d) Transfer the charcoal from the primary section and back-up section of the tube into separate Supelco desorption vials. Cool in wet ice 5 minutes while capped.

e) Pipet 5 mL of methanol into 95 mL of methylene chloride and mix well. Pipet 1.0 mL of this solvent into each desorption vial and cap securely.

f) Shake or vibrate gently for 30 minutes.

g) Solvent flush injection technique. This injection technique is designed to eliminate difficulties arising from blow-back or distillation within the needle of the microliter syringe.

h) Flush a 10-µL syringe with the methanol-methylene chloride desorption solution several times to wet the barrel and plunger.

i) Draw a 1 µL of methanol-methylene chloride solution into the syringe and remove the tip of the needle from the solution. Withdraw the plunger and additional 0.5 µL to separate the methanol-methylene chloride from the sample with a pocket of air.

j) Dip the needle into the sample solution in the desorption vial and withdraw the plunger until the air bubble between the solvent and the sample has passed the 3-µL mark on the syringe.

k) Remove the top of the needle from the sample solution and adjust the volume in the syringe until the meniscus of the air bubble rests on the 3-µL mark. Remove the excess sample solution from the tip of the needle.

l) Pull the plunger back an additional 0.5 µL to prevent the sample solution from evaporating from the tip of the needle.

m) Inject the entire contents of the syringe into the chromatograph.

n) Measure the peak area or height and determine the organic content from a previously prepared calibration curve.

o) Analyze the backup (small) section of charcoal tube in the same manner as the primary.

p) Analyze the blank tube in the same manner as the sample tube.

9. Analytical Procedure For 3M Organic Vapor Monitors

a) Open the center elutriation port and inject 1.5 mL of 5µ MeOH as CH_2Cl_2 with a syringe.

b) Close the center port and allow to elutriate for 1/2 hour with occasional gentle agitation. Be sure to not let any desorption solvent get on the elutriation cap.

c) Solvent flush injection technique. This injection technique is designed to eliminate difficulties arising from blow-back or distillation within the needle of the microliter syringe.

d) Flush a 10-µL syringe with the methanol-methylene chloride desorption solution several times to wet the barrel and plunger.

e) Draw 1 µL of methanol-methylene chloride solution into the syringe and remove the tip of the needle from the solution. Withdraw the plunger an additional µL to separate the methanol-methylene chloride from the sample with a pocket of air.

f) Dip the needle into the center elutriation port and withdraw the plunger until the air bubble between the solvent and sample has passed the 2-µL mark on the syringe.

g) Remove the top of the needle from the sample solution and adjust the volume in the syringe until the meniscus of the air bubble rests on the 3-µL mark. Remove the excess sample solution from the tip of the needle.

h) Pull the plunger back an additional 0.5 µL to prevent the sample solution from evaporating from the tip of the needle.

i) Inject the entire contents of the syringe into the chromatograph.

j) Measure the peak area or height and determine the organic content from a previously prepared calibration curve.

k) Analyze the blank monitor in the same manner as the sample monitor.

10. Calibration Curve

a) Determine quantities of analyte required to prepare standards in desired range based on a 15 liter sample by referring to Table A.

b) Inject standards in the chromatograph using the solvent flush procedure described in the analytical procedure.

c) Plot peak height or area versus micrograms of analyte per mL.

11. Desorption Efficiency

a) Desorption efficiency (percentage of adsorbed analyte desorbed from the charcoal by the desorbing solution) can vary from one laboratory to another and from one batch of charcoal to another.

b) Make up an analyte (glycol ether or acetate sampled) standard in the desorption solvent that will allow injection of 2 to 10 microliters of standard to cover the range desired. Use a 10 mL syringe to inject the standard in the charcoal and 3M Organic Vapor Monitor.

c) Calculate the microliters of analyte (glycol ether or acetate sampled) standard to be added to the adsorption tube based on a 15 liter sample of 0.5, 1.0 and 2.0 times the TLV-TWA or the expected concentration using the following equation:

$$\frac{\text{TLV or TWA} \times V \times MW}{G \times 24.450} = A_S$$

A_S	= µL of analyte to be added to the selected volume of solvent to produce a solution of the desired ppmv
G	= specific gravity of analyte at temperature being measured (specific gravity at 20/20°C ± Δ sp. gr. / Δ T × temperature difference)
MW	= molecular weight of analyte
TLV or TWA	= threshold limit value - time weighted average in ppm
V	= volume of air sample in liters
24.450	= molar volume (mL per mole) at 25°C and 101.3 kPa (760 mm of Hg)

d) The recommended number of tubes at each level is six plus three blanks for a total of twenty-one tubes. Tubes used for the desorption efficiency study ***must*** be of the same lot that will be used for monitoring the work place. If practical, analyte should be added to the front of the primary section of charcoal in the tube and humidified air (to approximate work place air) pulled across the tube to total twenty liters at flow rates up to 500 cc per minute by personal pumps or a vacuum manifold. Air can be humidified by passing cylinder air through three bubblers in series containing distilled water and directing the eluent into a sampling chamber. Total flow in the chamber must be more than that being withdrawn through the tubes. If this proves impractical, 100 mg of charcoal from the tubes may be transferred to each of a sufficient number of desorption vials (twenty-one), the analyte added, the vials capped and allowed to stand overnight to allow the analyte to permeate the charcoal. Analysis is accomplished using the procedure in Section 10.

e) The recommended number of 3M Organic Vapor Monitors at each level is six plus three blanks for a total of 21 monitors. The monitors used for the desorption efficiency study ***must*** be of the same lot that will be used for monitoring the work place. If practical, analyte should be added to the monitor through the white face onto the charcoal pad. Humidified air (to approximate work place air) is pulled across the monitor to total fifteen liters at flow rates up to 500 cc per minute by a 3M Organic Vapor Monitor Badge Sampling Device. Air can be humidified by passing cylinder air through three bubblers in series containing distilled water and directing the eluent into a sampling chamber. Total flow into the chamber must be more than that being withdrawn through the monitors. Analysis is accomplished using the procedure in Section 11.

f) Calculation of the desorption efficiency

$$\frac{A-B}{S} = DE$$

A = average peak area or peak height of sample
B = average peak area or peak height of blank
DE = desorption efficiency
S = average peak area or peak height of standard

Plot the description efficiency versus the µg/mL found.

12. Calculations

a) Read the weight in µg/mL corresponding to each peak area or height from the calibration curve and convert to total micrograms by multiplying the µg/mL by the desorbant volume in milliliters.

b) Correct each sample weight for the blank.
µg sample - µg blank = µg sample, corrected
µg sample = µg found in front section of sample tube
µg blank = µg found in front section of blank tube

c) Follow a similar procedure for the back-up section.

d) Add the amounts present in front and back-up sections to determine the total weight in the sample.

e) Read the desorption efficiency (DE) from the DEC curve for the amount found in the sample tube. Divide the total weight by the DE to obtain the corrected µg/sample.

$$\frac{\text{Total Weight}}{DE} = \text{corrected µg/sample}$$

DE = desorption efficiency
Total Weight = µg of analyte found in the front section of the sample tube - µg found in the front section of the blank tube + µg of analyte found in the backup section of the sample tube.

f) Correct the volume of air sampled to standard conditions of 25°C and 760 mm of pressure.

$$\frac{V \times P \times 298}{760 \times (T+273)} = \text{volume of sample in liters at 25° C and 760 mm of pressure}$$

P = barometric pressure in mm of mercury
T = temperature (°C) of air sampled
V = volume of air sample in liters as measured
760 = standard pressure in mm of mercury
298 = standard temperature (°K)

NOTE: The sampling rate for the 3M Organic Vapor Monitors has been determined by 3M as being 36.3 cc/min for methyl CELLOSOLVE®, 29.0 cc/min for methyl CELLOSOLVE® acetate, and 32.2 cc/min for CELLOSOLVE® Solvent.

g) The concentration of the analyte in the air sampled can be expressed in milligrams per cubic meter.

$$\frac{\text{Corrected micrograms}}{\text{Air volume samples (liters)}} = \text{mg/m}^3$$

h) Another way of expressing concentration is ppmv.

$$\frac{\text{mg/m}^3 \times 24.45}{\text{MW}} = \text{ppmv}$$

MW = molecular weight (g/mole) of the analyte
24.45 = molar volume (liters/mole) at 25° C and 760 mm of pressure

13. Other Relevant Information

The National Institute for Occupational Safety and Health has published other sampling and analytical methods for glycol ethers. The recently consolidated NIOSH Manual of Analytical Methods, Vol. 1 contains Method #1403, which can be used for Methyl CELLOSOLVE® and CELLOSOLVE® Solvent while Method #1450 can be used for CELLOSOLVE® Acetate. It is also stated in this manual that NIOSH intends to revise their previously published method for Methyl CELLOSOLVE® Acetate (S39).

In addition to the 3M #3500 Organic Vapor Monitoring Badge, passive dosimeter badges from other manufacturers, such as Dupont's Pro-Tek® Organic Badge, may also be used for monitoring glycol ethers. Please contact the manufacturer for information concerning the suitability of their monitors for specific glycol ethers or glycol ether acetates.

Some firms are also known to provide analytical services for these monitors for specific chemicals, including glycol ethers. This may be useful for some of the smaller locations which do not have air sampling equipment and/or on-site analytical capabilities of their own. Further information about the NIOSH methods or passive monitors may be obtained from the NIOSH regional office or equipment manufacturer.

Further information on this subject or the Union Carbide method may be obtained from

Union Carbide Corporation
Saw Mill River Road
Route 100 C
Tarrytown, NY 10591
(914) 789-2232

TABLE A
Calibration Curve Standards

Analyte	Molecular weight	Specific gravity at 25°C	Microliters for 10 mL solvent	Micrograms per mL	Air conc.(ppm), 15-liter sample
CELLOSOLVE® Acetate	132.16	0.9708	1.4	136	1.7
			4.2	408	5.0
			8.4	815	10.0
			21.0	2,039	25.1
CELLOSOLVE® Solvent	90.12	0.9269	1.0	93	1.7
			3.0	278	5.0
			6.0	556	10.1
			15.0	1,390	25.1
Methyl CELLOSOLVE®	76.10	0.9617	0.8	77	1.6
			2.4	231	4.9
			4.8	462	9.9
			12.2	1,173	25.1
Methyl CELLOSOLVE® Acetate	118.13	1.0012	1.2	120	1.7
			3.6	360	5.0
			7.2	721	9.9
			18.0	1,802	24.9

APPENDIX B

GLYCOL ETHER TOXICITY IN ANIMALS

B.1 MALE REPRODUCTIVE EFFECTS

B.1.1 EGEE and EGEEA

B.1.1.1 Subcutaneous and Intravenous Administration

Reports in the literature indicate that EGEE and EGEEA exert adverse effects on the male reproductive system. Histopathological testicular changes were reported in rats treated subcutaneously (s.c.) with varying doses of EGEE (93, 186, 372, or 744 mg/kg per day) [Stenger et al. 1971].* Treatment of five rats/group for 4 wk with 372 mg EGEE/kg per day caused testicular damage. The interstitium of the testes was edematously disintegrated; parent spermatophores were found in the tubuli between typical Sertoli cells, and in some instances, powdery spermatophores and spermatocytes were found in several layers. In most instances, there were no additional maturation stages; polynuclear cells were found occasionally. Limited changes in the liver and kidneys were also observed. Subcutaneous administration of 744 mg EGEE/kg per day caused occasional edema and hemorrhaging at the injection site. The histopathological changes described in the 372 mg EGEE/kg per day group were more pronounced in the 744 mg EGEE/kg per day group. Stenger et al. [1971] also noted that treating dogs (two per group) i.v. for 22 days with 93 mg EGEE/kg per day resulted in inflammation at the injection site, and treatment with 465 mg EGEE/kg per day caused pronounced thrombophlebitis.

B.1.1.2 Oral Administration

Twenty male albino rats were fed 1.45% EGEE in their basic diet for 2 yr [Morris et al. 1942]. Upon histological examination, testicular enlargement and edema and tubular atrophy were observed in two-thirds of the animals that had received EGEE. These changes were not seen in untreated controls. The testicular lesions were more often bilateral than unilateral and consisted of marked interstitial edema.

Oral administration of 46.5 or 93 mg EGEE/kg per day for 13 weeks to male dogs (three per group) had no adverse effect [Stenger et al. 1971]. On the other hand, oral administration of 186 mg EGEE/kg per day for 13 wk caused degenerative changes in the testes of all

*References for Appendix B can be found beginning on page 262.

three animals. In one dog, the lumen of the tubuli appeared to be expanded, and the last maturation stages of the seminal epithelium clearly were absent in many of the tubuli. In the second dog, tubuli were constricted, and parent and powdery spermatophores had been retained. In the third dog, there was a conspicuous flattening of germinal epithelium with complete absence of upper layers; the parent epithelium was, in some cases, absent in these tubuli. Slight kidney changes were observed in two of the three dogs; the lumen in the region of the tubuli contorti was expanded, and the epithelium was flattened.

In another set of experiments by Stenger et al. [1971], groups of five rats per dosage level were orally administered 46.5 or 93 mg EGEE/kg per day for 13 wk or 93 mg EGEE/kg per day for 59 days followed by an oral dose of 372 mg EGEE/kg per day for the remainder of the 13-wk period. No adverse effects were observed at these doses. Following oral administration of 186 mg EGEE/kg per day for 13 wk, the testicular interstitium was occasionally broken down edematously, and there was a lack of mature cells in the canals. The oral administration of 186 mg EGEE/kg per day for 59 days, followed by oral administration of 744 mg EGEE/kg per day for the 32 days remaining in the 13-wk period, also caused testicular changes that corresponded to findings following a 4-wk s.c. application of 744 mg EGEE/kg per day. The diameters of tubuli were also reduced.

Nagano et al. [1979] treated groups of five male JCL-ICR mice orally with various doses (500, 1,000, 2,000, or 4,000 mg/kg per day) of EGEE or EGEEA 5 days/wk for 5 wk. Testicular atrophy was observed and assessed in terms of testicular weight, both absolute and relative to body weight. Statistically significant decreases in the testicular weights of exposed animals in comparison to control animals were noted in those given doses of at least 1,000 mg/kg per day of either EGEE or EGEEA ($P<0.05$). Histologically, varying dosage-related degrees of seminiferous tubule atrophy were observed. In the 2,000 mg EGEE/kg per day and the 4,000 mg EGEEA/kg per day groups, the diameter of the seminiferous tubules decreased, spermatozoa and spermatids completely vanished, and spermatocytes existed in extremely small numbers in only some of the tubules; interstitial tissue also increased. When expressed as moles/kg per day, EGEE and EGEEA exerted the same degree of testicular toxicity [Nagano et al. 1979].

Foster et al. [1983] administered EGEE (250, 500, or 1,000 mg/kg per day) or EGEEA at 727 mg/kg per day (equimolar to 500 mg EGEE/kg per day) orally for 11 days to 36 male Sprague-Dawley rats/group. Animals treated with equivalent volumes of the water vehicle served as controls. A statistically significant decrease in testes weights was noted on day 11 in the 500 ($P<0.01$) and 1,000 mg ($P<0.05$) EGEE/kg per day groups. Although the degree of spermatocyte degeneration and depletion was similar for both dosage groups, the onset of degeneration was more rapid with the 500 mg EGEE/kg per day dose than with 1,000 mg/kg per day. Testicular degeneration was restricted to the later stages of primary spermatocyte development and secondary spermatocytes. Partial maturation depletion of early stage spermatids occurred, whereas Sertoli cells, Leydig cells, spermatogonia, and pre-pachytene spermatocytes were unaffected. Animals treated with EGEEA at a dose equimolar to 500 mg EGEE/kg per day showed a similar pattern of testicular damage [Foster et al. 1983]. These findings were confirmed in a similar set of experiments using

EGEE in which testicular lesions were examined at sequentially timed intervals (1/4, 1, 2, 4, 7, and 11 days) during the dosing period of 11 days [Creasy and Foster 1984]. EGEE exerted no adverse testicular effect at 250 mg/kg per day, but it did at doses of 500 and 1,000 mg/kg per day. Although no testicular abnormalities were observed in any of the groups 6 hr after dosing, degenerative spermatocytes were frequently seen 24 hr after dosing with EGEE. Dose levels of 500 and 1,000 mg EGEE/kg per day produced degeneration of the dividing and early-pachytene spermatocytes but had no effect on the middle and late stage of pachytene development. Although the 500 mg EGEE/kg per day induced a more extensive lesion than did 1,000 mg EGEE/kg per day after 48 hr of dosing, this trend was reversed with prolonged dosing. The authors concluded that primary spermatocytes undergoing pachytene development constitute the initial and major site of morphological damage [Creasy and Foster 1984].

Ethoxyacetic acid (EAA) and its glycine conjugate are known metabolites of EGEE [Jonsson et al. 1982; Cheever et al. 1984]. Foster et al. [1987] undertook the following study to support the contention that the testicular toxicity of EGEE [Foster et al. 1983] is due to the toxicity exerted by EAA. Foster et al. [1987] exposed groups of six male Alpk/AP (Wistar-derived) rats to a single oral dose of EAA (137, 342, or 684 mg/kg) to determine the initial target for testicular toxicity. Rats were sacrificed at 1, 2, 4, and 14 days post-treatment. Histological examination revealed that dosing with EAA induced testicular damage at the highest dose level only; diplotene, diakinetic, secondary, and early pachytene spermatocytes were affected at 24 hr, with effects on round spermatids seen at day 14. The pachytene spermatocytes had previously been identified [Foster et al. 1983] as the target of EGEE toxicity.

In a 2-yr study, groups of 50 Fischer 344/N rats and 50 B6C3F$_1$ mice of both sexes were administered EGEE by gavage at dose levels of 0, 500, 1,000, and 2,000 mg/kg per day [Melnick 1984]. Repeated administration of EGEE at the 2,000 mg/kg dose level was lethal to rats and mice, and death appeared to result from stomach ulcers. As a consequence of the high mortality rate, the high dose (2,000 mg/kg per day) group was terminated at wk 17 to 18. Gross and microscopic examinations at the end of the study revealed testicular atrophy in male rats and mice at all doses of EGEE.

The effect of EGEE on spermatogenesis was studied by Oudiz et al. [1984]. Groups of 16 Long-Evans hooded male rats were treated by gavage on 5 consecutive days with 0, 936, 1,872, or 2,808 mg EGEE/kg per day. The animals were then mated weekly for the following 14 wk with ovariectomized females, and ejaculated semen samples recovered from females immediately following copulation were analyzed at selected timepoints over a 16-wk period. The males were killed at wk 16, and the testes and epididymides were submitted for histological examination. Exposure to 936 mg EGEE/kg per day impaired testicular function as reflected in an increased percent of abnormal sperm forms as well as in decreased sperm count; azoospermia and oligozoospermia were observed in the higher-dose groups (1,872 and 2,808 mg EGEE/kg per day). Although there appeared to be no effect on motility, a significant decline in sperm count, relative to that of the controls, occurred as early as wk 4 post-exposure in the groups receiving 1,872 mg EGEE/kg per day ($P \leq 0.001$) and 2,808 mg EGEE/kg per day ($P \leq 0.01$). The most dramatic effects were noted at wk 7

postexposure; at this time, the low-dose group (936 mg EGEE/kg per day) also exhibited significantly decreased ($P \leq 0.01$) sperm counts and increased ($P \leq 0.05$) abnormal forms in the semen. Partial recovery of sperm count was evident in semen samples collected at wk 14 in the group receiving doses of 1,872 mg EGEE/kg per day where sperm counts were 40% of the baseline value of 58.8×10^6 sperm/ml of recovery fluid. Animals in the group receiving the high dose (2,808 mg EGEE/kg per day) manifested total recovery of sperm counts by wk 14. Insult resulting from EGEE treatment also occurred on the epididymis. Epididymal weights in the group receiving 1,872 mg EGEE/kg per day were significantly lower than those of the controls ($P \leq 0.05$), whereas differences between the high-dose (2,808 mg EGEE/kg per day) and control groups only approached significance ($P \leq 0.10$).

In a later study by Oudiz and Zenick [1986], the time course of effects on rat sperm parameters was examined. Male rats were treated orally with 936 mg EGEE/kg per day, 5 days/wk for 6 wk. Semen samples were collected on a weekly basis during the exposure period from ovariectomized, hormonally primed females 15 min after mating. The samples were analyzed for sperm count, sperm morphology, and sperm motility. All males were sacrificed 3 days after cessation of treatment. The weights of testes, epididymides, vas deferens, prostates, and seminal vesicles were recorded at termination. The EGEE-treated males had significantly decreased sperm counts at wk 5 and 6 when compared with those of the controls ($P<0.001$). A 30% to 40% decline in sperm counts was noted at wk 5, and by wk 6, 3 of the 10 EGEE-treated males were azoospermic. The remaining rats had severely reduced sperm counts ranging from 5 to 30 million compared with counts of 70 to 78 million sperm in the unexposed group. At wk 5 and 6, there were significant increases in abnormal sperm morphology for the EGEE-treated males ($P<0.01$), and at wk 6, a significant decrease in percent sperm motility ($P<0.01$) was seen in the EGEE-treated males. There were also significant decreases in the weights of testes and epididymides ($P \leq 0.01$), although there was no effect on the weights of vas deferens [Oudiz and Zenick 1986].

B.1.1.3 Inhalation

In two separate reports of a single study, Terrill and Daly [1983a,b] and Barbee et al. [1984] exposed Sprague-Dawley CD rats (15 per group) and New Zealand white rabbits (10 per group) of both sexes to EGEE vapor at 0, 25, 100, or 400 ppm for 6 hr/day, 5 days/wk for 13 wk. The only significant alterations noted in the rats were decreased pituitary weights in males exposed to 400 ppm ($P<0.05$) and reduced spleen weights in females exposed to 100 or 400 ppm EGEE ($P<0.01$). The rabbit was more sensitive to EGEE exposure. Mean body weights decreased for low (25 ppm EGEE, $P<0.05$) and high exposure groups (400 ppm EGEE, $P<0.01$), whereas animals in the middle (100 ppm EGEE) group showed no change. However, pathological changes supportive of these organ weight changes were not observed. The testis weights of rabbits were decreased significantly at 400 ppm EGEE ($P<0.01$). Microscopic examination of testes in this group revealed slight focal seminiferous tubule degeneration in 3 of 10 rabbits. The authors concluded that no biologically significant effects were observed in rats exposed at 400 ppm EGEE and in rabbits exposed at 100 ppm EGEE.

B.1.2 EGME and EGMEA

Toxicity of EGME on the male reproductive system was first demonstrated in rabbits by Wiley et al. [1938]. Two male rabbits received two or three injections of unspecified doses of EGME; both animals developed degeneration of the germinal epithelium.

B.1.2.1 Oral Administration

Nagano et al. [1979] treated groups of five male JCL-ICR mice by gastric intubation 5 days/wk for 5 wk with EGME or EGMEA (62.5, 125, 250, 500, 1,000, and 2,000 mg/kg). Testicular atrophy was assessed in terms of testicular weight, both absolute and relative to body weight. Statistically significant decreases ($P<0.01$) in testes weights were seen in animals given doses of 250 mg EGME/kg per day or greater or 500 mg EGMEA/kg per day or greater when compared with controls. Graphs of testes body weight ratios per dose were almost identical for EGME and EGMEA when doses were expressed as mmoles per kg body weight. Dose-related seminiferous tubular atrophy was observed in the mice with decreased testicular weight, with the 1,000 mg EGME/kg per day and 2,000 mg EGMEA/kg per day groups having no germ cells present. Histologically, varying dosage-related degrees of testicular seminiferous tubule atrophy were noted. At 250 mg of EGME and 500 mg of EGMEA, spermatozoa and spermatids were seen in small numbers in some of the tubules and spermatocyte numbers were reduced. At 500 mg EGME/kg and 1,000 mg EGMEA/kg, the diameter of the seminiferous tubules decreased and spermatozoa and spermatids completely vanished although extremely small numbers of spermatocytes existed in some of the tubules; interstitial tissue also increased.

The relationship between oral administration of EGME and testicular damage was also investigated by Foster et al. [1983]. Groups of 36 male Sprague-Dawley rats received EGME orally at dosages of 0, 50, 100, 250, or 500 mg/kg per day. Six animals from each group were sacrificed at 6 and 24 hr, and at 2, 4, 7, and 11 days. Significant decreases in testicular weight ($P<0.05$) were evident at day 2 in the 500 mg EGME/kg per day group and became more pronounced ($P<0.01$) with increasing total dose (day 4, 7, and 11). At days 7 and 11, statistically significant decreases in testicular weight ($P<0.01$) were also seen in the 250 mg EGME/kg per day group.

Foster et al. [1983] also conducted a recovery study in which groups of male Sprague-Dawley rats received 500 mg EGME/kg per day orally for 4 days. After cessation of treatment, six animals from treated and control groups were sacrificed at 0 (the day after the last treatment), 2, 4, and 8 wk. A statistically significant decrease ($P<0.001$) in relative testicular weights was noted at 0, 2, and 4 wk, with testes weights returning to control values 8 wk following treatment. Seminal vesicle weights were significantly increased ($P<0.05$) at wk 8; the authors suggested this might have been due to increased testosterone levels [Foster et al. 1983].

Histological examination of testes from rats exposed to EGME at 100, 250, and 500 mg/kg per day revealed degeneration of pachytene spermatocytes as early as 24 hr after a single

dose, whereas dosing with 50 mg EGME/kg per day for 11 days produced no testicular abnormalities (no-effect level) [Foster et al. 1983]. The proportion of the spermatocyte population affected at 24 hr was related to dose. Progressive depletion of spermatocytes and maturation depletion of early spermatids were observed with continued dosing. Degenerative changes (cellular shrinkage, increased eosinophilia, and nuclear pyknosis) were restricted to secondary spermatocytes and to pachytene, diplotene, diakinetic, and dividing stages of primary spermatocyte development. Preleptotene, leptotene, and zygotene spermatocytes were unaffected. After 4 days of treatment with 500 mg EGME/kg per day and 7 days of treatment with 250 mg EGME/kg per day, degenerative changes (chromatin margination) were evident in the spermatid population. After 11 days of treatment with 250 and 500 mg EGME/kg per day, spermatid and late spermatocyte populations were absent, and zygotene spermatocytes showed an increase in number; these events were indicative of maturation arrest. Treatment for 11 days with 100 mg EGME/kg per day produced partial depletion and continued degeneration of spermatocytes and partial maturation depletion of early spermatids. Ultrastructural examination of testes 24 hr after a single dose of 100 mg EGME/kg per day showed spermatocytes with mitochondrial swelling and disruption, cytoplasmic vacuolation, and early condensation of nuclear chromatin [Foster et al. 1983].

In the recovery study, the animals sacrificed 2 wk after 4 days of dosing with 500 mg EGME/kg per day showed maturation depletion of middle and late stage spermatids and maturation arrest of pachytene spermatocytes. At 4 wk after exposure, recovery was evident by the presence of maturation phase spermatids, and by 8 wk, full spermatogenesis was present in the majority of tubules from all animals [Foster et al. 1983]. The authors, in a separate publication [Creasy and Foster 1984], concluded that the data demonstrated a defined order of spermatocyte sensitivity: dividing spermatocytes (Stage 14) > early pachytene spermatocytes (Stages 1 through 3) > late pachytene spermatocytes (Stages 9 through 13) > mid-pachytene spermatocytes (Stages 4 through 8) > leptotene/zygotene spermatocytes (Stages 9 through 14).

Similar studies were conducted by Chapin and Lamb [1984] using a different age and strain of rat. Forty adult male F344 rats were treated orally with 150 mg EGME/kg per day for 5 days/wk for up to 10 days. Controls received daily doses of distilled water. Animals were killed on days 1, 2, 4, 7, and 10 after the start of dosing. As previously observed [Foster et al. 1983], degeneration of spermatocytes appeared in treated animals 24 hr after a single dose of EGME. Subsequently, a more consistent, progressive degeneration of spermatocytes and epithelial disruption were accompanied by a statistically significant reduction ($P<0.05$) in testicular weight. In contrast to the work of Foster et al. [1983], a broader range of spermatocytes was affected, including leptotene and zygotene stages as well as pachytene stage spermatocytes and spermatids. An additional purpose of this research was to correlate histologic changes with androgen binding protein (ABP), a Sertoli cell secretion, found in fluid collected at the rete testis after ligation of the efferent testicular ducts. Six animals were treated with EGME as previously described and were sacrificed on days 2, 4, 7, and 10. No significant difference in production of testis fluid was observed between the ligated animals from treated and control groups; total protein and ABP activity in this fluid were unchanged by EGME treatment. The authors concluded that early and late spermatocytes

are targets for EGME in the testes and that Sertoli cell functions, as measured by ABP levels, fluid production, and total protein profile, were unaffected [Chapin and Lamb 1984].

The following study was undertaken to assess possible effects of EGME on late stage and epididymal spermatids and on spermatogonia [Chapin et al. 1985a]. Male F344 rats (20 per group) were treated orally with EGME at 0, 50, 100, or 200 mg/kg per day for 5 days and then allowed to mate with two female F344 rats/week for 8 wk. At the end of the 8-wk period, the male rats were housed singly for an additional 8 wk, and then allowed to mate again for 5 days. The percentage pregnancies decreased significantly ($P<0.05$) during wk 4 for females mated to high-dose males (200 mg EGME/kg per day) and remained significantly lower than controls for the duration of the study. At the 100 mg EGME/kg per day dosage, males demonstrated significantly reduced fertility at week 5 only ($P<0.05$). The fertility rate of males dosed with 50 mg EGME/kg per day was not affected by treatment. The mean number of live fetuses per pregnant female was significantly decreased ($P<0.05$) in the high-dose animals during wk 4 through 16 when compared with controls. Mid-dose (100 mg EGME/kg per day) males sired significantly fewer pups ($P<0.05$) at wk 5 only, whereas the number of live young sired by the 50 mg EGME/kg per day males was not significantly different from that of the controls. Statistically significant increases ($P<0.05$) in resorptions in females were found only in the high-dose group at wk 5 and 6. The high-dose group also demonstrated significantly increased ($P<0.05$) preimplantation losses during wk 3 through 16. A significant increase ($P<0.05$) in preimplantation loss was also seen in the 100 mg EGME/kg per day group during wk 2 and 5 [Chapin et al. 1985a].

In addition to the above mating studies, Chapin et al. [1985a] also conducted sperm assessments in the same investigation using groups of 96 male F344 rats treated orally with EGME at the same doses as above. At weekly intervals for 8 wk, bilateral efferent duct ligation was performed on nine animals/group and the following day each was sacrificed. A dose and time-dependent change in the number of sperm/gram cauda epididymis was seen in the 100 and 200 mg EGME/kg per day groups. Both groups had significantly fewer ($P<0.05$) sperm/gram cauda at wk 2, and sperm counts remained significantly lower than did those of the controls for the 8-wk study. High-dose animals had lower sperm counts than mid-dose animals. Rats treated with 50 mg EGME/kg per day had lower sperm counts at wk 5 only. Sperm motility was also significantly decreased ($P<0.05$) for high- and mid-dose animals: high-dose (200 mg EGME/kg per day) rats were significantly affected from wk 3 through 8, and sperm of mid-dose (100 mg EGME/kg per day) rats showed decreased motility from wk 4 through 8. Motility depression for both groups reached a maximum at wk 5 and 6, and then began to recover. The percentage of morphologically abnormal sperm was significant ($P<0.05$) at wk 3 for the high-dose group and at wk 5 for the mid-dose group, and remained significantly high for both throughout the study, reaching a maximum at wk 6 (mean 80% $\pm$ 10%, high-dose group) and falling thereafter.

The authors [Chapin et al. 1985a] concluded that the fertility decline from wk 4 through wk 8 in the high-dose group suggested an effect of EGME on elongating testicular spermatids and cells at least as immature as intermediate or B spermatogonia. At 16 wk, fertility in these males was 70% that of controls, indicating a relatively prolonged recovery process. This slow recovery demonstrates that A spermatogonia were also affected by

EGME treatment at 200 mg/kg per day. They also concluded that, as the dose was increased, the number of types of affected cells increased and that EGME was a very weak inducer of dominant lethal mutations [Chapin et al. 1985a].

In a separate study, Chapin et al. [1985b] attempted to correlate the above noted fertility indices with changes in testicular histology, the activity of cell specific enzymes, and protein in fluid collected from the ligated rete testis. Adult F344 rats were treated orally with 0, 50, 100, or 200 mg EGME/kg per day for 5 days. Three days later (wk 1), and at weekly intervals for the next 7 wk, nine rats/group were subjected to bilateral efferent duct ligation and sacrificed 16 hr later. In the 50 mg EGME/kg per day group, no change in the morphology of the testes was seen until wk 4, when condensed spermatids lacking tails were seen close to the basement membrane of some tubules in some rats. At wk 5 through 7, 20% to 40% of stage 9 or 10 tubules contained these condensed spermatid nuclei near the basement membrane. By wk 8, none of the animals sacrificed had treatment-related lesions.

In the 100 mg EGME/kg per day group, numerous spermatid heads were seen near the basement membrane and pachytene spermatocyte death was frequent in stages 10 to 12 at wk 1. By wk 3, 100% of the tubules were affected by early and late stage spermatid and pachytene spermatocyte loss, delayed spermiation, or numerous spermatid heads near the basement membrane. These effects persisted through wk 6, and by wk 8, 50% of stage 1 to 5 tubules and some tubules of each stage were unaffected; delayed spermiation was less prominent [Chapin et al. 1985b].

All animals dosed with 200 mg EGME/kg per day showed severe testicular effects at wk 1. By wk 5, 10% to 30% of the tubules were indistinguishable from controls. Fifty percent appeared normal by wk 7; the remaining 50% were severely depopulated with delayed spermiation, and basally located spermatid heads were common in 50% to 80% of stage 9 to 11 tubules [Chapin et al. 1985b].

The effects of EGME on the epididymis were limited to tubular contents: high- and mid-dose groups had fewer sperm and many more immature germ cells than did the controls, whereas low-dose rats showed only a transient mild increase in the number of immature germ cells and decreased sperm density at wk 2. The amount of protein in rete testis fluid was elevated in the high-dose group at wk 2 through 5 and in the mid-dose group at wk 4 and 6.

The authors [Chapin et al. 1985b] concluded that although the low dose of EGME was designed to be a no-effect level, there were slight, previously noted [Chapin et al. 1985a] changes in epididymal sperm concentration and morphology, that is, a delay in spermiation and the presence of tailless, basally located spermatid heads. In the 100 mg EGME/kg per day group, the observed histologic effects tended to be more severe and to diminish with increased time after dosing, until many tubules appeared normal by wk 8. Previous fertility data [Chapin et al. 1985a] showed that the pregnancy rate and number of live pups were similar for the 100 mg EGME/kg per day group and controls at wk 8 also. The most widespread and persistent testicular damage was produced by 200 mg EGME/kg per day. Chapin et al. [1985b] also concluded that the elevation of fluid protein levels suggests first

that the ability of the testes to secrete protein is not inhibited by EGME and second that the lack of germ cells that normally take up this protein may have contributed to the elevated protein levels.

Anderson et al. [1987] investigated the stage-specific effect of EGME on spermatogenesis. Adult male CD rats and CD-1 mice were given single oral doses of EGME at 0, 500, 750, 1,000, or 1,500 mg/kg. Groups of 10 rats and 10 mice were sacrificed at weekly intervals, after dosing for a period of 8 wk, for analysis of epididymal sperm counts and morphology or testicular histology; additional groups of 10 EGME-treated animals were sequentially mated to pairs of virgin females to test for dominant lethality or gross fetal malformations in the F_1 generation (F_1 abnormalities). In the rat, a reduction in testes weights was observed at all dose levels at wk 3, 4, and 5, but this effect disappeared in all but the 1,500 mg EGME/kg group by wk 6. At wk 4, 5, 6, and 7, the sperm counts were significantly lower ($P<0.001$) in the EGME-treated groups compared with those of the controls. A dose-dependent increase in abnormal sperm morphology was noted at all dose levels ($P<0.01$). In the EGME-treated mice, the mean testes weights were significantly lower than those of the control groups at wk 2 to 5, and appeared to increase again towards the end of the study (statistics not given); there was also a tendency towards a dose-response relationship in the incidence of abnormal sperm (statistics not given).

In the rat dominant lethal study, the total implant numbers among females mated at wk 5 to EGME-dosed rats were reduced in a dose-dependent manner ($P<0.001$). Although there was a rise in preimplantation loss rate, there was no statistically significant evidence for the induction of dominant lethality. All rats were infertile at wk 6 after dosing except for those given the lowest dose (500 mg EGME/kg). No induction of gross abnormalities in the offspring was noted (data not given). The histological study in the rats revealed a dose-dependent response to EGME-treatment. One day after treatment with 500 mg EGME/kg, primary spermatocytes undergoing pachytene development were either degenerate or absent. Other stages of spermatocytes, including those in midpachytene, zygotene, and leptotene, were affected with increasing doses of EGME. Depletion of early pachytene spermatocytes 2 and 4 wk after dosing with 1,000 or 1,500 mg EGME/kg suggested early spermatogonial damage. In the mouse, however, the sensitive cells were the late spermatocytes and spermatids [Anderson et al. 1987].

B.1.2.2 Inhalation

Inhalation exposure to EGME has also caused testicular damage [Miller et al. 1981]. Groups of five male Fischer 344 rats and five male $B6C3F_1$ mice were exposed to EGME (0, 100, 300, or 1,000 ppm) 6 hr/day for 9 days in an 11-day interval. EGME at concentrations of 100 or 300 ppm exerted no adverse effects on rat or mouse testes. At 1,000 ppm, however, EGME exerted statistically significant decreases ($P<0.05$) in testes weights when compared with controls. Histopathologic changes in this group included severe degeneration of the testicular germinal epithelium with necrosis of all spermatogenic elements.

Miller et al. [1983a] continued their investigation of the inhalation toxicity of EGME by exposing groups of 10 male Sprague-Dawley rats and 5 male New Zealand white rabbits to

0, 30, 100, or 300 ppm EGME 6 hr/day, 5 days/wk, for a total of 13 wk. The mean testes weights of the rats and rabbits in the 300-ppm group were significantly reduced ($P<0.05$). Testes weights of rabbits in the 100-ppm group were also decreased when compared with those of the controls, but not in a statistically significant manner. Gross pathology showed small, flaccid testes in the males of both species at 300 ppm. Microscopic lesions were found in rats only at the 300-ppm EGME-exposure level; these lesions included bilateral, diffuse, and moderate-to-severe degeneration of the tubular germinal epithelium and reduced numbers of spermatozoa or degenerating spermatozoa. Rabbits demonstrated a dose-related increase in the incidence and severity of the testicular degeneration. In the three surviving rabbits at 300 ppm EGME, severe degeneration affected every tubule, with only Sertoli cells and occasional spermatogonia remaining. At 100 ppm EGME, three of five rabbits had some normal tubules and some tubules contained no germinal elements. Two animals from this group had normal testes. Microscopic degenerative changes were seen in one rabbit from the 30-ppm group. The authors concluded that rabbits were apparently more sensitive than rats to EGME [Miller et al. 1983a].

In reproductive and dominant lethal studies, Rao et al. [1983] exposed Sprague-Dawley rats to EGME vapor. Male rats were exposed to EGME (30 per group at 0 and 30 ppm; 20 per group at 100 and 300 ppm) 6 hr/day, 5 days/wk for 13 consecutive wk. Immediately after the 13-wk exposure period, the males were paired with unexposed female rats for breeding. The fertility index (number of fertile males per number housed with unexposed females) was significantly decreased ($P<0.05$) only in males exposed to 300 ppm EGME. To assess the recovery of reproductive function in males exposed to 300 ppm EGME, additional breedings were conducted at 13 and 19 wk after the termination of exposure. A continued significant decrease ($P<0.05$) in the fertility index was found (50% of males were infertile), although it was not as great as that found in this group immediately after exposure (when 80% of males were infertile). Data suggested that the decreased reproductive function induced by EGME was partially reversible [Rao et al. 1983]. Reproductive parameters examined were normal for males exposed to 30 or 100 ppm EGME; male rats exposed to 300 ppm EGME failed to sire any litters. No dominant lethal effects were found in male rats exposed to 30 or 100 ppm EGME for 13 wk. It was not possible to assess dominant lethality in male rats exposed to 300 ppm due to the complete infertility of these animals. All implantations from the 20% fertile group were nonviable. There was no indication of an increased incidence of resorptions when males exposed to 300 ppm EGME were bred again with unexposed virgin females 26 wk and 32 wk post-exposure after fertility had partially recovered. The authors concluded that the no-adverse-effect level of EGME for fertility and reproduction was 100 ppm in male rats [Rao et al. 1983].

Doe et al. [1983] reported the same 100 ppm EGME no-adverse-effect level for male rats. Groups of 10 male Wistar-derived, Alderly Park strain rats were exposed to 0, 100, or 300 ppm EGME 6 hr/day for 10 consecutive days. The testes of the 300 ppm group were flaccid, reduced in size, and lighter than controls, whereas testes of rats exposed to 100 ppm EGME did not differ from controls. Histological examination of the testes revealed pronounced tubular atrophy in all the rats exposed to 300 ppm EGME, with 70% to 100% of the tubules affected. In contrast, the testes of rats exposed to 100 ppm EGME could not be distinguished from those of controls.

The same laboratory also investigated the effects of a single inhalation exposure of EGME in male rats [Samuels et al. 1984]. Groups of 20 SPF Alpk/AP male albino rats were exposed to 150, 300, 625, 1,250, 2,500, or 5,000 ppm EGME for 4 hr. The control group consisted of 40 rats. Following the single exposure, they were returned to their cages for 13 days and were sacrificed on day 14. Statistically significant reductions ($P<0.01$) in testes weights were seen in the 1,250-, 2,500-, and 5,000-ppm exposure groups when compared with controls. Histological examination revealed severe bilateral tubular atrophy with disordered spermatogenesis in the 5,000-ppm group. Many tubules showed only stem cells and Sertoli cells. Similar but less marked changes were seen in the 2,500- and 1,250-ppm exposure groups, and at 625 ppm, testes weights were not reduced but maturing spermatids showed unspecified evidence of damage.

Samuels et al. [1984] conducted a second study in which groups of 90 SPF Alpk/AP male albino rats were exposed to 0, 1,000, or 2,500 ppm EGME for a single 4-hr period. Ten rats per group were sacrificed on each of days 1, 2, 3, 4, 5, 8, 10, 15, and 19 following exposure. Forty-eight hours following exposure, testes weight reduction was observed in both exposed groups. Damage to the germinal epithelium was observed 24 hr postexposure with primary spermatocytes the target cells for EGME. At day 19, recovery was not evident in the 2,500-ppm EGME group and the germinal epithelium remained disordered. Cytoplasmic retraction and swollen mitochondria in Sertoli cells were observed 4 days following exposure using electron microscopy. The authors concluded that even a relatively brief exposure to EGME vapor can cause marked testicular atrophy [Samuels et al. 1984].

B.1.2.3 Dermal Exposure

EGME has been shown to penetrate human skin in vitro [Dugard et al. 1984]. To determine if EGME produced toxicity following subchronic dermal exposure, six male Hartley guinea pigs were dermally dosed with 1 g EGME/kg per day, 5 days/wk for 13 wk [Hobson et al. 1986]. EGME was applied to 2 × 2 cm gauze patches that were affixed to the shaved backs of the guinea pigs and held in place for 6 hr with a stockinette bandage. At the end of 13 wk, the mean and relative testicular weights were significantly decreased ($P<0.01$) when compared with those of the controls. All animals had severe testicular atrophy, with moderate to severe segmental degeneration of the seminiferous tubules characterized by complete loss of spermatogenic cells. Sertoli cells and Leydig cells remained largely unaffected.

B.2 EFFECTS ON THE FEMALE REPRODUCTIVE SYSTEM AND THE DEVELOPING EMBRYO

B.2.1 EGEE and EGEEA

B.2.1.1 Subcutaneous Administration

The effects of EGEE-treatment on pregnant rats, mice, and rabbits were examined in a study by Stenger et al. [1971]. Groups of 20 pregnant rats were treated s.c. with varying

concentrations of EGEE (0, 23, 46.5, 93 mg/kg per day) on gestation days (g.d.) 1 through 21; pregnant mice (20 per group) were treated s.c. on g.d. 1 through 18 with 0, 46.5, or 93 mg/kg per day; and rabbits (15 per group) were treated s.c. on g.d. 7 through 16 with 0 or 23 mg/kg per day. At the highest doses used, no adverse effects were noted in mice (93 mg EGEE/kg per day) and rabbits (23 mg EGEE/kg per day), but fetal skeletal defects were observed in rats treated s.c. with 93 mg EGEE/kg per day.

B.2.1.2 Oral Administration

In the Stenger et al. study [1971], groups of 20 pregnant rats were treated orally with EGEE (0, 11, 23, 46.5, 93, 186, or 372 mg/kg per day) on g.d. 1 through 21. A significant increase in embryonic and fetal deaths occurred in rats treated orally with doses of 46.5 mg EGEE/kg per day and higher; at oral doses of 93 to 372 mg EGEE/kg per day, the incidence of skeletal aberrations increased in a dose related pattern (no statistical treatment given).

Using an in vivo mouse screening bioassay, a group of 10 pregnant CD-1 mice was treated orally with 3,600 mg EGEE/kg per day on g.d. 7 through 14. Results indicated 10% maternal mortality and no viable litters [Schuler et al. 1984].

The in vitro culture system of Yonemoto et al. [1984] was used by Rawlings et al. [1985] to demonstrate the fetotoxicity of EAA, the alkoxy acid metabolite of EGEE [Jonsson et al. 1982; Cheever et al. 1984]. Conceptuses were explanted from pregnant Wistar-Porton rats at embryonic age 9.5 days and cultured for 48 hr with 2 mM or 5 mM EAA. At the end of the culture period, crown-rump length, head length, and yolk sac diameter were measured, and the degree of differentiation and development was evaluated by a morphological scoring system. EAA at the 5 mM concentration had an adverse effect on fetal development. EAA-exposed embryos had statistically significant reductions ($P<0.01$) in morphological score, crown-rump length, head length, and yolk sac diameter. Additionally, EAA produced statistically significant reductions ($P<0.01$) in somite number and in protein content of the embryo. No statistically significant reductions in growth parameters were seen at the 2-mM level. Irregularity of the neural suture line was found in 100% of the EAA-exposed embryos. Other abnormalities seen in the EAA groups were abnormal otic and somite development, turning failure, open cranial folds, and abnormal yolk sac [Rawlings et al. 1985].

B.2.1.3 Inhalation

In inhalation studies [Andrew et al. 1981; Hardin et al. 1981], pregnant New Zealand white rabbits were exposed 7 hr/day on g.d. 1 through 18 to 0, 160, or 615 ppm of EGEE. Five of 29 rabbits died at the high dose (615 ppm); the other 24 suffered severe anorexia and weight loss. Maternal toxicity was mild in rabbits exposed at 160 ppm; a statistically significant reduction in food consumption and body weight gain and increased maternal liver weight was noted ($P<0.05$). In the 615-ppm group, all litters were totally resorbed, and in the 160-ppm group, the number of live fetuses was significantly reduced and resorptions were increased ($P<0.001$). Fetal morphological examinations revealed a significantly increased incidence ($P<0.05$) of renal, cardiovascular, and ventral body wall

defects in fetuses from the 160-ppm exposure group; there were also increases in certain minor skeletal variations.

In the same studies [Andrew et al. 1981; Hardin et al. 1981], female Wistar rats were exposed to 0, 150, or 650 ppm EGEE for 7 hr/day, 5 days/wk for 3 wk before breeding, and then for 7 hr/day on g.d. 1 through 19 to 0, 200, or 765 ppm EGEE. Exposure to EGEE under these conditions exerted no effect on fertility (i.e., mating success or the establishment of pregnancy). A statistically significant ($P<0.05$) reduction in maternal liver weight and an increase in lung and kidney weight ($P<0.05$) occurred with the higher EGEE-exposure regimen (i.e., 650 ppm before breeding followed by 765 ppm on g.d. 1 through 19), and no maternal toxicity occurred at the lower EGEE-exposure regimen (i.e., 150 ppm before breeding followed by 200 ppm on g.d. 1 through 19). Although the incidence of resorptions was not significantly increased in the lower exposure group, all the litters were totally resorbed in the higher exposure group. Fetal toxicity was evident in the lower exposure group as a significant reduction ($P\leq0.05$) in fetal body weight and crown-rump length. Morphological examinations of fetuses from the lower EGEE-exposure group revealed a significantly increased incidence ($P<0.05$) in cardiovascular and skeletal defects.

Nelson et al. [1981] also conducted an inhalation study in which EGEE was evaluated for possible functional effects in the offspring of Sprague-Dawley rats allowed to deliver litters following exposures during gestation to 0, 100, 200, or 900 ppm. The pilot dose-finding study revealed complete resorption of litters in dams exposed to 900 ppm EGEE for 7 hr/day during g.d. 7 through 13, and no live pups in litters of dams exposed on g.d. 14 through 20. There was 34% mortality of pups after exposure of dams to 200 ppm EGEE on g.d. 7 through 13 or 14 through 20. Exposure to 900 ppm EGEE during days 14 through 20 of gestation also produced a consistent pattern of a 48-hr extended gestation period. The only maternal effect observed in rats exposed to 100 ppm EGEE for 7 hr/day on g.d. 7 through 13 and 14 through 20 was a slightly prolonged gestation period (0.7 day, $P<0.001$) in the rats exposed on g.d. 14 through 20. Six behavioral tests were selected to assess central nervous system functions in the control group (filtered air) and in the 100-ppm EGEE-treated groups: neuromuscular ability (ascent and rotorod tests), exploratory activity (open field test), circadian activity (activity wheel test), aversive learning (avoidance conditioning test), and operant conditioning (appetitively motivated test of learning). Behavioral testing of offspring from dams exposed on days 7 through 13 of gestation revealed: (1) impaired performance on a rotorod test ($P=0.002$); (2) prolonged latency of leaving the start of an open field ($P=0.009$); and (3) marginal superiority in avoidance conditioning begun on day 34 of age (not significant, $P=0.061$). Offspring from dams exposed on g.d. 14 through 20 were less active than were controls in a running wheel (not significant, $P=0.32$); they also received an increased number and duration of shocks in avoidance conditioning begun on day 60 of age ($P=0.004$).

Neurochemical alterations also occurred in newborn and 21-day-old rats from dams exposed prenatally to 100 ppm EGEE. Levels of norepinephrine in offspring from both exposure periods (g.d. 7 through 13 and 14 through 20) were decreased significantly ($P<0.01$). In 21-day-old offspring of dams exposed to 100 ppm EGEE on g.d. 7 through 13, the cerebrum had significant elevations in acetylcholine ($P<0.01$), norepinephrine ($P<0.01$), and

dopamine ($P<0.05$); the cerebellum had nearly a threefold increase in acetylcholine ($P<0.01$); the brainstem had an increase in norepinephrine ($P<0.01$); and the midbrain had excesses of acetylcholine ($P<0.01$), norepinephrine ($P<0.05$) and protein ($P<0.05$). In 21-day-old offspring from dams exposed on g.d. 14 through 20, the cerebrum had significant elevations in acetylcholine, dopamine, and 5-hydroxytryptamine ($P<0.05$) [Nelson et al. 1981].

Neuromotor ability of offspring, assessed by ascent and rotorod tests, was reduced ($P<0.05$) when pregnant Sprague-Dawley rats were exposed by inhalation to 200 ppm EGEE 7 hr/day on g.d. 7 through 13; the 200 ppm treatment group was also less active than controls in exploratory activity in the open field and in the shuttle box [Nelson et al. 1982a]. Exposure of pregnant Sprague-Dawley rats to 200 ppm EGEE 7 hr/day on g.d. 7 through 13 altered neurochemical transmitter levels in all brain regions except for the brainstem of 21-day-old offspring. Dopamine levels increased significantly in the cerebrum and midbrain ($P<0.01$ and $P<0.05$, respectively). Norepinephrine levels increased significantly ($P<0.01$) in the cerebrum and cerebellum [Nelson et al. 1982b].

Female Dutch rabbits were exposed to 0, 50, 150, or 400 ppm EGEE on g.d. 6 through 18 [Tinston 1983]. On g.d. 21, animals were sacrificed and necropsied. Although maternal, mean body-weight gain and food consumption of the 400 ppm EGEE-exposure group were markedly lower than those of the controls, they were not statistically different. At 400 ppm EGEE, the group mean number of live fetuses ($P<0.01$), gravid uterus weight ($P<0.01$), and litter weight ($P<0.01$) were statistically lower than they were in the control group. The group mean percentage post implantation loss ($P<0.01$), percentage of early fetal deaths ($P<0.01$), and percentage of late deaths ($P<0.05$) were statistically higher in the 400 ppm EGEE-exposure group compared with controls. No adverse effects were observed in the groups exposed to either 50 or 150 ppm EGEE. No macroscopic pathological abnormalities or external fetal abnormalities could be attributed to EGEE exposure.

EGEE and EGEEA were examined in an inhalation study [Doe 1984a] in which groups of 24 pregnant Alpk/AP rats were exposed to 0, 10, 50, or 250 ppm EGEE 6 hr/day on g.d. 6 through 15, and groups of 24 pregnant Dutch rabbits were exposed either to 0, 10, 50, or 175 ppm EGEE or to 0, 25, 100, or 400 ppm EGEEA on g.d. 6 through 18. Animals were sacrificed on g.d. 21 (rats) or 29 (rabbits), and fetuses were examined for external, visceral, and skeletal malformations. In the rat study, the only sign of maternal toxicity was an effect on the hematopoietic system; reductions in Hb, Hct, and MCV were observed in the group exposed to 250 ppm and are reported in Chapter 4, Section 4.3.4.1. Although there was a higher incidence of preimplantation losses in all exposure groups, this was statistically significant only in the 10- and 50-ppm groups ($P<0.05$). Fetal weights were significantly reduced ($P<0.05$) in the 250-ppm group. In addition, reduced ossification and an increased incidence of skeletal variants ($P<0.05$) were observed in this exposure group. A small and statistically insignificant number of these changes (unossified cervical centra, partial ossification of the second sternebra, extra ribs) also occurred at 50 ppm EGEE. No statistically significant increase in visceral malformations was observed. Data indicated that although EGEE was not teratogenic in rats at the concentrations tested, it was fetotoxic in rats at 250 ppm (98% of fetuses affected) and slightly fetotoxic (51% of fetuses affected) at 50 ppm

($P<0.05$). Exposure of rabbits to 10, 50, or 175 ppm EGEE resulted in no evidence of maternal toxicity. The incidence of skeletal defects and variants at the 175-ppm dose was statistically greater than in the control group ($P<0.05$). This was a result of retarded skeletal ossification, an increased incidence of presacral vertebrae, and an increased number of fetuses with extra ribs, both of short and of normal length.

Exposure of rabbits to 400 ppm EGEEA in the same study [Doe 1984a] caused reduced maternal weight gain and food consumption, whereas no adverse maternal effects were noted in the groups exposed to 25 or 100 ppm EGEEA. At 400 ppm EGEEA, there was an increase in resorptions and a reduction in fetal body weight per litter ($P<0.05$). Reduced fetal body weight also occurred at 100 ppm EGEEA ($P<0.05$). There was no effect on fetal number or weight at 25 ppm EGEEA. Retarded ossification was seen at 400 ($P<0.05$) and 100 ppm ($P<0.05$) but not at 25 ppm EGEEA. Major malformations of the vertebral column were noted at 400 ppm EGEEA, and the incidence of minor defects and variants was elevated at both 400 and 100 ppm EGEEA ($P<0.05$). The investigator concluded that EGEEA was teratogenic in rabbits exposed at 400 ppm, slightly fetotoxic at 100 ppm, and exerted no effect at 25 ppm [Doe 1984a].

In another series of experiments, groups of 15 pregnant Sprague-Dawley rats were exposed 7 hr/day to 0, 130, 390, or 600 ppm EGEEA on g.d. 7 through 15 and sacrificed on g.d. 20 [Nelson et al. 1984b]. All implantations from dams exposed to 600 ppm EGEEA were resorbed, and there was a 56% increase in resorptions at 390 ppm. At 390 and 130 ppm EGEEA, fetal weights were significantly reduced compared with those of the controls ($P<0.05$). Visceral malformations of the heart and umbilicus occurred in fetuses of the 390 ppm group ($P<0.01$). One fetus from the 130 ppm group had a heart defect. The authors concluded that both 130 ppm and 390 ppm EGEEA were teratogenic in the rat [Nelson et al. 1984b].

Tyl et al. [1988] evaluated the teratogenic potential of EGEEA. Pregnant Fischer 344 rats (30 per group) and New Zealand white rabbits (24 per group) were exposed to EGEEA vapor by inhalation 6 hr/day on g.d. 6 through 15 (rats) or 6 through 18 (rabbits) at concentrations of 0, 50, 100, 200, or 300 ppm; the animals were then sacrificed on g.d. 21 (rats) or 29 (rabbits). This study indicated that exposure of rabbits to EGEEA during organogenesis resulted in maternal toxicity at 100 to 300 ppm. Signs of this included significantly decreased weight gain and reduced gravid uterine weight ($P<0.001$) and elevated absolute liver weight ($P<0.05$). In rats, significantly ($P<0.001$) reduced weight gain and reduced food consumption were noted at 200 and 300 ppm EGEEA; significantly elevated relative liver weights were noted at 100, 200, and 300 ppm EGEEA (no statistics given). In rabbits, an increased incidence of totally resorbed litters at 200 ppm ($P<0.05$) and 300 ppm ($P<0.001$), an increase in nonviable fetuses at 300 ppm ($P<0.05$), and a decrease in viable fetuses per litter at 200 ppm and 300 ppm EGEEA ($P<0.05$) were observed. Fetotoxicity (reduced ossification) was observed at 100, 200, and 300 ppm EGEEA. The incidence of external visceral and skeletal malformations was increased at 200 ppm and 300 ppm ($P<0.05$). In rats, embryo/fetotoxicity was observed at 100, 200, and 300 ppm EGEEA. Observations included increased nonviable implantations/litter at 300 ppm ($P<0.05$), reduced fetal body weight/litter at 200 and 300 ppm ($P<0.05$), and increased incidence

(P<0.05) of external variations at 300 ppm and visceral and skeletal variations at 100, 200, and 300 ppm. There was no evidence of maternal, embryonic, or fetal toxicity (including teratogenicity) at 50 ppm EGEEA in either species. Tyl et al. [1988] concluded that 50 ppm EGEEA was the no observable effect level.

B.2.1.4 Dermal Exposure

The effects of dermal exposure to EGEE on pregnant Sprague-Dawley rats have been investigated by Hardin et al. [1982]. Applications of EGEE (0.25 mL or 0.5 mL) were made 4 times per day on g.d. 7 through 16 to the shaved interscapular region of pregnant rats (20 per group); control rats were treated similarly with water. The only signs of maternal toxicity were ataxia and significantly reduced body weight gain in the last half of gestation following treatment with 0.5 mL EGEE (P<0.001). All litters were completely resorbed in the high exposure group, and the incidence of resorptions (76%) was significantly increased in the low exposure group (P<0.001). There was a significant reduction in fetal body weight (P<0.001), and both cardiovascular malformations (ventricular septal defects) and skeletal variations were significantly increased (P<0.05) in the litters treated with 0.25 mL EGEE.

Using the preceding experimental design, equimolar volumes of EGEE (0.25 mL) and EGEEA (0.35 mL) were applied cutaneously to pregnant rats [Hardin et al. 1984]. Data demonstrated that EGEE and EGEEA treatment reduced maternal body weight gain, and at days 17 and 21, body weight gain in the EGEEA group was significantly lower than that in the controls (P<0.001). Gravid uterus weights were also significantly reduced in both treatment groups compared with those of the controls (P<0.001). Although extragestational body weights did not differ significantly (P<0.1), extragestational body weight gain was significantly reduced (P<0.05) in the treated groups. A reduction in body weight, which was associated with completely resorbed litters and significantly fewer live fetuses per litter (P<0.01), was noted in EGEE- and EGEEA-treated rats relative to that of the controls. Fetal body weights were also significantly decreased (P<0.001). Cardiovascular malformations and skeletal variations were significantly increased compared with untreated controls (P<0.001) in both EGEE- and EGEEA-treated groups.

B.2.2 EGME and EGMEA

B.2.2.1 Oral Administration

Female JCL-ICR mice were mated with males of the same strain and assigned to experimental and control groups of 21 to 24 animals [Nagano et al. 1981]. EGME was administered by gavage on g.d. 7 through 14 at doses of 0, 31.25, 62.5, 125, 250, 500, or 1,000 mg/kg per day, and the animals were sacrificed on g.d. 18. The incidence of dead fetuses was significantly increased at 250, 500, and 1,000 mg EGME/kg per day (P<0.01). Only one fetus survived in the 500 mg EGME/kg per day group, and none survived in the 1,000 mg EGME/kg per day group. Fetal weights were significantly reduced at the 125 and 250 mg EGME/kg per day doses (P<0.01). The incidence of gross anomalies in the 250 mg EGME/kg per day exposure group was significantly increased when compared with the controls and included exencephaly, abnormal digits, and umbilical hernia (P<0.01). The

one live fetus from the 500 mg EGME/kg per day group also had exencephaly and abnormal digits. The incidence of skeletal malformations was also significantly higher ($P<0.01$) in the 250 mg EGME/kg per day group than in the control group. All fetuses examined in this group had skeletal malformations, including fusion and/or agenesis (nondevelopment) of vertebrae or ribs, spina bifida occulta, syndactyly (fusion of digits), oligodactyly (fewer than five digits), and polydactyly (more than five digits). A significant increase ($P<0.01$) in skeletal malformations was seen also in the 125 mg EGME/kg per day exposure group (fused ribs, fusion and/or agenesis of vertebrae, and spina bifida occulta) and the 62.5 mg EGME/kg per day exposure group (spina bifida occulta). Bifurcated or split cervical vertebrae ($P<0.05$) were observed in the 31.25 mg EGME/kg per day exposure group. The ossification of fetuses was significantly retarded ($P<0.05$) in all treatment groups when compared with the controls, as indicated by decreased numbers of proximal and middle phalanges of fore and hind limbs. The authors concluded that the severity and frequency of the malformations noted following administration of EGME at doses greater than 31.25 mg/kg per day were dose dependent [Nagano et al. 1981].

Pregnant CD-1 mice dosed by gavage with 1,400 mg EGME kg/day on days 7 to 14 of gestation produced no viable litters. EGME caused 14% maternal mortality [Schuler et al. 1984].

The developmental phase-specific and dose-related embryotoxic effects of EGME were investigated by Horton et al. [1985]. Initially, 250 mg EGME/kg per day was administered orally on g.d. 7 through 14 to 10 pregnant CD-1 strain mice, which were subsequently sacrificed on g.d. 18. This group demonstrated gross malformations (exencephaly and paw lesions) similar to those reported by Nagano et al. [1981]. The treatment period was then reduced to 250 mg/kg on g.d. 7 through 9, 8 through 10, 9 through 11, or 250 mg/kg on g.d. 7 and 8, 9 and 10, 10 and 11, or 500 mg EGME/kg on g.d. 9, 10, 11, 12, or 13 to define the developmental phase specificity of the embryotoxic effects observed. Multiple doses of 250 mg EGME/kg per day or single doses of 500 mg EGME/kg significantly reduced fetal weights in all dose groups ($P<0.05$) and significantly increased embryolethality (percentage of implantations resorbed) in all groups except the single 500 mg EGME/kg exposure on g.d. 12 or 13 ($P<0.05$).

Studies with mice dosed during different gestational stages also demonstrated phase-specific teratogenic effects [Horton et al. 1985]. Groups of 9 or 10 pregnant mice treated on g.d. 7 through 9 or 8 through 10 with 250 mg EGME/kg per day had significantly more exencephalic fetuses than did the controls ($P<0.05$). Exposure during later stages of development did not result in excess exencephaly. The incidence of digit malformations (syndactyly, oligodactyly, and polydactyly) increased significantly after three doses on days 8 through 10, or 9 through 11, as well as with two doses on days 10 and 11 ($P<0.05$).

A single oral administration of 500 mg EGME/kg to groups of 9 to 12 mice on g.d. 9, 10, 11, or 12 produced significant increases in paw malformations ($P<0.05$) [Horton et al. 1985]. Peak susceptibility to paw malformations occurred on g.d. 11 and 12 and included syndactyly and oligodactyly. Treatment with EGME on g.d. 9, 10, or 11 produced a prevalence of forepaw anomalies; treatment on g.d. 12 shifted the higher incidence to hind paw syndactyly.

Horton et al. [1985] also investigated the dose dependence of digit anomalies in groups of 9 to 11 mice orally dosed with 100, 175, 250, 300, 350, 400, or 450 mg EGME/kg on g.d. 11. Exposure to 100 mg EGME/kg did not induce digit anomalies. Digit anomalies occurred at 175 mg EGME/kg (not statistically significant), and their frequency increased in a statistically significant dose-related manner ($P<0.05$) to a maximum incidence at 350 mg EGME/kg, with intermediate responses at 250 and 300 mg EGME/kg. The authors concluded a no observed effect level of 100 mg EGME/kg for digit malformations after a single oral dose of EGME [Horton et al. 1985].

The role of cytotoxicity in digital maldevelopment in CD-1 mouse embryos was examined following oral treatment of dams with 100, 250, or 350 mg EGME/kg on g.d. 11 [Greene et al. 1987]. Pregnant mice were sacrificed 6 or 24 hr later. The embryos were removed and incubated for 15 min in Nile blue A stain. The right forelimb buds of EGME-treated embryos were compared with the right forelimb buds from control embryos of the same gestational age. Right forelimbs were examined for the pattern of cell death as determined by uptake of the dye into the tissue, and the overall shape and conformation were recorded by photography and drawings. None of the treatment regimens produced maternal toxicity. Forelimb buds collected 6 or 24 hr after administration of EGME showed marked cytotoxic responses, which were dose related. Cell death was induced in the mesenchymal tissue and to some extent in the limb bud ectoderm. Forelimb buds from the dams treated with 350 mg EGME were consistently malformed in the preaxial region; virtually all of the limb buds examined were extremely altered in appearance. Necrosis was evident in forelimb buds from the dams treated with 250 mg EGME, but the lesions were less severe. In the embryos from the dams treated with 100 mg EGME only slight increases in cell death were noted in approximately 50% of the limb buds from embryos collected 24 hr after EGME treatment [Greene et al. 1987].

Pregnant mice that had been treated with 350 mg EGME/kg on g.d. 11 were sacrificed 2, 6, 24, or 48 hr later [Greene et al. 1987]; a single untreated mouse was included for each time point. Forelimb buds from at least five embryos/dam were excised and prepared for examination by light or electron microscopy. Microscopic evaluations of forelimb buds revealed the presence of phagocytic vacuoles and condensed, fragmented cytoplasm, indicative of cytotoxicity, as early as 2 hr after EGME treatment. The maximum effect was observed 6 hr after EGME treatment, and the severity of the effect appeared to be dose-related.

In the same study [Greene et al. 1987], pregnant mice were given a single oral dose of EGME (100, 175, 250, 300, 350, 400, 450, or 500 mg) on g.d. 11 and were sacrificed on g.d. 18. Near-term fetuses were removed and examined for digit malformations. Although digital malformations were not detected in near-term fetuses following treatment with 100 mg EGME, they were induced in all other treatment groups in a dose-dependent manner (statistics not given). The percentage of fetuses with paw malformations ranged from 12% to 93%. The primary anomalies observed were preaxial syndactyly (fusion of digits of No. 2 and No. 3) and ectrodactyly (absence of digit No. 1).

Hardin and Eisermann [1987] studied the potency of dimethyl-substituted ethylene glycol ethers relative to EGME in inducing paw malformations. EGME, ethylene glycol dimethyl ether (EGdiME), diethylene glycol dimethyl ether (diEGdiME), and triethylene glycol dimethyl ether (triEGdiME) were administered orally in single equimolar doses (304, 361, 537, and 713 mg/kg, respectively) to CD mice on g.d. 11. On g.d. 18, fetuses were collected, weighed, and examined for gross external malformations. None of the treatment regimens produced maternal toxicity. In the fetuses, only paw malformations were observed; they occurred with significantly increased frequency ($P<0.05$) in litters of mice treated with EGME, EGdiME, diEGdiME, but not in litters of triEGdiME-treated dams. The average percent of fetuses affected per litter was 69% (EGME), 34% (EGdiME), and 40% (diEGdiME). Only in litters of dams treated with EGME was polydactyly observed with significantly increased frequency ($P<0.05$) in forepaws. Syndactyly appeared in increased frequency ($P<0.05$) in hindpaws of EGME, EGdiME, and diEGdiME litters. The frequency of short digits was significantly increased ($P<0.05$) in both forepaws and hindpaws of EGME litters but only in hindpaws of diEGdiME-treated litters. Oligodactyly appeared in both forepaws and hindpaws of EGME litters, forepaws of EGdiME litters, and hindpaws of diEGdiME litters more often ($P<0.01$) than in controls. It was suggested by Hardin and Eisenmann [1987] that these paw malformations were attributable to in vivo conversion of these glycol ethers to a common teratogen, MAA.

Toraason et al. [1985] studied the effect of EGME on the developing cardiovascular system using electrocardiography. Pregnant Sprague-Dawley rats were treated by gavage with 0, 25, 50, or 100 mg EGME/kg per day on g.d. 7 through 13. All fetuses from the eight rats treated with 100 mg EGME/kg per day were resorbed. There was a dose-dependent increase in cardiovascular defects in fetuses exposed to EGME, including ventricular septal defects and right ductus arteriosus in the 50 mg EGME/kg per day exposure group. No cardiovascular malformations were seen in control fetuses. Significantly more litters in the 25 and 50 mg EGME/kg per day exposure groups had fetuses with aberrant heart QRS intervals than did the controls ($P<0.05$). The most prevalent abnormality was a prolonged QRS complex, which the authors suggest indicated the presence of an intraventricular conduction delay. There was no association between abnormal electrocardiograms (EKGs) and any morphological defect.

To assess the risk for women of childbearing age exposed to EGME, Scott et al. [1989] exposed nonhuman primates, *Macaca fasicularis* females, orally to 12, 24, or 36 mg EGME/kg on g.d. 20 through 45 (8, 11, and 13 animals/group, respectively). The fetuses were collected by Caesarean section at day 100. Two groups of three monkeys served as controls. One of the control groups was treated orally on g.d. 20 through 45 with 15 mL of ethanol. Although no statistics were presented, the data indicated that EGME caused a dose-related loss of maternal body weight. This was accompanied by anorexia, the severity of which was dose-related.

Because the loss of appetite was so severe at times, especially in the high-dose animals, the investigators administered gruel and/or electrolytes by gavage to prevent serious physical deterioration of the adult animals. After the cessation of treatment at g.d. 45, the animals

regained their appetites, and body weights were similar to control body weights at the time of Caesarean section on g.d. 100 [Scott et al. 1989].

Hematologic analysis of the EGME-treated monkeys did not reveal any dose-related effects. Embryotoxicity of EGME in these monkeys was manifest mainly in the form of embryonic death. At the 36 mg/kg dose, all eight pregnancies ended in death. One of these dead embryos, judged to have been about 40 days old at the time of death, was missing one digit on each forelimb. This malformation has never been seen in macaque pregnancies, and EGME has caused the same type of defect in mice [Horton et al. 1985], rats [Ritter et al. 1985], and rabbits [Hanley et al. 1984a]. The authors [Scott et al. 1989] therefore attributed this malformation to EGME treatment. Three of 10 pregnancies (30%) at the 24-mg/kg dose and 3 of 13 pregnancies (23%) at the 12-mg/kg dose ended in embryonic death. An additional pregnancy in each of the 12- and 24-mg/kg groups was lost to abortion, but both were thought to be spontaneous (spontaneous abortions occur in 10% to 20% of untreated macaque pregnancies). All surviving fetuses were free from malformation. Despite the maternal toxicity associated with the higher doses of EGME, the authors concluded that EGME acted directly on the embryo to cause its demise [Scott et al. 1989].

B.2.2.2 Inhalation

A rapid assessment of the effect of inhaled EGME on the developing embryo was conducted by Doe et al. [1983]. Groups of 20 pregnant female Wistar-derived, Alderly Park strain rats were exposed to 0, 100, or 300 ppm EGME for 6 hr/day on g.d. 6 through 17. The rats were allowed to deliver their litters, which were observed for 3 days. Maternal body weight gain was significantly reduced in the 300 ppm group ($P<0.05$), and none of these rats produced litters. The gestation period was significantly increased for the nine rats producing litters in the 100 ppm EGME group when compared with that of the controls (23.6 vs. 22 days, $P<0.05$). This group also showed a significant reduction in the total number of pups ($P<0.001$), the proportion of live pups at birth ($P<0.01$), and the proportion surviving to 3 days ($P<0.01$). All the pups were normal externally [Doe et al. 1983].

Hanley et al. [1984a] conducted a study to compare the teratogenic potential of exposure to low vapor concentrations of EGME in F344 rats, CF-1 mice, and New Zealand white rabbits. Groups of 24 to 32 pregnant mice, rats, and rabbits were exposed to EGME via inhalation for 6 hr/day on g.d. 6 through 15 (rats and mice) or g.d. 6 through 18 (rabbits). Exposure concentrations were 0, 3, 10, or 50 ppm EGME for rats and rabbits, and 0, 10, or 50 ppm EGME for mice. Mice were sacrificed on g.d. 18, rats on g.d. 21, and rabbits on g.d. 29. Statistically significant increases ($P<0.05$) in lumbar spurs and delayed ossification of the ventral centra (minor skeletal variations) were seen in rats at 50 ppm. Maternal effects found in rats were minimal. At 50 ppm, a slight transient decrease in body weight gain was observed, and decreases in mean Hb, packed cell volume (PCV), and RBC values were found. Hanley et al. [1984a] concluded that these decreases were of no toxicologic significance. The mice demonstrated a pattern of effects similar to that observed in rats. The only maternal effect was a statistically lower ($P<0.05$) body weight gain on g.d. 12 through 15. There was a significant increase ($P<0.05$) in the incidence of extra ribs, and the

incidence of unilateral testicular hypoplasia in animals exposed to 50 ppm indicated slight fetotoxicity [Hanley et al. 1984a].

Rabbits demonstrated a greater sensitivity to EGME at these concentrations than did rats or mice [Hanley et al. 1984a]. At 50 ppm EGME, significant decreases in maternal body weight gain during exposure ($P<0.05$) and significant increases in the absolute weights of the liver ($P<0.05$) occurred. Changes in reproductive and developmental parameters in the 50 ppm EGME group included a significant increase in the resorption rate ($P<0.05$) and a significant decrease in the mean fetal body weights ($P<0.05$) when compared with those of the controls. Examination of fetuses revealed a statistically significant increase ($P<0.05$) in the total incidence of malformations in the 50 ppm group. External malformations involved the extremities and included persistent joint contracture (arthrogryposis) and digit anomalies such as absence of nails (anonychia), shortness of digits (brachydactyly), and absence of digits (ectrodactyly). Visceral examination of rabbit fetuses revealed ventricular septal defects and coarctation (segmental constriction) of the aortic arch, splenic hypoplasia, and severe dilation of the renal pelvis. Malformations seen at skeletal examination of the 50-ppm EGME exposure group included missing bones of the paws and a variety of rib malformations. Numerous minor variations considered evidence of fetotoxicity at 50 ppm EGME included patent ductus arteriosus (delayed development), pale spleen, and convoluted or dilated ureters. Other variations were delayed ossification of the hyoid, tarsals, and sternebrae and an irregularity in the pattern of the palatine rugae. At 3 or 10 ppm EGME, there were no differences among fetal rabbits suggesting any adverse developmental effect. Hanley et al. [1984a] concluded that these results established no observed effect levels of 10 ppm EGME in these three species.

Nelson et al. [1984a] determined how offspring were affected when male or female rats were exposed at 25 ppm EGME. Pregnant female Sprague-Dawley rats were exposed either on g.d. 7 through 13 or 14 through 20 and then allowed to deliver their young. Males were exposed to EGME 7 hr/day, 7 days/wk for 6 wk and then mated with unexposed females. Six behavioral tests were selected to evaluate CNS functions in offspring: ascent on a wire mesh, rotorod, open field, activity wheel, avoidance conditioning, and operant conditioning. Offspring from the group exposed on g.d. 7 through 13 showed significant differences ($P<0.05$) in performance of avoidance conditioning (aversive learning) when compared with the control animals. No other significant behavioral differences were seen.

Chemical analyses were performed on whole brain samples from newborns of each group, and on cerebrum, cerebellum, brain stem, and midbrain samples from 21-day-old animals. Concentrations of total brain protein and four neurotransmitters (acetylcholine [Ach], dopamine [DA], norepinephrine [NE], and 5-hydroxytryptamine [5-HT]) were measured. Significant differences in concentrations of Ach, DA, NE, and 5-HT were apparent in 21-day-old rats from all three exposed groups when compared with the controls ($P<0.05$). Protein levels were significantly ($P<0.05$) different only in 21-day-old offspring exposed from day 14 through 20 of gestation. In whole brain samples from newborns, increases were found in Ach and 5-HT for the offspring of exposed males, but no other differences were significant when compared with the controls [Nelson et al. 1984a].

B.2.2.3 Dermal Exposure

The teratogenic potential of dermal exposure to EGME was estimated using the Chernoff and Kavlock in vivo assay. Groups of 10 pregnant Alpk/AP (Wistar derived) rats were exposed to 3%, 10%, 30%, or 100% EGME in physiological saline at 10 mL/kg [Wickramaratne 1986]. The test compound was applied for 6 hr (occluded exposure) on g.d. 6 through 17. Rats were then allowed to deliver litters normally and rear their litters until day 5 post-partum. The application of 100% EGME was lethal to all dams and 30% was lethal to all developing fetuses. At 10% EGME, the litter size was reduced by 26% as was survival at day 5 (neither statistically significant). No adverse effects were seen in the 3% group. The results were evaluated using "rules" generated from the Chernoff and Kavlock in vivo teratology screen assay. The authors concluded that the data demonstrated a clear dose-response and that a 10% solution of EGME is likely to be a rat teratogen [Wickramaratne 1986].

Feuston et al. [1990] studied the effect of a single dermal application of EGME as a function of both gestation day administered and dose level. Pregnant Sprague-Dawley rats (8 to 10 rats/group) received a single dermal application of 0, 250, 500, 1,000, or 2,000 mg EGME/kg on g.d. 12. In the other part of the study, pregnant Sprague-Dawley rats (8 to 10 rats/group) received a single dermal application of 2,000 mg EGME/kg on g.d. 10, 11, 12, 13, or 14. The control group was sham treated on g.d. 10 through 14 to correspond to all of the days of 2,000 mg EGME/kg exposure. Dose levels were based on a pilot study at this facility (data not presented). Each female rat was observed daily; body weights were measured on g.d. 0, 6, 10 through 15, and 20. On g.d. 20, each female rat was necropsied and the fetuses were examined for normal development.

Maternal toxicity consisted of a statistically significant ($P<0.05$) decrease in mean body weight gain for female rats on the day following their exposure. This occurred at all EGME exposure concentrations on g.d. 10 through 14, except for animals exposed to 250 mg EGME/kg on g.d. 12. This weight loss was transient.

Adverse reproductive effects were noted in the female rats who had received 2000 mg EGME/kg on g.d. 10. These effects included a statistically significant increase ($P<0.05$) in both the mean number of resorptions and the mean percentage resorptions. The number of dams in this group with resorptions was also higher than the number of dams with resorptions in the untreated group.

There was a statistically significant decrease ($P<0.05$) in fetal body weights in the female rats exposed to 1,000 mg EGME/kg on g.d. 12 or 2,000 mg EGME/kg on g.d. 10 and 12. In general, female fetuses were more affected than were male fetuses.

Application of 500, 1,000, or 2,000 mg EGME/kg on g.d. 12 caused statistically significant ($P<0.05$) increases in external, visceral, and skeletal malformations. Cardiovascular and urinary system defects were the prominent visceral malformations. The most frequently observed skeletal defects were limb (primarily of the digits) and vertebral column (primarily of the tail) defects. The application of 250 mg EGME/kg caused no adverse developmental

effects and was considered to be the no observable adverse effect level (NOAEL) by the investigators [Feuston et al. 1990]. Examination of the effects on the various days of exposure indicated that application of 2,000 mg EGME/kg on g.d. 11, 12, or 13 produced the highest incidence and greatest variety of fetal visceral malformations. The application of EGME on g.d. 12 or 13 resulted in a predominance of external and skeletal malformations. Exposure to EGME on g.d. 14 produced minimal developmental effects.

B.3 HEMATOLOGY

B.3.1 EGEE and EGEEA

An early report [von Oettingen and Jirouche 1931] indicated that adding 1 cc of EGEE or EGEEA to 5 cc suspensions of dog or beef red blood cells in Ringer solution caused hemolysis. The investigators noted that hemolysis was more marked with EGEEA than with EGEE.

B.3.1.1 Oral Administration

In a study by Stenger et al. [1971], EGEE administered orally 7 days/wk for 13 wk to dogs (186 mg/kg per day) and rabbits (186, 372, or 744 mg/kg per day) decreased the Hb and Hct values. No statistical analysis was presented. Hemosiderin accumulation and isolated hematopoietic foci were observed in the spleens of all dogs and rabbits treated with EGEE.

In a study by Nagano et al. [1979], oral administration to mice of 2,000 mg EGEE or EGEEA/kg per day, 5 days/wk for 5 wk significantly reduced WBC counts compared with control values ($P<0.05$). No disturbances of erythrocytic parameters were observed following administration of 500, 1,000, or 2,000 mg EGEE/kg per day. However, administration of 4,000 mg EGEEA/kg per day, reduced the MCV ($P<0.01$).

B.3.1.2 Inhalation

When rats were exposed to 370 ppm EGEE 7 hr/day, 5 days/wk for 5 wk, an adverse effect on both the RBC and WBC populations was evident from (1) the increase in the hemosiderin content and the decrease in myeloid cells in the spleen, (2) fat replacement in the bone marrow, and (3) an increase in the proportion of circulating immature granulocytes [Werner et al. 1943a]. Hemosiderin was still present in the 3-wk interval following termination of EGEE exposure. Exposure of dogs 7 hr/day, 5 days/wk for 12 wk to 840 ppm EGEE also increased the numbers of circulating immature granulocytes [Werner et al. 1943b]. Although the hemosiderin content in the spleen was increased, RBC counts, Hb concentration, and MCV were only marginally reduced in the exposed dogs. These blood changes occurred at exposure concentrations not sufficiently severe to cause overt signs of toxicity. These studies demonstrated hematologic changes from EGEE exposure that were not severe and were reversible.

In a study by Carpenter et al. [1956], a single 4-hr inhalation exposure of rats to either EGEE or EGEEA increased erythrocyte osmotic fragility. The lowest concentrations causing osmotic fragility were 125 ppm EGEE and 62 ppm EGEEA. In another study, a single 4-hr exposure of rats and rabbits to 2,000 ppm EGEEA caused transient hematuria and/or hemoglobinuria only in rabbits [Truhaut et al. 1979]. In the same study [Truhaut et al. 1979], exposure of rats and rabbits of both sexes to 200 ppm EGEEA 4 hr/day, 5 days/wk for 10 months caused no effect on RBC or Hb levels.

Adverse effects on hematologic parameters were observed in rats and rabbits exposed to 0, 25, 100, or 400 ppm EGEE 6 hr/day, 5 days/wk for 13 wk [Terrill and Daly 1983a,b; Barbee et al. 1984]. In the rabbit study, Hct and Hb levels and erythrocyte counts were reduced significantly in males ($P<0.05$, $P<0.01$, $P<0.05$, respectively) and females ($P<0.05$) exposed to 400 ppm EGEE. No hematologic changes were observed in either sex at lower concentrations. In the rat study, WBC counts were significantly reduced ($P<0.05$) in females exposed to 400 ppm EGEE; no effects were observed in male rats.

Exposure of pregnant rats and rabbits during gestation to EGEE or EGEEA also affected hematologic parameters [Doe 1984a]. Pregnant Alpk/AP rats were exposed to 0, 10, 50, or 250 ppm EGEE 6 hr/day on g.d. 6 through 15. In the 250 ppm EGEE-exposure group, there were reductions in Hb, Hct, and MCV in erythrocytes. There were no effects at either 50 or 10 ppm EGEE in rats. No hematologic effects were observed in pregnant Dutch rabbits exposed to 0, 10, 50, or 175 ppm EGEE 6 hr/day on g.d. 6 through 18. In the same study, pregnant rabbits were exposed to 0, 25, 100, or 400 ppm EGEEA 6 hr/day on g.d. 6 through 18. Doe [1984a] concluded that a significant reduction in Hb concentration and a slight reduction in the associated RBC parameters were seen in the 400 ppm EGEEA-exposure group but provided no specific statistical data. No effects were observed in rabbits at the lower exposure concentrations.

Exposure of New Zealand white rabbits and Fischer 344 rats to 0, 50, 100, 200, or 300 ppm EGEEA 6 hr/day on g.d. 6 through 18 (rabbits) and 6 through 15 (rats) resulted in adverse hematologic parameters in both species [Tyl et al. 1988]. In rabbits, there was evidence of enlarged erythrocytes (elevated MCV) at 300 ppm EGEEA ($P<0.01$) and significant dose-related decreases in the number of platelets at 100 ($P<0.05$), 200 ($P<0.01$) and 300 ppm EGEEA ($P<0.001$). In rats, the WBC count was significantly increased ($P<0.001$) at 200 and 300 ppm EGEEA. Statistically significant reductions in rat RBC count ($P<0.0$), Hb level ($P<0.01$), and Hct and RBC volume (0.05) were seen at the three highest exposures (100, 200, and 300 ppm EGEEA). Platelet counts were also significantly reduced at 200 ppm ($P<0.001$) and 300 ppm EGEEA ($P<0.01$) in the rat.

B.3.1.3 Dermal Exposure

In a study by Truhaut et al. [1979], rabbits were exposed to a single 24-hr dermal application (10,500 mg/kg) of EGEEA; death followed between 1 and 4 days after application. The reduction in RBC count did not exceed 15% to 20% and blood Hb levels showed little variation; however, a 50% to 70% decrease in WBC count was noted.

B.3.2 EGME and EGMEA

B.3.2.1 Oral Administration

Oral administration of EGME and EGMEA has induced hematologic changes in laboratory animals. Nagano et al. [1979] found a statistically significant decrease ($P<0.01$) in WBC counts following oral administration of 500 mg EGME/kg or 1,000 mg EGMEA/kg to male JCL-ICR mice 5 times/wk for 5 wk. Statistically significant decreases were also observed in RBC and Hb values for the 1,000 mg EGME/kg group ($P<0.01$) and in Hb values for the 2,000 mg EGMEA/kg group ($P<0.01$). Treatment of female JCL-ICR mice with 1,000 mg EGME/kg on g.d. 7 through 14 also significantly decreased the leukocyte counts ($P<0.01$) [Nagano et al. 1981].

Grant et al. [1985] investigated the effects of subchronic oral exposure to EGME on the hematopoietic system of rats and the reversibility of such effects. Groups of 24 male F344 rats were orally dosed with EGME at 0, 100, or 500 mg/kg per day for 4 consecutive days. Six animals from each group were then sacrificed 1, 4, 8, and 22 days after the last treatment. Rats in the high-dose group displayed severely hemorrhagic femoral bone marrow with major loss of the normal nucleated tissue and damage of sinus endothelial cells on day 1. The normal architecture of the marrow was restored by day 4 post-treatment. Treatment with 500 mg EGME/kg for 4 days abolished extramedullary hemopoiesis (EMH) in the spleen; partial recovery was seen on day 4, followed by marked improvement on day 8, and a return to control values by day 22. The high-dose group also showed mild anemia characterized by reductions of the Hct and Hb values at day 4 ($P<0.05$ and $P<0.001$, respectively), and RBC, Hct, and Hb values at day 8 ($P<0.05$, $P<0.05$, and $P<0.01$, respectively). Leukocyte counts (neutrophils and lymphocytes) were significantly reduced in this group on day 1 ($P<0.001$) and did not return to control values by the end of the recovery period. Low dose (100 mg EGME/kg per day) rats also had reduced leukocyte counts on day 1 ($P<0.05$). The authors [Grant et al. 1985] concluded that the major hematological effect of EGME was leukopenia characterized by reductions in lymphocytes and neutrophils. Changes in the circulating blood together with reduced splenic EMH and bone marrow toxicity suggested an inhibitory action on erythropoiesis.

B.3.2.2 Inhalation

Hematologic effects from exposure to EGME were first reported by Werner et al. [1943b] who exposed two dogs by inhalation to 750 ppm EGME for 7 hr/day, 5 days/wk for 12 wk. This exposure to EGME resulted in microcytic anemia as indicated by depressed erythrocyte and Hb values, which appeared at 4 to 6 wk of exposure; these values remained depressed throughout the exposure period. Recovery, as measured by Hb and Hct values, was gradual in proportion to the severity of the anemia. RBC were found to have increased osmotic fragility at the end of 11 and 12 wk of exposure. When Werner et al. [1943a] exposed Wistar rats to 310 ppm EGME 7 hr/day, 5 days/wk for 5 wk, increased levels of hemosiderin and immature granulocytes were observed; this indicated destruction of blood cell populations.

In a study by Carpenter et al. [1956], hemolytic effects in the rat erythrocyte were demonstrated by a single 4-hr inhalation exposure of six female rats to EGME or EGMEA. The lowest concentrations causing significant osmotic fragility were 2,000 ppm EGME and 32 ppm EGMEA.

In a study by Miller et al. [1981], Fischer 344 rats and $B6C3F_1$ mice were exposed by inhalation to 0, 100, 300, or 1,000 ppm EGME 6 hr/day for a total of 9 days in an 11-day period. WBC counts of both rats and mice exposed to 1,000 ppm EGME were statistically lower than those of the controls ($P<0.05$). MCV, RBC counts, and Hb levels of male and female rats and male mice in the 1,000 ppm EGME-exposure group were also statistically depressed ($P<0.05$). At 300 ppm EGME, similar but less severe effects were seen in rats; statistically lower ($P<0.05$) WBC counts in both sexes and Hb and RBC counts in females were noted. Hematologic parameters in mice exposed at 300 ppm EGME were stated to be similarly affected, but data were not presented. Histopathology was performed on rats only, revealing reduced bone marrow cellularity, lymphoid depletion in the cortex of the thymus, and reduced numbers of lymphoid cells in the spleen and in the mesenteric lymph nodes in the 1,000-ppm EGME group. Both myeloid and erythroid elements of the bone marrow were markedly reduced in all rats exposed to 1,000 ppm EGME, and megakaryocytes were present in decreased numbers and were smaller than those of controls. The entire thymic cortical lymphoid population was depleted, with less dramatic reductions in the lymph nodes and spleen. Lymphoid organ toxicity persisted at 300 ppm EGME, but to a much lesser extent. In addition, serum total protein, albumin (males only), and globulin values in the 1,000 ppm EGME-exposure group (rats) were significantly reduced ($P<0.05$).

In a longer inhalation study, Miller et al. [1983a] exposed Sprague-Dawley rats and New Zealand white rabbits to 0, 30, 100, or 300 ppm EGME 6 hr/day, 5 days/wk for 13 wk. Hematologic analyses were performed after 4 or 12 wk of exposure. After 12 wk, both rats and rabbits from the 300 ppm EGME-exposure groups had significantly decreased mean WBC counts, platelet counts, MCV, and Hb concentrations ($P<0.05$); RBC counts were significantly reduced only in the 300 ppm EGME-exposed rabbits. These same hematologic changes were also seen after 4 wk (data not given). Mean values for total protein, albumin, and globulins were significantly lower than those of the controls in rats exposed to 300 ppm EGME ($P<0.05$) but were normal in rabbits. Microscopic lesions in rats occurred in the 300-ppm group only as a decrease in cortical lymphocytes indicating thymic atrophy. No histopathologic changes were seen in bone marrow. In rabbits, microscopic lesions were also present at 300 ppm EGME, including lymphoid atrophy of the thymus and gut-associated lymphoid organs and a decrease in the size of hepatocytes [Miller et al. 1983a].

B.3.2.3 Dermal Exposure

Subchronic dermal exposure of male guinea pigs to EGME demonstrated adverse hematologic effects [Hobson et al. 1986]. Six male Hartley guinea pigs were exposed to 1,000 mg EGME/kg per day, 5 days/wk for 13 wk. EGME was applied to gauze patches affixed to the shaved backs of the guinea pigs and held in place with a stockinette bandage

6 hr/day, 5 days/wk for 13 wk. Statistically significant decreases in RBC counts and increases in MCV were noted when compared with the control values ($P<0.05$). Differential white cell counts demonstrated significant ($P<0.05$) lymphopenia with neutrophilia. Additionally, significantly increased serum creatinine kinase (CK) and lactate dehydrogenase (LDH) activity were noted in this group ($P<0.01$).

B.4 METABOLISM, UPTAKE, AND ELIMINATION

B.4.1 EGEE/EGEEA

Jonsson et al. [1982] investigated the biotransformation of EGEE in albino rats exposed either to 10 ppm EGEE via inhalation for 1 hr or to single doses of 9.3 or 93 mg EGEE by gastric intubation. Ethoxyacetic acid (EAA) and N-ethoxyacetyl glycine were the two major metabolites present in the urine of animals dosed by either route. In the oral-dosing study, urine was collected after dosing for 48 hr, in 24-hr portions. The combined excretion of the two metabolites amounted to 30% of the administered oral dose for both dose groups. No recovery was given for the animals dosed by inhalation.

The biotransformation and excretion of EGEE was studied by Cheever et al. [1984] in Sprague-Dawley rats. The animals received a single oral dose of 230 mg/kg of EGEE [ethanol or ethoxy labeled ^{14}C]. The animals were sacrificed for assay of tissue radioactivity at the end of a 96-hr experimental period. Rats treated with the ethanol-labeled material excreted 81% of the radioactive dose in urine over a 96-hr period, whereas rats treated with the ethoxy-labeled compound excreted 76% of the dose in urine. Within the first 24 hr, 72% of the ethanol label and 70% of the ethoxy label were excreted in urine. The major urinary metabolites were EAA and N-ethoxyacetyl glycine, which accounted for 73% to 76% of the administered radioactivity. Results of this study confirmed previous work by Jonsson et al. [1982] and indicated that, in the rat, metabolism of EGEE proceeds primarily through oxidation via alcohol dehydrogenase to EAA, with some subsequent conjugation of the acid metabolite with glycine. It is noteworthy that in this study, 2 hr after administration of EGEE, EAA was found in the rat testes; these data suggest that adverse testicular effects of EGEE may be due to EAA [Cheever et al. 1984].

Absorption and elimination of EGEEA were studied by Guest et al. [1984] in beagle dogs following inhalation, intravenous (i.v.), or dermal exposure. EGEEA was rapidly absorbed through the lungs during exposure to 50 ppm EGEEA for 5 hr. After 10 min of exposure, the concentration of EGEEA in expired breath was 9 ppm (80% absorption), and it reached the plateau value of 16 ppm at 3 hr, indicating that 68% of the inhaled compound was absorbed. The breath concentration of EGEEA decreased to 2 ppm at 3 hr post-exposure. Following single i.v. dosing with 1 mg/kg, 20% and 61% of the dose appeared in urine in 4 and 24 hr, respectively. The blood elimination half-life was 7.9 hr. Estimated over a 60-min period, the percutaneous absorption rate of EGEEA following dermal application to the dog's thorax was 110 mM/cm^2 per min. The rate of absorption of EGEEA through dog skin in vitro was 292 $nmol/cm^2$ per hr (2.3 mg/cm^2 per hr).

Groeseneken et al. [1986a] developed a method for measuring urinary EAA. Five healthy male volunteers were exposed at rest via face mask to air containing 5.4 ppm EGEE during four 50-min periods. Experimental conditions are described in Groeseneken et al. [1986b]. Urinary EAA concentration rose significantly 1 hr after the exposure period. Urinary EAA concentration rose from 0.07 mg/liter before exposure to 2.39 ± 1.03 mg/liter 1 hr after the exposure period ($P<0.005$). One of the subjects showed measurable levels of EAA before exposure. Questioning of the subject indicated that he may have had occupational exposure to EGEE some days before the experiment. Preliminary results of the excretion of EAA in urine suggested that measurement of EAA could be a specific and sensitive parameter for monitoring worker exposure to EGEE.

Groeseneken et al. [1986b] next investigated the respiratory uptake and elimination of EGEE in 10 male volunteers under controlled experimental conditions of exposure concentration and physical workload. The subjects were divided into two groups, five subjects per group, and were exposed to EGEE for 4 hr, the equivalent of half a workshift. At the end of each 50 min during exposure, a short break of 10 min was inserted. All subjects participated in three experiments according to their group assignment. Experimental conditions are presented in Table B-1.

Table B-1.—Experimental conditions for Groeseneken et al. [1986b]

Group	Exposure concentration		Workload
	ppm	mg/m^3	(W)
I	2.7	10	0
	5.4	20	0
	10.8	40	0
II	5.4	20	0
	5.4	20	30
	5.4	20	60

This study showed that in man, EGEE is rapidly absorbed through the lungs. About 64% of the inhaled vapor was retained at rest, and retention increased as physical exercise was performed during exposure. The absorbed dose was apparently proportional to the inhaled concentration, and a linear relation was observed between uptake rate and exposure concentration. The rate of uptake increased when physical exercise was performed during exposure. The rate of uptake was higher as exposure concentration, or pulmonary ventilation rate, or both increased. Individual uptake rates seemed dependent only on transport mechanisms (pulmonary ventilation, or cardiac output, or both) and not on anthropometric data or body fat content. Respiratory elimination of unchanged EGEE accounted for ≤0.4% of the total body uptake and occurred rapidly after cessation of exposure, followed by a much slower decrease. This slow decrease indicated that two pharmacological compartments were involved.

Groeseneken et al. [1986c] also studied the urinary excretion of EAA in the 10 male volunteers who inhaled various concentrations of EGEE for 4 hr both at rest and during physical exercise in the previously described study [Groesenken et al. 1986b]. The subjects, divided into two groups of five, were either exposed at rest to concentrations of 2.7, 5.4, or 10.8 ppm EGEE (10, 20, or 40 mg/m^3, respectively) or were exposed to 5.4 ppm EGEE at rest and during physical exercises (see Table B-2). Urine samples were collected at hourly intervals during exposure and up to 4 hr after exposure ended. Additional urine samples were collected at 2-hr intervals for the rest of the day; four 8-hr samples were collected during the next 2 days. Urine samples were analyzed for EAA using the method of Groeseneken et al. [1986a]. During both experimental protocols, the rate of excretion of EAA increased and continued to do so to a maximum level 3 to 4 hr after the end of the exposure period. After attaining the maximum level, a slow decrease began with a biological half-life between 21 and 24 hr. In both the resting condition under increasing EGEE concentrations and during physical exercise at a constant EGEE concentration, the rate of urinary excretion of EAA increased ($P<0.001$ and $P<0.005$, respectively) and appeared to be related to the rate of uptake of EGEE. The rate of uptake increased under both experimental conditions in a statistically significant manner ($P<0.001$).

The total amount of EAA excreted within 42 hr was significantly related ($P<0.001$) to the EGEE concentration in inspired air, uptake rate, pulmonary ventilation rate, oxygen consumption during exposure, and heart rate during and after exposure. EAA was negatively related ($P<0.05$) to height, body weight, and lean body mass. Multiple linear regression analysis revealed that only the relations between EAA excretion and EGEE uptake rate ($P<0.001$), heart rate ($P<0.001$), oxygen consumption during exposure ($P<0.05$), and height ($P<0.001$) were significant. Respiratory frequency was a contributing factor to EAA excretion. On the average, 23% of inhaled EGEE was recovered as EAA within 42 hr in both experiments at rest and during physical work. The authors concluded that good correlations between EAA excretion and EGEE uptake were found following the exposure period. Although biological monitoring of exposed workers is usually based on urinary metabolite levels in samples taken immediately after the end of a workshift, a maximal excretion rate of EAA may be reached several hours later. In addition, as a result of the long biological half-life of EAA, EAA will not be cleared from the urine the next morning, and accumulation can be expected through repetitive exposures [Groeseneken et al. 1986c].

The urinary excretion of EAA was studied in a group of five female silk-screen printing operators during repeated daily inhalation exposure to a mixture of EGEE and EGEEA [Veulemans et al. 1987]. The subjects worked in weekly, alternating morning and evening shifts. They agreed to wear rubber gloves at all times to avoid occasional skin contact with inks and thinners. Air and urine samples were collected each day during 5 days of normal production and 7 days after a 12-day production stop. Urine samples were collected immediately before and after work; air samples were collected as individual half-shift samples. Urinary EAA excretion increased during the workweek, and elimination proved to be far from complete over the weekends. In the last observation period, urinary EAA values on Monday morning still attained about half the urinary concentration on Friday evening (30 mg EAA/g creatinine versus 64 mg EAA/g creatinine). Even after a prolonged nonexposure period of 12 days, traces of the metabolite (1.2 to 2.6 mg EAA/g creatinine)

were still detectable. On a number of days, the preshift EAA concentrations were even higher than the immediate postshift values on the preceding and same day. For this reason, and because of the more constant exposure profiles, an estimation of the maximum EAA levels after prolonged daily exposure was made on the basis of the results of the first exposure period. A linear correlation (r=0.92) was found between average exposure to EGEE and EGEEA over the 5 exposure days and EAA excretion at the end of the 5-day workweek. EAA estimate of 150 mg ± 35 mg/g creatinine was found to correspond with repeated 5-day full-shift exposures to 5 ppm of EGEE or 5 ppm of EGEEA.

Groeseneken et al. [1988] compared urinary EAA excretion in man and the rat after experimental exposure to EGEE. The human data were drawn from the previously mentioned inhalation study [Groeseneken et al. 1986c] in which five subjects had been exposed to 2.7 ppm, 5.4 ppm, or 10.8 ppm EGEE. Urine samples collected at short intervals were pooled into 12-hr groups for comparison with rat data. Groups of five male Wistar rats were treated by oral intubation with 0.5, 1, 5, 10, 50, or 100 mg EGEE/kg. Rat urine samples were collected before EGEE exposure and then at 12-hr intervals up to 60 hr after the dosing. The maximal excretion rate of EAA in human and rat urine was found within 12 hr after exposure or dosing. Afterwards, the decline of urinary EAA was much slower in man than in the rat. In man, the half-life of EAA was on average 42.0 ± 4.7 hr, a longer half-life than reported in the original study (21 to 24 hr) [Groeseneken et al. 1986c]. The author attributes the longer half-life to the use of 12-hr pooled urine specimens in this study [Groeseneken et al. 1988] rather than to specimens collected at 1- to 2-hr intervals in the previous study [Groeseneken et al. 1986c]. In the previous study, half-lives were calculated from the peak exposure time (8 hr after the start of exposure). Examination of the excretion curves from the previous paper showed that elimination between 8 and 12 hr was more rapid than at longer time intervals, leading to a shorter calculated elimination half-life [Groeseneken et al. 1986c]. The authors concluded that the longer elimination half-life was more consistent with half-lives seen in occupational exposure, which were as high as 48 hr [Groeseneken et al. 1988; Veulemans et al. 1987]. The recovery of EAA in human urine after 48 hr averaged 23%. Based on the half-life of EAA elimination of 42 hr, the authors estimated total recovery of EAA as 30% to 35% of the absorbed dose.

In the rat, the half-life of EAA was 7.20 ± 1.54 hr. On the average, 27.6% ± 6.1% of urinary EAA in rats was present as the glycine conjugate, with the extent of conjugation being independent of the dose. The extent of conjugation demonstrated a diurnal variation; the lowest extent of conjugation was found during the night. EAA glycine conjugates were absent in human urine. In man, the recovery of EAA was higher than in the rat for equivalent low doses of EGEE (0.5 and 1 mg/kg). When urinary excretion data for the lower dose range were normalized for body weight in both species, rats excreted EAA at a higher rate than did man for equivalent doses. The authors concluded, that although nonlinear kinetics had been observed in some animal studies at high doses, the elimination kinetics seen at low doses in this study were not dose-dependent in either rats or humans [Groeseneken et al. 1988].

Groeseneken et al. [1987a] studied the pulmonary absorption and elimination of EGEEA in 10 male subjects under various conditions of exposure and physical workload; subjects were

assigned into two groups, 5 per group. Exposures were by mask for 50 min/hr. Experimental conditions are presented in Table B-2.

Table B-2.—Experimental conditions for Groeseneken et al. [1987a]

Group	Exposure concentration		Workload
	ppm	mg/m^3	(W)
I	2.6	14	0
	5.2	28	0
	9.3	50	0
II	5.2	28	0
	5.2	28	30
	5.2	28	60

All subjects performed three experiments according to their group assignment. The subjects remained unexposed for at least 1 wk between experimental sessions. The pharmacokinetics of respiratory uptake are more complicated for EGEEA than for EGEE. Retention, atmospheric clearance, and uptake rate decreased with time and reached steady-state levels at 3 to 4 hr; retention increased with exposure and workload. Retention at steady state for the three exposure concentrations was 53%, 57%, and 62%, respectively. Although retention of EGEEA increased proportional to the workload, no further increase was noticed for EGEE after 30 w [Groeseneken 1986b]. Individual uptake of EGEEA was determined by pulmonary ventilation, cardiac output, height, and fat content, whereas uptake of EGEE seemed mainly determined by the cardiopulmonary transport parameters alone [Groeseneken 1986b]. The hypothesis that EGEEA is first converted to EGEE by plasma esterases was confirmed by the observation of partial respiratory elimination of EGEE. The amount of EGEE expired during steady state conditions correlated with the uptake rate of EGEEA rather than with EGEEA exposure concentrations. Respiratory elimination of unmetabolized EGEEA accounted for ≤0.5% of total body uptake. This slow decrease could be represented as a regression equation with two exponential terms, indicating at least two pharmacologic compartments were involved. The author speculated that the complex pulmonary kinetics may be due to metabolic competition in the conversion of EGEEA to EGEE and to possible redistribution into the fat soluble compartment.

Groeseneken et al. [1987b] examined urinary EAA excretion in the experimental groups exposed to EGEEA in the previous study [Groeseneken et al. 1987a]. Urine samples were taken at the beginning of the exposure period and at every hour until the fourth hour after exposure. Then three 2-hr samples followed by four 8-hr samples were collected. Urine samples were analyzed for EAA by the method of Groeseneken et al. [1986a]. EAA levels appeared with a half-life of 2.3 ± 0.1 hr during the 4-hr EGEEA exposure period. Maximal EAA excretion rate was attained 3 to 4 hr after the exposure period. The half-life was

23.6 ± 1.8 hr. However, 3 hr after the first peak EAA excretion, a second maximum excretion of EAA was observed; this second peak was especially pronounced after exposure during physical exercise. Redistribution of EGEEA, or EAA, or both from a peripheral to central compartment could explain this phenomenon. Urinary EAA excretion was dependent on the EGEEA uptake rate, as a consequence of higher exposure (P<0.001), and on the uptake rate of EGEEA at constant exposure, as a consequence of physical workload (P<0.001). On average, 22.2% ± 0.9% of the absorbed EGEEA was metabolized and excreted in the urine as EAA within 42 hr. The total excretion of EAA in 42 hr was related both to total uptake from increasing concentrations of EGEEA (P<0.001) and to total uptake, at constant exposure, with increasing workload (P<0.001). Total EAA excretion was correlated to EGEEA concentration, uptake rate, and transport mechanisms (pulmonary ventilation, oxygen consumption, respiratory rate, etc.). In addition, EAA excretion was correlated to body fat (r=0.40, P<0.001). Groeseneken et al. [1987b] concluded that the metabolism of EGEEA proceeded through EGEE via esterases and then continued through the same excretion pathway as EGEE. Indeed, the kinetics of EAA excretion after exposure to EGEEA were very similar to those found after exposure to EGEE [Groeseneken et al. 1987a].

Workers from a shipyard painting operation who applied paint containing EGEE were evaluated for EGEE exposure [Lowry 1987]. Work conditions and practices varied considerably between brush and spray painters. Some workers were in confined spaces below deck, whereas others were in the open. The study was conducted in the winter, and the temperatures varied greatly 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, and the use of personal protective equipment was gathered from questionnaires.

Environmental breathing zone samples were collected for each worker for 3 days. Urine samples were collected every day for 1 wk, at the beginning and end of each workday, and EAA levels were measured. A wide range of EAA levels was noted in workers using EGEE-containing paints; this was probably due to variation in work assignments, work areas, and use of personal protective equipment. This study has not gone through extensive evaluation to determine the importance of the many variables on the levels of EAA in urine. The author could only conclude that there appeared to be a relationship between urinary EAA excretion and the use of paints containing EGEE [Lowry 1987].

Clapp et al. [1987] investigated EGEE exposure of workers engaged in casting precision metal parts. The 8-hr TWAs of EGEE ranged from nondetectable to 23.8 ppm. EGEE was not detected in any of the blood samples from the EGEE-exposed workers, but exposed workers were found to have measurable levels of EAA in urine (163 mg/g creatinine). EAA was not detected in the urine of unexposed control subjects.

B.4.2 EGME and EGMEA

EGME has been shown to be a possible substrate for alcohol dehydrogenase (ADH) [Tsai 1968; Blair and Vallee 1966], and thus oxidation of EGME via ADH and aldehyde dehydrogenase to methoxyacetic acid (MAA) is a potential route of metabolism [Miller et al. 1982].

The toxicity of MAA will be discussed next to evaluate the importance of metabolism as a detoxification or bioactivation mechanism for EGME. In a study by Miller et al. [1982], groups of five male F344 rats were given daily doses of 0, 30, 100, or 300 mg MAA/kg per day orally on 8 days out of 10 and were then sacrificed 24 hr after the final dose. Rats given the high dose had significantly lower body weights on the fifth day and again when recorded on the tenth day ($P<0.05$). Absolute and relative weights of spleen, thymus, and testes were also significantly reduced in the 300 mg MAA/kg per day exposure group ($P<0.05$). In the 100 mg MAA/kg per day exposure group, relative thymus weight was significantly reduced ($P<0.05$). Hematology revealed significantly lower RBC, Hb concentration, MCV, and WBC in the group dosed with 300 mg MAA/kg per day ($P<0.05$). Significant but less pronounced reductions in RBC, Hb, and MCV were seen in those receiving 100 mg MAA/kg per day ($P<0.05$). Testicular atrophy and a decrease in the size of the thymus were seen in the 300 mg MAA/kg per day group; thymus size was decreased in the 100 mg MAA/kg per day group also. Histological evaluation revealed diffuse, severe depletion of cortical lymphoid elements in the thymus of all rats treated with 300 mg MAA/kg per day and a slight reduction in the same cell population in all rats treated with 100 mg MAA/kg per day. All rats treated with 300 mg MAA/kg per day had severe degenerative changes in the germinal epithelium of the seminiferous tubules, and slight degenerative changes were observed in the rats treated with 100 mg MAA/kg per day [Miller et al. 1982].

Miller et al. [1983b] used radiolabeled EGME to isolate and identify urinary metabolites in rats. Groups of three male F-344 rats were given a single oral dose of approximately 76.1 mg/kg or 660 mg/kg of ^{14}C EGME; animals were sacrificed 48 hr after dosing. Urine was the major route of elimination (50% to 60% of ^{14}C) at both dose levels, with approximately 18% and 12% of the radioactivity remaining in the carcasses of low- and high-dose animals, respectively. Target organs of EGME such as testes, thymus, and spleen did not show an accumulation of EGME or its metabolites. Blood had the greatest amount of ^{14}C per gram of tissue at 48 hr postexposure. The profile of radioactivity in a composite sample of urine collected during the 0 to 12 hr interval for both high- and low-dose groups was very similar. The majority of the ^{14}C (83% to 95%) was found in one major peak identified as MAA. The authors [Miller et al. 1983b] proposed that oxidation to MAA is a major route for elimination of EGME and occurs via ADH to methoxyaldehyde and, thereafter, via aldehyde dehydrogenase to MAA.

Foster et. al. [1983] exposed six male Sprague-Dawley rats orally to 592 mg MAA/kg per day (equimolar to 500 mg EGME/kg per day) for 4 days. Significant decreases in actual and relative liver and testes weights were seen ($P<0.01$). The severity and nature of testicular changes were essentially similar to those of the corresponding dosage of EGME given for the same period [Foster et al. 1983].

Foster et al. [1987] exposed groups of six male Alpk/AP (Wistar-derived) rats to a single oral dose of MAA to determine the initial target for testicular toxicity. Dose levels were administered equimolar with 100, 250, or 500 mg EGME/kg (i.e., 118, 296, or 592 mg MAA/kg). Rats were sacrificed at 1, 2, 4, and 14 days post-treatment. A significant decrease in testes weight relative to body weight was seen only in the high dose MAA group at days

4 and 14 ($P<0.05$). Histological examination of testes revealed damage 24 hr after dosing in all groups treated with MAA. Pyknosis and nuclear condensation were seen in late pachytene, diplotene, diakinetic, and secondary spermatocytes in high-dose rats at 24 hr. At 2 days, these effects were more extensive and included the loss of early and late pachytene, diplotene, and secondary spermatocytes; some signs of degeneration to zygotene spermatocytes (precursor cells to pachytene spermatocytes); and partial loss of the succeeding generation of early round spermatids. By day 4, the lesion had progressed to midpachytene spermatocytes, although by day 14, resolution of the damage had begun.

Degeneration seen in the mid-dose MAA-exposed rats included fewer stages of spermatogenesis with some loss of affected cells and early round spermatids at day 2. Low-dose MAA-exposed rats demonstrated minimal effects in diplotene secondary spermatocytes and early pachytene spermatocytes [Foster et al. 1987].

Wistar-Porton rats were given single injections of 224 mg MAA/kg on g.d. 8, 10, 12, or 14, and then sacrificed on g.d. 20 to study the teratogenicity of MAA [Brown et al. 1984]. Embryotoxicity was indicated by increased embryo-fetal death, structural malformations, and decreased fetal weight (no statistical treatment given). Embryo-fetal mortality was greatest after MAA administration on g.d. 8 (93%), decreasing to 3% for g.d. 14. The highest incidence of fetal malformations followed exposure on g.d. 12, although malformations were induced on each day of treatment. Defects included skeletal malformations, hydrocephalus, and urogenital abnormalities [Brown et al. 1984].

The teratogenicity of MAA compared with that of EGME was further studied in pregnant Wistar rats (six, seven, or eight per group). The rats received single oral doses of 186 or 373 mg MAA/kg or 158 or 315 mg EGME/kg on g.d. 12 [Ritter et al. 1985]. Pregnancy was terminated on g.d. 20, and total embryotoxicity was calculated as the sum of dead, resorbed, and malformed fetuses as percent of total implantations. MAA demonstrated a dose response at 186 mg MAA/kg (58% total embryotoxicity) and at 373 mg MAA/kg (99%); these responses were not significantly different from that produced by EGME doses of 158 (54%) and 315 mg EGME/kg (100%). The authors noted that between 80% and 96% of the total defects found in any of the treatment groups were classified as hydronephrosis and heart, tail, and limb defects. These defects included dilated ductus arteriosus, dilated aortic arch, and ventral polydactyly; the authors report these are rarely seen with any other teratogenic agent.

The role of metabolism in EGME-induced testicular toxicity was investigated by Moss et al. [1985] using groups of nine male Sprague-Dawley rats pretreated i.p. with 400 mg pyrazole/kg, an alcohol dehydrogenase (ADH) inhibitor, or pretreated with 300 mg disulfiram/kg, an aldehyde dehydrogenase inhibitor. One hr after pretreatment with pyrazole or 24 hr after pretreatment with disulfiram, animals were injected i.p. with 250 mg of labeled ^{14}C EGME/kg. Controls with no pretreatment also received 250 mg(^{14}C) EGME/kg i.p. Urinary excretion was the major route of elimination of EGME metabolites after 24 hr (40.4% $\pm$ 3.6% of dose) and 48 hr (14.8% $\pm$ 0.6% of dose) in controls. High performance liquid chromatography (HPLC) analysis identified MAA as the major urinary metabolite at 0 to 24 hr (63% of the radioactivity) and at 24 to 48 hr (50% of the radioactivity). The

second major urinary metabolite was identified as methoxyacetylglycine (approximately 20% of radioactivity). Analysis of radioactivity in the plasma demonstrated rapid disappearance (t1/2 = 0.56 hr) of EGME between 0 and 4 hr after dosing with a corresponding appearance of MAA. Radioactivity clearance from plasma (t1/2) was estimated to be 19.7 hr.

In the rats pretreated with pyrazole, the metabolism of EGME to MAA was inhibited. Analysis of radioactivity in plasma showed a slower disappearance of EGME (t1/2 = 42.6 ± 5.6 hr) and radioactivity clearance from plasma (t1/2 = 51.0 ± 7.8 hr) than in the controls. The percentage of the dose found in urine after 24 hr (9.8% ± 2.4%) and 48 hr (7.9% ± 2.2%) showed urinary excretion not to be the major route of elimination. MAA was not a major urinary component, and methoxyacetylglycine was not found in urine from these rats. Pretreatment with the aldehyde dehydrogenase inhibitor disulfiram had no significant effect on plasma or urinary metabolic profiles. Administration of EGME by i.p. injection demonstrated extensive degeneration and necrosis of rat primary spermatocytes in the early and late pachytene stages of development. Pretreatment with pyrazole appeared to protect against spermatocyte damage, whereas pretreatment with disulfiram had no effect on the degree of spermatocyte damage observed [Moss et al. 1985].

Ritter et al. [1985] investigated the effect of an ADH inhibitor, 4-methylpyrazole (4-MP), on EGME-induced teratogenicity in pregnant Wistar rats. Groups of seven animals were administered 315 mg EGME/kg i.p. on g.d. 12 with or without a concurrent dose of 100 mg 4-MP/kg. Pregnancy was terminated on g.d. 20. Coadministration of EGME and 4-MP resulted in significantly decreased total embryotoxicity: 16.8% compared with 100% with EGME alone ($P<0.05$). Ritter et al. [1985] stated that 4-MP inhibits ADH and might interfere with the metabolism of EGME to MAA and consequently prevent the embryotoxicity or teratogenicity dependent on the production of MAA.

Sleet et al. [1988] conducted a series of experiments on the role of EGME metabolism in the induction of paw malformations in CD-1 mice. Pregnant dams were dosed on g.d. 11 and sacrificed on g.d. 18. A comparison was made of dose-dependent digit anomalies produced by oral exposure to a single dose of EGME (99 to 463 mg/kg) or of MAA (99 to 693 mg/kg). MAA and EGME were equipotent in producing digit anomalies (syndactyly, oligodactyly, and polydactyly) as expressed on the basis of percent of litters affected and percent of fetuses affected. Fetal body weights and incidence of resorbed implants were not significantly different between EGME- and MAA-exposed animals.

The effects of gavage and i.v. injection on the teratogenicity of MAA were also compared by Sleet et al. [1988]. MAA was administered to pregnant mice on g.d. 11 by gavage or tail vein injection at doses of 261 mg/kg or 342 mg/kg. The incidence of digit malformations in both i.v. groups was statistically lower than that of the corresponding gavage group ($P<0.05$). These results are expected since gavage and i.v. routes of administration differ with respect to the metabolic fate of MAA [Sleet et al. 1988].

Sleet et al. [1988] administered EGME (251 or 350 mg/kg) orally to pregnant CD-1 mice on g.d. 11 in combination with ethanol (2,901 mg/kg) to investigate competition for

oxidation by ADH to teratogenic metabolites of EGME. Three experimental conditions were used: (1) ethanol concomitantly with EGME (251 and 350 mg/kg) and again 5 hr and 10 hr later; (2) ethanol 5 hr and 10 hr after 251 mg EGME/kg; and (3) single doses of ethanol concomitantly with 251 mg EGME/kg or 5 hr later. Single and multiple dosings of ethanol attenuated EGME teratogenicity as expressed by digit malformations. Experimental condition No. 1 provided the greatest reductions in incidences of total anomalies ($P \leq 0.05$) when compared with controls exposed to EGME only. At 251 and 350 mg EGME/kg, ethanol administration decreased the incidence from 47% to 6% and 94% to 36%, respectively. The single dose of ethanol at 0 hr (condition No. 3) significantly decreased, from 47% to 23%, the occurrence of digit anomalies caused by 251 mg/kg of EGME ($P \leq 0.05$). Reduction of paw malformations decreased when ethanol was administered following EGME exposure. Condition No. 2 lowered paw malformations from 47% to 35% ($P \leq 0.05$), but condition No. 3 of a single dose of ethanol 5 hr after EGME treatment had no protective effect.

Levels of EGME, MAA, and (^{14}C) in maternal and conceptus compartments were quantitated by isotope dilution analysis for up to 6 hr after oral administration of (^{14}C) EGME (251 mg/kg) and ethanol (2,901 mg/kg) [Sleet et al. 1987]. HPLC measurements demonstrated that ethanol caused only a transient delay in EGME metabolism to MAA and embryonal accumulation of ^{14}C MAA. Using (^{14}C) EGME only, approximately 90% of the radioactivity in the maternal plasma and in the embryo was (^{14}C) MAA at 1 hr and 100% at 6 hr after treatment. Additionally, the (^{14}C) level of the embryo was greater than that of maternal blood at both times. Concomitant dosing with ethanol reduced the proportion of (^{14}C) MAA in maternal plasma and embryo. At 1 hr, MAA represented 17% of radioactivity in both compartments, and at 2 hr, it increased to 40% in plasma and 32% in the embryo. At 3 hr, plasma levels of EGME and MAA were equivalent to the 1-hr levels following EGME administration alone; 80% of the total radioactivity in the embryo was MAA.

In light of the previous results, Sleet et al. [1988] investigated the possibility that further metabolism of MAA was necessary for expression of embryotoxicity by coadministering metabolic intermediates common to alcohol oxidation with EGME (251 mg or 350 mg/kg) on g.d. 11 and sacrificing the dams on g.d. 18. The incidence of paw malformations induced by EGME at either dosage was significantly lowered ($P<0.05$) by coadministration of sodium acetate (43 mmol/kg), formic acid (4.3 mmol/kg), or glycine (43 mmol/kg). The authors concluded that the marked decline in the incidence of digit malformations demonstrated that EGME teratogenicity is dependent on events subsequent to the formation of MAA [Sleet et al. 1988].

Yonemoto et al. [1984] used an in vitro culture system [New 1978] to determine the effects of EGME and MAA on the development of post-implantation rat embryos. On g.d. 9, conceptuses were removed from the dams (Wistar-Porton strain) and placed in pairs in bottles that contained 3 mL of heat-inactivated male rat serum and 1 mL of test compound. Ten to 15 conceptuses per group were cultured for 48 hr in 381 mg EGME or in 90, 180, 270, or 450 mg MAA and then examined under a stereoscopic dissecting microscope. EGME had no significant effects on embryonic growth and development when compared with that of the controls. MAA, however, produced statistically significant reductions in morphological development, crown-rump length, head length, number of somites, and yolk

sac diameter when compared with those of the controls ($P<0.001$). These effects demonstrated a dose response, as all were seen at 450 mg MAA; all but yolk sac diameters were affected at 270 mg, and only head length and morphological development were affected at 180 mg. No significant effects were seen at 90 mg MAA. The predominant abnormalities seen in affected conceptuses were irregular fusion of the neural tube (wavy or open neural suture line) and irregular segmentation of the somites. The authors [Yonemoto et al. 1984] concluded that the data demonstrated that MAA or its metabolites are the proximal toxins in vivo and that, at the organogenesis stage, the rat fetus in vitro lacks alcohol dehydrogenase activity.

The in vitro culture system used by Yonemoto et al. [1984] was used by Rawlings et al. [1985] to study the mechanism of teratogenicity of EGME. Conceptuses were explanted from pregnant Wistar-Porton rats at embryonic age 9.5 days and cultured for 48 hr with 2 or 5 mM MAA. At the end of the culture period, crown-rump length, head length, and yolk sac diameter were measured, and the degree of differentiation and development was evaluated by a morphological scoring system. MAA at the 5 mM concentration had an adverse effect on fetal development. MAA-exposed embryos had statistically significant reductions ($P<0.01$) in morphological score, crown-rump length, head length, and yolk sac diameter compared with those of the controls. MAA also produced statistically significant reductions ($P<0.05$) in the protein content of the embryo. No statistically significant reductions in growth parameters were seen at the 2 mM level. However, irregularity of the neural suture line was seen in 100% of the MAA-exposed embryos. Other abnormalities observed in the MAA-exposed groups included abnormal otic and somite development, turning failure, open cranial folds, and abnormal yolk sac [Rawlings et al. 1985].

As has been demonstrated, the induction of paw malformations following in utero [Brown et al. 1984; Ritter et al. 1985] as well as in vitro [Yonemoto et al. 1984] exposure to EGME appears to depend on the oxidation of EGME to MAA. Sleet et al. [1988] investigated the relationship between the induction of paw malformations and the disposition of EGME in the maternal and embryonal compartments. Pregnant CD-1 mice were dosed by gavage on g.d. 11 with either EGME (1.3 to 6.6 mmol/kg, 100 to 500 mg/kg, or 5.2 µl/g) or MAA (1.1 to 7.7 mmol/kg, 100 to 693 mg/kg, or 4.9 µl/g) and were sacrificed on g.d. 18. Fetuses were delivered by laparotomy and weighed before external examination for paw defects. The embryotoxic potencies of EGME and MAA were determined by comparing the dose-dependent incidence of digit anomalies. EGME and MAA were equipotent in causing digit malformations. The ADH inhibitor 4-methylpyrazole administered orally 1 hr before EGME reduced the incidence of malformations 60% to 100%, depending on the dosing regimen. Oxidation of EGME to MAA was nearly complete after 1 hr when approximately 90% of (^{14}C) in maternal compartment and conceptus coeluted with authentic (^{14}C)-MAA on HPLC. Embryonic (^{14}C)-MAA levels were 1.2 times those in plasma 1 hr and 6 hr after dosing; by 6 hr, however, concentrations in the embryo had declined to approximately 50% of 1-hr values. Dams treated i.v. with (^{14}C) MAA had higher (^{14}C) blood levels than did dams treated orally, but the offspring of the former had fewer digit malformations. The authors concluded that peak and steady-state plasma levels of MAA, as well as embryonic MAA levels, do not appear to determine the embryotoxic outcome whereas further metabolism of MAA does [Sleet et al. 1988].

EGME uptake and urinary MAA excretion were examined in seven male subjects exposed at rest to 5.1 ppm EGME (16 mg/m^3) by mask for four 50-min periods [Groeseneken et al. 1989a]. There was a short 10-min break at the end of each 50-min period to allow for urine collection. Urine samples were collected immediately before the beginning of the experiment and at hourly intervals until the fourth hour after exposure. Collections were taken until the morning of the fifth day after the exposure period (four 2-hr collections, one 8-hr collection, and eight 12-hr collections). Urinary MAA was then measured by the method of Groeseneken et al. [1989b]. Retention of EGME was 76% during the 4-hr exposure period. The uptake rate showed no significant variation because of constant pulmonary ventilation and a fixed exposure concentration. On average, 19.4 $\pm$ 2.1 mg EGME was inhaled during the 4-hr exposure period. MAA was detected in the urine during and up to 120 hr after exposure. The elimination half-life averaged 77.1 $\pm$ 9.5 hr. On average, 54.9% $\pm$ 4.5% of inhaled EGME was excreted within 120 hr of the start of exposure; half of this amount was excreted within 48 hr. By extrapolation, the total amount of MAA was estimated at 85.5% $\pm$ 4.9% of inhaled EGME.

APPENDIX C

OCCUPATIONAL EXPOSURES TO THE GLYCOL ETHERS BY WORKSITE OR PROCESS

Table C-1.—Occupational exposures by worksite or process

Glycol ether	Worksite or process	Reference*	Number and type of samples	Concentration	
				Range (ppm)	Average (ppm)
EGEE	Leather dyeing	Gill 1977	1 BZ†	ND‡	ND
	Spray painting	Lee 1982	2 BZ	both 25	25
	Painting (brush and spray)	Love and Donohue 1983	8 BZ	ND–128	22
		Sparer et al. 1988	90 BZ	0–21.5	2.6
	Manufacture of solid state circuits	Gunter 1985	6 BZ	ND–96	17
	Hospital housekeeping	Apol and Cone 1983	3 BZ	<0.2	<0.2

(Continued)

See footnotes at end of table.

Table C-1 (Continued).—Occupational exposures by worksite or process

Glycol ether	Worksite or process	Reference	Number and type of samples	Concentration	
				Range (ppm)	Average (ppm)
EGEE (Cont'd)	Construction of plastic and wood boats	Crandall and Hartle 1983	7 BZ	0.2–1.1	1.1
	Printing	Burroughs 1979	16 BZ	<2.4–<49	<14
			5 area[§]	<3.0–<17	<5.9
	Ceramic shell production	Ratcliffe et al. 1986	10 BZ	ND–24	Not presented
			8 area	10–17	Not presented
EGEEA	Painting, molding, inspection	Gunter and Lucas 1974	21 BZ	<0.4–20	2.4
	Spray painting	Hervin and Thoburn 1975	22 BZ	13–4,657	543
			20 area	11–1,262	191
		Gunter et al. 1980	6 BZ	ND	ND
			1 area	ND	ND
		Hartle 1980	3 BZ	5.7–14	8.8
			6 area	0.3–3.4	2.2
		Apol 1976	8 BZ	ND–5	1.3
			2 area	ND	ND
		Chrostek and Levine 1981	8 BZ	0.5–8.1	3.3

Paint compounding and mixing	Gilles 1977
Degreasing	Johnson and Boxer 1983
Manufacture of solid state circuits	Gunter 1985
Mixing and application of epoxy-type paint	Cohen and Maier 1973
Graphic arts department	McLouth and Gorman 1980
Silk-screening	Boiano 1983
Construction of plastic and wood boats	Crandall and Hartle 1983
Coatings processes	Bryant 1978
Spray painting and curing operations	McQuilken 1980

24 BZ	ND–1.0	0.11
4 area	ND	ND
2 BZ	Trace	Trace
2 area	Trace	Trace
14 BZ	ND–1.3	0.2
15 BZ	0.83–98	27
5 area	ND	ND
7 BZ	1.2–3.8	2.3
6 BZ	0.5–4.0	2.6
7 BZ	0.4–2.7	1.1
4 area	ND–0.6	0.2
6 BZ	ND–1.6	0.5
6 area	ND	ND
2 BZ	4.6–8.9	6.8
1 area	24	24

(Continued)

Table C-1 (Continued).—Occupational exposures by worksite or process

Glycol ether	Worksite or process	Reference	Number and type of samples	Concentration	
				Range (ppm)	Average (ppm)
EGME	Degreasing and paint stripping	Hervin et al. 1974	24 BZ	ND	ND
	Painting, molding, inspection	Gunter and Lucas 1974	35 BZ	<0.8–5	1.4
	Painting (brush and spray)	Love and Donohue 1983	1 BZ	15	15
		Sparer et al. 1988	81 BZ	0–5.6	0.8
	Coating of paper and fabric with resin	Ramos and Lucas 1973	9 BZ 8 area	ND–11 0.7–9.0	4.1 5.0
	Press room and reel room	Markel and Moody 1982	5 BZ 3 area	ND–0.5 ND–0.4	0.4 0.2
EGMEA	Photo etching	Levy 1976	1 BZ	37	37

*See References beginning on page 262.
†Breathing zone sample.
‡Not detectable.
§Immediate work area sample(s).

Table C-2.—Long-term sampling results for 2-methoxyethanol (2-ME), 2-ethoxyethanol (2-EE), and 2-ethoxyethyl acetate (2-EEA)*

Industry	Glycol ether(s) sampled	No. of samples	Samples below limit of detection		Concentration range (ppm)†
			No.	Percent	
Aerospace	2-ME	8	8	100	all ≤0.27‡
	2-EE	5	5	100	all ≤0.22‡
	2-EEA	15	15	100	all ≤0.23‡
Electronics	2-EEA	8	8	100	all ≤0.02§
Airlines	2-EEA	13	0	0	0.29-2.69
Coating mfg.	2-EEA	6	0	0	0.07**-0.35
Automotive	2-EEA	12	10	80	≤0.02§-0.05**
Fuel distribution	2-ME	10	3	34	≤0.03§-0.34
Paperboard mfg.	2-ME	9	6	66	≤0.04§-1.06
Glycol ether mfg.	2-EEA	31	25	81	≤0.02§-0.44
Summary	2-ME	27	17	63	≤0.02§-1.06
	2-EE	5	5	100	all ≤0.22‡
	2-EEA	85	58	68	≤0.02§-2.69
Total		117	80	60	≤0.02§-2.69

*Adapted from Piacitelli et al. [1989].
†Samples were not time-weighted to 8-hr concentrations.
‡Laboratory analysis was below limit of detection (0.03 mg/sample).
§Laboratory analysis was below limit of detection (0.01 mg/sample).
**Laboratory analysis was below limit of quantitation (0.03 mg/sample).

Table C-3.—Distribution of ethylene glycol ethers among the various industrial operations as detected in air samples*

Operation	Number of air samples	Number of glycol ethers detected			
		EGME	EGMEA	EGEE	EGEEA
Printing	94	0	2	76	61
Painting	81	4	0	19	66
Car repair	20	10	1	0	9
Various	67	0	12	11	38
Total	262	14	15	106	174

*Table taken from Veulemans et al. [1987b].

Table C-4.—Concentration (ppm) of ethylene glycol ethers used in various industrial operations*

Operation		EGME	EGMEA	EGEE	EGEEA
Printing	G.M.†	---	0.9	2.6	3.04
	Range	---	0.8-0.9	0.18-47.9	0.06-34.6
Painting	G.M.	9.8	---	2.5	1.8
	Range	1.75-42.8	---	0.37-55.3	0.22-14.6
Car repair	G.M.	2.47	0.48	---	1.7
	Range	1.8-5.0	---	---	0.28-7.8
Various	G.M.	---	2.4	4.5	1.8
	Range	---	0.08-29.9	0.82-332	0.11-151.8

*Table adapted from Veulemans et al. [1987].
†Data are geometric means.

APPENDIX D

MATERIAL SAFETY DATA SHEET

The following sections describe the information that must be supplied for each product or material in the appropriate blocks of the Material Safety Data Sheet (MSDS).

To facilitate filing and retrieval, insert the product designation in the block in the upper left corner of the first page. Print in upper case letters as large as possible. The MSDS should be printed to read upright with the sheet turned sideways. For the product designation, use the name or code that appears on the label or the name by which the product is sold or known by workers. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication entitled *A Recommended Standard: An Identification System for Occupationally Hazardous Materials* [NIOSH 1974b]. The company identification may be printed in the upper right corner if desired.

D.1 SECTION I. PRODUCTION IDENTIFICATION

Insert the manufacturer's name, address, and regular and emergency telephone numbers (including area code) in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or competitor's trade name need not be listed.

D.2 SECTION II. HAZARDOUS INGREDIENTS

The "materials" listed in Section II shall be those substances that are part of the hazardous product covered by the MSDS and that individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, and a third component for both its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

List chemical substances according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such

as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) that each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount (i.e., 10% to 40% vol. or 10% max. wt.) to avoid disclosure of trade secrets.

State toxic hazard data in terms of concentration, mode of exposure or test, and animal used (e.g., 100 ppm LC_{50}-rat, 25 mg/kg LD_{50}-skin-rabbit, 75 ppm LC man, permissible exposure from 29 CFR 1910.1000) or, if not available, from other sources such as NIOSH RELs and publications of the American Conference of Governmental Industrial Hygienists (ACGIH) or the American National Standards Institute, Inc. (ANSI). Flashpoint, shock sensitivity, or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

D.3 SECTION III. PHYSICAL DATA

The data in Section III should be for the total mixture. Include the boiling point and melting point in degrees Fahrenheit (Celsius in parenthesis); vapor pressure, in conventional millimeters of mercury (mm Hg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70°F (21.1°C); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for designing and deploying adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers or spilled substances.

D.4 SECTION IV. FIRE AND EXPLOSION DATA

Section IV should contain complete fire and explosion data for the product. Include flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses), flammable limits in percent by volume in air, suitable extinguishing media or materials, special fire-fighting procedures, and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

D.5 SECTION V. HEALTH HAZARD INFORMATION

For the "Health Hazard Data" line, use a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LD_{50} if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Indicate the severity of the effect and the basis for the statement, if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

> Skin Contact—single short contact, no adverse effects likely; prolonged or repeated contact, possibly mild irritation.
>
> Eye Contact—some pain and mild transient irritation; no corneal scarring.

Write "Emergency and First Aid Procedures" in lay language. The procedure should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Include in the "Notes to Physician" section any special medical information of assistance to an attending physician, e.g, required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed workers.

D.6 SECTION VI. REACTIVITY DATA

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. Be sure to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. Include in "Hazardous Decomposition Products" those products released under fire conditions. Also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, indicate shelf life.

D.7 SECTION VII. SPILL OR LEAK PROCEDURES

List detailed procedures for cleanup and disposal; place emphasis on precautions to be taken to protect workers assigned to cleanup detail. Describe specific neutralizing chemicals or procedures in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill" or "incineration." Warnings such as "comply with local, State and Federal antipollution ordinances" are proper but not sufficient. Identify specific procedures.

D.8 SECTION VIII. SPECIAL PROTECTIONS INFORMATION

Section VIII requires specific information concerning ventilation requirements and personal protective equipment. Statements such as "yes," "no," or "if necessary" are not informative. Specify the type and preferred methods of ventilation. Specify the type and NIOSH or Mine Safety and Health Administration approval class (e.g., supplied air or organic vapor canister for respirators). Specify the type and materials of construction for protective equipment.

D.9 SECTION IX. SPECIAL PRECAUTIONS

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Insert in this section additional information on any aspect of safety or health not covered in other sections. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

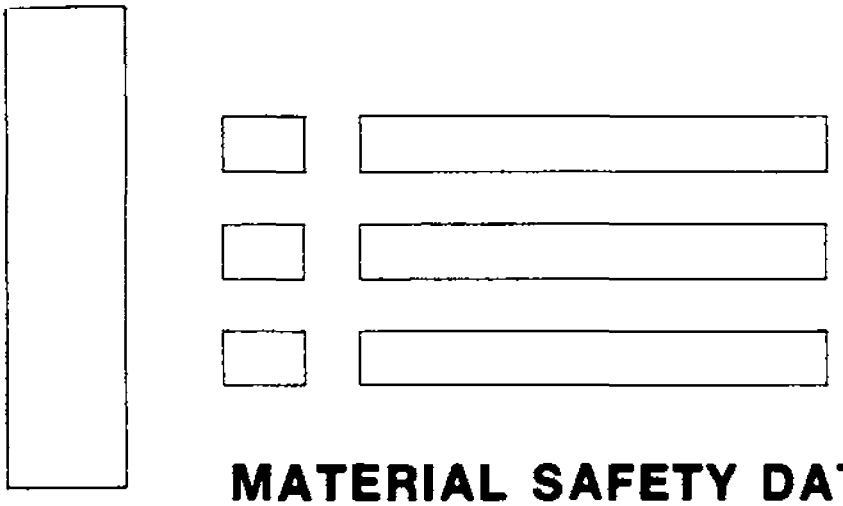
D.10 SIGNATURE AND FILING

Finally, enter the name and address of the responsible person who completed the MSDS and the date of completion. This will facilitate correcting errors and identifying a source of additional information.

File the MSDS in a location readily accessible to workers exposed to the hazardous substance. The MSDS can be used as a training aid and as the basis for discussion during safety meetings and training of new workers. Its purpose is to assist management by directing attention to the need for specific control engineering, work practices, and protective measures that will ensure safe handling and use of the material. The MSDS will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of workers.

MATERIAL SAFETY DATA SHEET

Sections I – III



MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION	
MANUFACTURER'S NAME	REGULAR TELEPHONE NO EMERGENCY TELEPHONE NO
ADDRESS	
TRADE NAME	
SYNONYMS	

II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA			
BOILING POINT, 760 MM HG		MELTING POINT	
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE	
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O, % BY WT	
% VOLATILES BY VOL		EVAPORATION RATE (BUTYL ACETATE = 1)	
APPEARANCE AND ODOR			

MATERIAL SAFETY DATA SHEET (Continued)

Sections IV – V

IV FIRE AND EXPLOSION DATA					
FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE			
FLAMMABLE LIMITS IN AIR, % BY VOL.	LOWER		UPPER		
EXTINGUISHING MEDIA					
SPECIAL FIRE FIGHTING PROCEDURES					
UNUSUAL FIRE AND EXPLOSION HAZARD					

V HEALTH HAZARD INFORMATION
HEALTH HAZARD DATA
ROUTES OF EXPOSURE
INHALATION
SKIN CONTACT
SKIN ABSORPTION
EYE CONTACT
INGESTION
EFFECTS OF OVEREXPOSURE ACUTE OVEREXPOSURE
CHRONIC OVEREXPOSURE
EMERGENCY AND FIRST AID PROCEDURES
EYES
SKIN
INHALATION:
INGESTION
NOTES TO PHYSICIAN

MATERIAL SAFETY DATA SHEET (Continued)

Sections VI – VIII

VI REACTIVITY DATA
CONDITIONS CONTRIBUTING TO INSTABILITY
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APPENDIX E

OTHER GLYCOL ETHERS

Table E–1.—Methyl-based glycol ethers, amides, etc.*

CAS† number	Name
3610-27-3	Methoxytriethylene glycol acetate
3121-61-7	2-Methoxy-ethanol acrylate
24493-59-2	Methoxytriethylene glycol methacrylate
45103-58-0	2-(2 Methoxyethoxy) ethyl methacrylate
6976-93-8	2-Methoxyethyl methacrylate
68133-26-6	N-(5-Amino-2-methoxyphenyl)-beta-alanine, 2-methoxyethyl ester
68133-25-5	N-(2-Methoxy-5-nitrophenyl)-beta-alanine, 2-methoxyethyl ester
16501-01-2	1,2-Benzenedicarboxylic acid, mono (2-methoxyethyl) ester
117-82-8	1,2-Benzenedicarboxylic acid, bis (2-methoxyethyl) ester
106-00-3	Hexanedioic acid, bis (2-methoxyethyl) ester
140-05-6	Ethylene glycol monomethyl ether acetylricinoleate
111-10-4	Ethylene glycol monomethyl ether oleate
111-07-9	Hexadecanoic acid, 2-methoxyethyl ester
70703-47-8	Acetylated ethylene glycol monomethylether hydroxystearate
6522-67-4	N-[5-(Acetylamino)-4-[(2-bromo-4,6-dinitrophenyl)azo]-2 methoxyphenyl]-beta-alanine, 2-methoxyethyl ester
51248-73-8	N-[4-[2-Chloro-4-nitrophenyl)azo]-3-(acetylamino)phenyl]-N-(2-cyanoethyl)-beta-alanine, 2-methoxyethyl ester
49744-35-6	Aminobenzoic acid, 2-(2-methoxyethoxy) ethyl ester

(Continued)

*Adapted from TSCA [1977] and SANSS/CIS [1988].
†Chemical Abstracts Service.

Table E–1 (Continued).—Methyl-based glycol ethers, amides, etc.

CAS number	Name
49744-26-5	4-[5-Cyano-1-ethyl-1,6-dihydro-2-hydroxy-4-methyl-6-oxy-3-pyridinyl)azo] benzoic acid, (2-methoxyethoxy) ethyl ester
42861-47-2	N-Ethyl-N(4-(2-bromo-4,6-dinitrophenyl)azo)-5-(acetylamino)-2-methoxyphenyl)-beta-alanine, 2-methoxyethyl ester
42228-65-9	N-[5-(Acetylamino)-2-methoxyphenyl]-N-ethyl-beta-alanine, 2-methoxyethyl ester
18016-42-7	Cholesteryl 2-(2-methoxyethoxy) ethyl carbonate
40228-74-8	Cholesteryl methoxy ethyl carbonate
68479-79-8	N,N'-(4,8-Dihydroxy-9,10-dioxo-1, 5-anthracenediyl) bis [beta-alanine], bis(2-methoxyethyl) ester
1616-88-2	Carbamic acid, 2-methoxyethyl ester
10143-22-3	Carbamic acid, bis(hydroxymethyl)-, 2-methoxyethyl ester
50883-78-8	Carbamic acid, dimethyl-, 2-methoxyethyl ester
16672-66-5	2-Methoxyethyl methylocarbamate
14983-42-7	Boric acid, tris (2-methoxyethyl) ester
6163-73-1	Phosphoric acid, methoxyethyl ester
42372-33-8	1-Naphthalenesulfonic acid, 6-diazo-5, 6-dihydro-5-oxo-, 2-methoxyethyl ester
17178-10-8	2-Methoxyethyl p-toluenesulfonate
71550-36-2	1-Naphthalenesulfonic acid, 6-diazo-5, 6-dihydro-5-oxo-, 2-(2-methoxyethoxy) ethyl ester

Table E-2.—Butyl-based glycol ether esters, amides, etc.*

CAS† number	Name
124-17-4	Butoxyethoxyethyl acetate
112-07-2	Butoxyethyl acetate
7251-90-3	Acrylic acid, 2-butoxyethoxy ester
5330-17-6	2-Butoxyethyl chloroacetate
27447-53-6	2-Butoxyethyl mercaptoacetate
68797-46-6	Propanic acid, 2-chloro-, 2-butoxyethyl ester
20442-06-2	2-Butoxyethyl butanoate
20442-11-9	2-Butoxyethyl pelargonate
109-37-5	Ethylene glycol monobutyl ether laurate
109-38-6	Butoxyglycol stearate
109-39-7	Ethylene glycol monobutyl ether oleate
65520-45-8	Butanedioic acid, di-2-[2-(2-butoxyethoxy) ethoxy] ethyl ester
65520-42-5	Pentanedioic acid, di-2-[2-(-2-butoxyethoxy) ethoxy] ethyl ester
65520-46-9	Hexanedioic acid, di-2-[2-(2-butoxyethoxy) ethoxy] ethyl ester
141-18-4	Adipic acid, bis (ethylene glycol monobutyl ether) ester
141-17-3	Adipic acid, bis (diethylene glycol monobutyl ether) ester
63021-23-8	Nonanedioic acid, bis (2-butyoxyethyl) ester
70900-47-9	Nonanedioic acid, bis [2-(2-butoxyethoxy) ethyl] ester
70900-46-8	Decanedioic acid, bis [2-(2-butoxyethoxy) ethyl] ester
141-19-5	Decanedioic acid, bis (2-butoxyethyl) ester
117-83-9	1,2-Benzenedicarboxylic acid, bis (2-butoxyethyl) ester
16672-39-2	Phthalic acid, bis [2-(2-butoxyethoxy) ethyl] ester
70900-48-0	1,2,4-Benzenetricarboxylic acid, tris [2-(2-butoxyethoxy) ethyl] ester
62778-23-8	Cholest-5-en-3-ol (3-beta)-, 2-butoxyethyl carbonate
5451-76-3	Benzoic acid, 2-butoxyethyl ester

(Continued)

*Adapted from TSCA [1977] and SANSS/CIS [1988].
†Chemical Abstracts Service.

Table E–2 (Continued).—Butyl-based glycol ether esters, amides, etc.

CAS number	Name
6661-54-7	Ethanol, 2-butoxy-, 4-methylbenzesulfonate
53404-31-2	2-(2,4-Dichlorophenoxy) propionic acid, butoxyethanol ester
19480-43-4	Acetic acid, (4-chloro-2-methylphenoxy)-, 2-butoxyethyl ester
30387-70-3	2,4,5-Trichlorophenoxypropionic acid n-butylglycol ester
32357-46-3	2,4-Dichlorophenoxybutyric acid, butoxyethyl ester
72152-95-5	Carbamic acid, [5-isocyanato-1,3,3-trimethylcyclohexyl) methyl]-, 2-butoxyethyl ester
78-51-3	Butoxyethyl phosphate
7332-46-9	2-(2-Butoxyethoxy) ethanol phosphate
64051-22-5	2-Butoxyethanol, hydrogen phosphate, diethylamine salt
14260-97-0	Dibutoxyethyl phosphate
64051-23-6	2-Butoxyethanol, dihydrogen phosphate, bis(diethylamine) salt
68133-43-7	Ethanol, 2-butoxy-, dihydrogen phosphate, dipotassium salt
14260-98-1	Butoxyethylphosphate

Table E–3.—Branched glycol ether esters, carbamates, etc.*

CAS† number	Name
68413-83-2	N,N-Dimethylol isopropoxyethyl carbamate
67952-46-9	Isopropoxyethyl carbamate
67952-44-7	Carbamic acid, (hydroxymethyl)-, 2-(1-methylethoxy) ethyl ester
16006-09-0	Carbamic acid, (2-isobutoxyethyl) ester
16005-83-7	Carbamic acid, bis (hydroxymethyl)-, 2-isobutoxyethyl ester
1464-69-3	2-Methyl-2-propenoic acid, 2-(ethenyloxy ethyl ether))
16839-48-8	Methacrylic acid, 2-(allyloxy) ethyl ester

*Adapted from TSCA [1977] and SANSS/CIS [1988].
†Chemical Abstracts Service.

Table E–4.—Longer chain (butyl) glycol ether esters, phosphates, etc.*

CAS† number	Name
20207-36-7	Lauric acid, 2-(hexyloxy) ethyl ester
3538-36-1	Ethanol, 2-(hexyloxy)-, hydrogen phosphate
64051-25-8	Ethanol, 2-(hexyloxy)-, dihydrogen phosphate, cmpd. with N-ethylethanamine (1:2)
64051-24-7	Ethanol, 2-(hexyloxy)-, hydrogen phosphate, cmpd. with N-ethylethanamine (1:1)
63294-54-2	Ethanol, 2-(hexyloxy)-, dihydrogen phosphate
68757-58-4	Propanoic acid, 2,2-dimethyl-, 2-(hexyloxy) ethyl ester
3694-74-4	Ethanol, 2-(tetradecyloxy)-, hydrogen sulfate, sodium salt
56049-85-5	Triethylene glycol monohexadecyl ether sulfate ammonium salt
55901-67-2	2-Decyloxyethyl sodium sulfate
61894-66-4	2-Decyloxyethyl hydrogen sulfate
14858-61-8	2-(Octadecyloxy) ethyl sodium sulfate
14858-54-9	2-(Hexadecyloxy) ethyl sodium sulfate
13150-00-0	Ethanol, 2-[2-[2-(dodecyloxy) ethoxy] ethoxy]-, hydrogen sulfate sodium salt
15826-16-1	Ethylene glycol monododecyl ether sulfate sodium salt
25446-80-4	Triethylene glycol monomyristyl ether sodium sulfate
25446-78-0	Sodium tridecyl tri(oxyethyl) sulfate
3088-31-1	Diethylene glycol monododecyl ether sodium sulfate
67923-90-4	Ethanol, 2-[2-[2-(decyloxy)ethoxy]ethoxy]-, hydrogen sulfate, ammonium salt
66104-67-4	2-Butenedioic acid (2)-, mono[2-[2-(dodecyloxy) ethoxy] ethoxy] ethyl]ester
65138-77-4	Ethanol, 2-[20(tridecyloxy) ethoxy]-, dihydrogen phosphate
65087-01-6	Ethanol, 2-[2-(tridecyloxy) ethoxy]-, hydrogen phosphate
57119-83-2	2-[2-[[4-[(2-Bromo-4,6-dinitrophenyl)azo]-1-naphthyl]amino] ethoxy] ethanol, acetate (ester)
57119-69-4	Ethanol, 2-[2-[[4-[(2-chloro-4,6-dinitrophenyl)azo]-1-naphthalenyl] amino]ethoxy]-, acetate (ester)

(Continued)

*Adapted from TSCA [1977] and SANSS/CIS [1988].
†Chemical Abstracts Service.

Table E–4 (Continued).—Longer chain (butyl) glycol ether esters, phosphates, etc.

CAS number	Name
21116-11-0	Ethanol,2-[p-[[4-[(p-hydroxyphenyl)azo]-o-tolyl]azo] phenoxy]-,1-(hydrogen sulfate), monosodium salt
65993-31-5	Dicyclopentyloxyethyl acrylate
66710-97-2	2-Propenoic acid, (1-methylethylidene) bis [(2,6-dibromo-4,1-phenylene) oxy-2, 1-ethanediyl] ester
68400-37-3	7-Amino-4-hydroxy-3-[[4-[2-(sulfooxy)ethoxy]phenyl]azo]-2-napthalenesulfonic acid
68586-19-6	2-Propenoic acid, 2-methyl-, 2-[[2,3,3a,4,7,7a (or 3a,4,5,6,7,7a)-hexahydro-4,7-methano-1H-indenyl]oxy] ethyl ester
70865-23-5	3-[[4-[2-(Sulfoxy)ethoxy]phenyl]azo][1,1'-biphenyl]-4-ol, monosodium salt
71701-31-0	2-Naphthalenesulfonic acid, 4-hydroxy-3-[[4-[2-(sulfooxy)ethoxy]phenyl]azo] -7-[(2,5,6-trichloro-4-pyrimidinyl)amino]-, disodium salt

Table E–5.—Phenoxy ethanol-based glycol esters, maleates, etc.*

CAS† number	Name
68141-05-0	Benzenoctadecanoic acid, 2-phenoxyethyl ester
103-60-6	Ethanol, 2-phenoxy-, isobutyrate
10534-77-7	Di(phenoxyethyl)maleate
46841-90-1	Mono(phenoxyethyl)maleate
48145-04-6	Ethanol, 2-phenoxy-, acrylate
58214-96-3	Butanoic acid, 3-methyl-, 2-phenoxyethyl ester
10595-06-9	2-Propenoic acid, 2-methyl-, 2-phenoxyethyl ester
23495-12-7	Propionic acid, 2-phenoxyethyl ester
23495-13-8	Pentanoic acid, 2-phenoxyethyl ester
23511-70-8	Butanoic acid, 2-phenoxyethyl ester
67845-81-2	Ethanol, 2-(2-phenoxyethoxy)-, benzoate
65379-23-9	Ethanol, 2-phenoxy-, dihydrogen phosphate, dipotassium salt

*Adapted from TSCA [1977] and SANSS/CIS [1988].
†Chemical Abstracts Service.

Table E–6.—Substituted phenoxy ethanol glycol esters, acetates, etc.*

CAS† number	Name
6807-11-0	Ethanol, 2-(4-methylphenoxy)-, acetate
63217-11-8	Ethanol, 2-[2-(4-dodecylphenoxy) ethoxy]-dihydrogen phosphate
52368-50-0	Decanoic acid, 2-[2-(nonylphenoxy) ethoxy] ethyl ester
7347-19-5	2-(2,4,6-Tribromophenoxy) ethyl acrylate
40184-38-1	2-(4′-Aminophenoxy) ethyl hydrogen sulfate
68140-43-2	m-(2-Acetoxyethoxy) phenol
56744-60-6	2-Propenoic acid, 2-methyl-, (1-methylethylidene) bis (4,1-phenyleneoxy-2, 1-ethanediyloxy-2,1-ethanediyl) ester
56361-55-8	2-Propenoic acid, (1-methylethylidene) bis (4,1-phenyleneoxy-2, 1-ethanediyloxy-2, 1-ethanediyl) ester
24447-78-7	2-Propenoic acid, (1-methylethylidene) bis (4,1-phenyleneoxy-2,1-ethanediyl) ester
65133-66-6	2-Propenoic acid, 2-methyl-, 2-[4-[1-methyl-1-[4-[2-[2-[(2-methyl-1-oxo-2-propenyl)oxy] ethoxy]ethoxy] phenyl]ethyl[phenoxy] ethyl ester

*Adapted from TSCA [1977] and SANSS/CIS [1988].
†Chemical Abstracts Service.

Table E-7.—Glycol ether acetals*

CAS† number	Name
5405-88-9	Diethylene glycol monomethyl ether formal
71563-31-0	Propionaldehyde, bis (2-methoxyethyl acetal)
71808-63-4	Butyraldehyde, bis (2-methoxyethyl acetal)
71808-62-3	Isovaleraldehyde, bis (2-methoxyethyl acetal)
71808-60-1	3,3-di (beta-Methoxyethoxy)-2-butanone
71808-59-8	Isobutyraldehyde, bis(2-methoxyethyl acetal)

*Adapted from TSCA [1977] and SANSS/CIS [1988].
†Chemical Abstracts Service.

Table E-8.—Alkyl glycol ethers (methyl)*

CAS† number	Name
52788-79-1	Diethylene glycol methyl tert-butyl ether
112-49-2	1,2 bis(2-Methoxyethoxy)-ethane (Glyme-3)
111-96-6	bis(2-Methoxyethyl) ether
110-71-4	Dimethoxyethane
7382-32-3	2-Butoxyethyl 2-methoxymethyl ether
19685-21-3	Methyl triethylene glycol allyl ether
66728-50-5	1-tert-Butoxy-2-methoxyethane
54303-31-0	3-(2-Methoxyethoxy)-propanenitrile
52808-36-3	2-(2-Methoxyethoxy) ethyl chloride
3970-21-6	2-Methoxyethoxymethyl chloride

*Adapted from TSCA [1977] and SANSS/CIS [1988].
†Chemical Abstracts Service.

Table E-9.—Phenoxy-based glycol ethers*

CAS† number	Name
68385-79-5	N-[3-Amino-4-(2-methoxyethoxy) phenyl] acetamide
67674-33-3	1-[(2-Methoxy)ethoxy]-2,4-dinitrobenze
63810-51-5	2-(2-Methoxyethoxy)-4-nitrobenzenamine
63810-54-8	2-(2-Methoxyethoxy)-5-nitrobenzenamine
68703-73-1	N-[3-(Diethylamino)-4-(2-methoxyethoxy)phenyl] propanamide
68703-72-0	N-[3-(Diethylamino)-4-(2-methoxyethoxy)phenyl] propionamide
68703-71-9	N-[3-(Diethylamino)-4-(2-methoxyethoxy)phenyl] acetamide
71230-65-4	N-[3-Amino-4-(2-methoxyethoxy)phenyl] propionamide
71077-38-8	N-[3-(Ethylamino)-4-(2-methoxyethoxy)phenyl] acetamide
71077-37-7	4-[2-Methoxyethoxy]-1,3-benzenediamine
72175-36-1	2-[2-(2-Methoxyethoxy) ethoxy]-9,10-anthracenedione
17869-10-2	1-Amino-4-hydroxy-2-(2-methoxyethoxy)-9,10-anthracenedione
67846-62-2	N-[2-[(2-Chloro-4,6-dinitrophenyl)azo]-5-(ethylamino)-4-(2-methoxyethoxy) phenyl] propanamide
65059-45-2	1,4-Diamino-9,10-dihydro-N-[3-(2-methoxyethoxy)propyl]-9,10-dioxo-2,3 anthracenedicarboximide
68597-67-5	N-[2-[(2-Chloro-4,6-dinitrophenyl)azo]-5-(ethylamino)-4-(2-methoxyethoxy) phenyl] acetamide
71889-11-7	N-[2-[(2 Bromo-4,6-dinitrophenyl)azo]-5-(diethylamino)-4-(2-methoxyethoxy) phenyl] propionamide
71889-12-8	N-[2-Bromo-4,6-dinitrophenyl)azo]-5-(diethylamino)-4-(2-methoxyethoxy) phenyl] acetamide
72066-86-5	N-[2-[(2-Bromo-4,6-dinitrophenyl)azo]-5-(ethylamino)-4-(2-methoxyethoxy) phenyl] acetamide
72066-87-6	N-[2-[(2-Bromo-4,6-dinitrophenyl)azo]-5-(ethylamino)-4-(2-methoxyethoxy) phenyl] propionamide
75198-92-4	1-Amino-4-[[2-[[[2-chloro-4-(2-methoxyethoxy)1,3,5-triazin-6-yl] amino]methyl]-4-methyl-6-sulfophenyl]amino]-2-anthraquinonesulfonic acid, disodium salt
73398-97-7	4-[[4-[[5-Cyano-2-[(8-methoxyoctyl)amino]-6-[(3-methoxy-propyl)amino]-4-methyl-3-pyridinyl]azo]-2,5-di-methylphenyl]azo]-N-[3-(2-phenoxyethoxy) propyl] benzamide

*Adapted from TSCA [1977] and SANSS/CIS [1988].
†Chemical Abstracts Service.

Table E–10.—Ethoxy-ethanol based glycol ethers*

CAS† number	Name
41771-35-1	1-Chloro-2-(2-ethoxyethoxy) ethane
629-14-1	Ethylene glycol diethyl ether
112-36-7	bis (2-Ethoxyethyl) ether
10143-53-0	Diethylene glycol ethylvinyl ether
51422-54-9	Ethylene glycol tert-butyl ethyl ether
52788-80-4	Diethylene glycol ethyl-tert-butyl ether

*Adapted from TSCA [1977] and SANSS/CIS [1988].
†Chemical Abstracts Service.

Table E–11.—Siloxy glycol ethers

CAS* number	Name
2157-45-1	Silicic acid (H_4SiO_4), tetrakis (2-methoxyethyl) ester
1067-53-4	Tris (2-methoxyethoxy) vinyl silane
45117-69-9	Methylvinylbis (2-methoxyethyl) silane
57069-48-4	[(3-Methacryloxy)propyl] tris (2-methoxyethoxy) silane
17903-05-8	Tris(2-methoxyethoxy) phenyl silane
17980-64-2	Tris(2-methoxyethoxy) methyl silane
73545-23-0	N-[2-[[2-[[2-[(2-Aminoethyl) amino] ethyl] amino] ethyl] amino] ethyl]-N^{1111}-[3-[tris(2-methoxyethoxy) silyl] propyl]nonanamide hydrochloride
24685-89-0	Ethanol, 2-(2-methoxyethoxy)-, tetraester with silicic acid (H_4SiO_4)
18407-94-8	Ethanol, 2-ethoxy-, tetraester with silicic acid (H_4SiO_4)
18765-38-3	Ethanol, 2-butoxy-, tetraester with silicic acid (H_4SiO_4)
68400-59-9	4,7,10-Trioxaundecyldimethylsilyl chloride

*Chemical Abstracts Service.

Table E-12.—Ethoxy-ethanol based glycol ether esters, amides, etc.

CAS* number	Name
112-15-2	Ethanol, 2-(2-ethoxyethoxy)-, acetate
54396-97-3	Propanoic acid, 2-methyl-, 2-ethoxyethyl ester
106-74-1	2-Propenoic acid, 2-ethoxyethyl ester
7328-17-8	2-Propenoic acid, 2-(2-ethoxyethoxy) ethyl ester
2370-63-0	2-Propenoic acid, 2-methyl-, 2-ethoxyethyl ester
39670-09-2	Triethylene glycol monoethyl ether acrylate
104-28-9	2-Propenoic acid, 3-(4-methoxyphenyl)-, 2-ethoxyethyl ester
106-13-8	2-Ethoxyethyl dodecanoate
67906-29-0	Octadecanoic acid, 10-hydroxy-9-sulfo-, 1-(2-ethoxyethyl) ester, monosodium salt
68134-05-4	9-Octadecenoic acid, 2-ethoxyethyl ester
37460-43-8	Ethanol, 2-ethoxy-, 4-nitrobenzoate
605-54-9	Diethylglycol phthalate
624-10-2	Sebacic acid, bis (2-ethoxyethyl) ester
109-44-4	Hexanedioic acid, bis (2-ethoxyethyl) ester
15484-00-1	2-(2-Ethoxyethoxy) ethyl carbonate
68214-66-4	Carbamic acid, [2-[(2-chloro-4-nitrophenyl)azo]-5-(diethylamino)phenyl]-, 2-ethoxyethyl ester
628-65-9	Carbamic acid, (2-ethoxyethyl) ester
21578-97-2	2-Ethoxyethyl N-(7-hydroxynaphth-1-yl) carbamate
70146-08-6	Carbamic acid, [3-(diethylamino)phenyl]-, 2-ethoxyethyl ester

*Chemical Abstracts Service.

Table E–13.—Acids and salts of glycol ethers

CAS* number	Name
67990-17-4	2-[(2-Butoxy)ethoxy] acetic acid, sodium salt
67990-18-5	2-[2-[(2-Hexyloxy)ethoxy]ethoxy] acetic acid, sodium salt
7420-07-7	Butoxyethoxypropionic acid
3139-99-9	2-Methoxyethanol, sodium salt
38321-18-5	Sodium 2-(2-butoxyethoxy) ethanolate
28099-67-4	bis (2-Methoxethoxy) calcium
14064-03-0	Magnesium ethoxyethoxide
52663-57-7	Sodium 2-butoxyethoxide
4084-36-0	Ethoxyethanol, compound with trifluoroborane
109-86-4	beta-Methoxyethanol
111-77-3	Diethylene glycol methyl ether
112-35-6	Methoxytriethylene glycol
111-90-9	Carbitol or 2-(2-ethoxyethoxy) ethanol
112-50-5	Ethoxytriethylene glycol
4353-29-1	3,6,9,12,15-Pentaoxaheptadecan-1-ol
2807-30-9	Ethylene glycol mono-N-propyl ether
6881-94-3	2-(2-Propoxyethoxy) ethanol
109-59-1	beta-Hydroxyethyl isopropyl ether
111-45-5	Ethylene glycol monoallyl ether
33065-62-2	1-(2-Hydroxyethoxy)-3-(2-propenyloxy)-2-propanol
3973-18-0	Ethylene glycol monopropargyl ether
111-76-2	Butoxyethanol
112-34-5	Butoxy diethylene glycol
143-22-6	Triethylene glycol mono-n-butyl ether
4439-24-1	Ethylene glycol isobutyl ether
18912-80-6	Diethylene glycol monoisobutyl ether
1606-85-5	bis(Hydroxyethyl) ether butynediol

(Continued)

*Chemical Abstracts Service.

Table E–13 (Continued).—Acids and salts of glycol ethers

CAS number	Name
112-25-4	Ethylene glycol monohexyl ether
112-59-4	Diethylene glycol hexyl ether
25961-89-1	Triethylene glycol monohexyl ether
16394-44-8	2,2′-(1,4-Cyclohexylenedioxy) diethanol
1559-35-9	Ethylene glycol ethylhexyl ether
1559-37-1	Triethylene glycol 2-ethylhexyl ether
4536-30-5	Ethylene glycol monolauryl ether or lauryl alcohol oxy ethanol
3055-93-4	Lauryl alcohol mono (oxyethylene) ethanol
3055-94-5	Dodecyl triethylene glycol ether
14663-73-1	2-[2(Tridecyloxy) ethoxy] ethanol
4403-12-7	2-[2-[2-(Tridecyloxy) ethoxy] ethoxy] ethanol
56049-80-0	Diethylene glycol monopentadecyl ether
628-89-7	Ethylene glycol mono (2-chloroethyl) ether
68003-29-2	bis [2-(2-Hydroxyethoxy) ethyl] octylamine
53815-85-3	2-(2-(1-Naphthalenylamino) ethoxy) ethanol
1704-62-7	Dimethylaminoethoxyethanol
112-33-4	Diethylene glycol mono (aminopropyl) ether
140-82-9	Diethylaminoethoxyethanol
929-06-6	Aminoethoxyethanol
68141-01-5	2-[2-(3-Aminopropoxy) ethoxy] ethanol hydroxyacetic acid salt
68156-16-1	2-[2-(3-Aminopropoxy) ethoxy] ethanol hydrochloride
622-08-2	Benzyl hydroxyethyl ether
122-99-6	beta-Hydroxethyl phenyl ether
104-68-7	Diethylene glycol phenyl ether
711-82-0	Ethylene glycol alpha-naphthyl ether
901-44-0	Bisphenol A bis (2-hydroxyethyl) ether
15149-10-7	beta-Hydroxyethyl p-methylphenyl ether
104-39-2	2-[2-(p-Tolyloxy) ethoxy] ethanol
104-38-1	p-Di(2-hydroxyethoxy)benzene

(Continued)

Table E–13 (Continued).—Acids and salts of glycol ethers

CAS number	Name
102-40-9	m-bis (2-Hydroxyethoxy) benzene
6382-07-6	2-(p-tert-Pentylphenoxy) ethanol
20427-84-3	Diethylene glycol p-nonylphenyl ether
27176-93-8	Diethylene glycol mono(nonylphenyl) ether
61886-41-7	2-(p-Aminophenoxy) ethanol hydrochloride
18790-97-1	2-[2-[2-(p-Aminophenoxy) ethoxy] ethoxy] ethanol
66422-95-5	2-(2,4-Diaminophenoxy) ethanol dihydrochloride
16365-27-8	2-(p-Nitrophenoxy) ethanol
63134-26-9	2-[2-[2-(4-Nitrophenoxy) ethoxy] ethoxy] ethanol
1892-43-9	p-Chlorophenyl glycol ether
60593-02-4	Hydroxyethyl pentabromophenyl ether
15480-00-9	2-(o-Chlorophenoxy) ethanol
23976-66-1	2-(2,4,6-Tribromophenoxy) ethanol
70715-17-2	2-[3-(6-Methyl-2-pyridinyl) propoxy] ethanol
64346-25-4	2-[(2,2,6,6-Tetramethyl-4-piperidinyl) oxy] ethanol
65104-24-7	2-[2-[[4-[(2-Bromo-4,6-dinitrophenyl) azo]-1-naphthalenyl] amino] ethoxy] ethanol
68039-37-2	2-[(3a,4,5,6,7,7a-Hexahydro-4,7-methano-1H-inden-5-yl)oxy] ethanol
67906-59-6	2-[4-[(4-Amino-5-methoxy-o-tolyl) azo] phenoxy] ethanol
57119-91-2	2-[2-[[4-[(2-Chloro-4,6-dinitrophenyl) azo]-1-napthalenyl] amino] ethoxy] ethanol
2192-20-3	2-[2[[4-(p-Chloro-alpha-phenylbenzyl)-1-piperazinyl] ethoxy] ethanol dihydrochloride
7070-15-7	beta-Hydroxyethyl isobornyl ether
4162-45-2	2,2'-[Isopropylidenebis [(2,6-dibromo-p-phenylene)oxy]] diethanol
2831-60-9	2-(2,4-Dinitrophenoxy) ethanol

Table E–14.—Miscellaneous glycol ethers*

CAS† number	Name
72403-65-7	Chromate (5-), bis [4-[[6-[[4-chloro-6-(2-ethoxyethoxy)-1,3,5-triazin-2-yl] amino]-1-hydroxy-3-sulfo-2-naphthalenyl] azo]-1-hydroxy-7-nitro-1-naphthalenesulfonato(4-)]-, pentasodium
71673-20-6	1-[2-(2-Ethoxyethoxy)ethyl]-2,2,4-trimethyl-1,2,3,4-tetrahydroquinoline
71673-19-3	7-Nitro-1-[2-(2-ethoxyethoxy) ethyl]-2,2,4-trimethyl-1,2,3.4- tetrahydroquinoline
71673-14-8	7-Amino-1-[2-(2-ethoxyethoxy) ethyl]-2,2,4-trimethyl-1,2,3,4- tetrahydroquinoline
71637-13-7	7-Acetamido-6-(2-bromo-4,6-dinitrophenylazo)-1-[2-(2-ethoxyethoxy) ethyl]-1,2,3,4-tetrahydro-22,4-trimethylquinoline
71637-12-6	7-Acetamido-6-(2-cyano-4,6-dinitrophenylazo)-1-[2-(2-ethoxyethoxy) ethyl}-1,2,3,4-tetrahydro-2,2,4-trimethylquinoline
71673-02-4	7-Acetamido -1-[2-(2-ethoxyethoxy) ethyl]-2,2,4-trimethyl -1,2,3,4- tetrahydroquinoline
70210-27-4	1-Amino-4-[[3-[[4-chloro-6-(2-ethoxyethoxy) -1,3,5-triazin-2-yl] amino} -2,4,6-rimethyl -5-sulfophenyl] amino]-9,10-dihydro-9,10-dioxo-2-anthracenesulfonicacid, disodium salt
65208-31-3	N-[2-[(2,6-Dibromo-4-nitrophenyl) azo] -5-[[2-(2-ethoxyethoxy) ethyl] ethylamino]phenyl] acetamide
65916-12-3	4-[(2,6-Dicyano-4-nitrophenol) azo]-N-[2-(2-ethoxyethoxy)ethyl] -N-ethyl-3-acetamidoaniline
67338-58-3	N-[2-(2-Ethoxyethoxy) ethyl] -N-ethyl-m-acetamidoaniline
23119-35-9	1,5-Dihydroxy-4,8-diamino-2-[4-(2-ethoxyethoxy) phenyl] anthraquinone
55993-15-2	2-[2-(2-Ethoxyethoxy) ethyl]-6-hydroxy -5-[(2-methyl 4-nitrophenyl) azo]-1H-benz[de] isoquinoline -1,3 (2H)-dione
68298-23-7	Propanoic acid, 3-(2-butoxyethoxy)-, sodium salt
68140-97-6	Propanoic acid, 3-(2-butoxyethoxy)-, potassium salt
68140-96-5	3-(2-Butoxyethoxy) propanenitrile
52788-78-0	Diethylene glycol butyl tert-butyl ether
1120-23-6	2-Butoxyethyl 2-chloroethyl ether
764-99-8	Diethylene glycol divinyl ether
143-29-3	bis (Butoxyethoxyethoxy) methane

(Continued)

*Adapted from TSCA [1977] and SANSS/CIS [1988].
†Chemical Abstracts Service.

Table E-14 (Continued).—Miscellaneous glycol ethers

CAS number	Name
124-16-3	Butoxyethoxy propanol
112-73-2	Dibutoxy diethylene glycol
51-03-6	alpha-[2-[2-)n-Butoxy)ethoxy] ethoxy] -4,5-methylene dioxy-2-propyltoluene
7529-27-3	Ethylene glycol diallyl ether
57947-82-7	Diethylene glycol bis (allyl) ether
18854-51-8	1-[2-[2-Propenyloxy)ethoxy] butane
68134-24-7	1-(2-(1,1-Dimethylethoxy)ethoxy) butane
112-26-5	Triethylene glycol dichloride
13483-18-6	Ethylene glycol bis (chloromethyl ether)
66028-01-1	1-[2-[2-(2-Chloroethoxy) ethoxy]ethoxy]-4-octyl benzene
66028-00-0	Diisobutylphenoxyethoxyethylchloride
65925-28-2	1-[2-(2-Chloroethoxy)ethoxy]-4-(1,1,3,3-tetramethylbutyl) benzene
2997-01-5	di (3-Aminopropoxy) ethane
4246-51-9	Diethylene glycol bis (3-aminopropyl) ether
5442-83-1	N,N-Dimethyl-2-[2-[4-(1,1,3,3-tetramethyl butyl) phenoxy]ethoxy - ethanamine
21697-94-9	3,3'-(Ethylenedioxy) bis (propylammonium) adipate
66027-99-4	Diisobutylphenoxyethoxyethyldimethylamine
66027-97-2	Diisobutylcresoxyethoxyethyldimethylamine
2224-15-9	Ethylene diglycidyl ether
22397-31-5	Diethylene glycol bis (2-cyanoethyl) ether
3386-87-6	Ethylene glycol bis (2-cyanoethyl) ether
68132-81-0	(Diisobutylphenoxy) ethoxyethoxyethane sulfonic acid, sodium salt
70198-21-9	2-[2-[[2,2,4(or 2,4,4)-Trimethylpentyl]phenoxy]ethoxy] ethanesulfonic acid, sodium salt
71550-69-1	N,N-Dimethyl-2-[2-[2-methyl-4-(1,1,3,3-tetramethylbutyl) phenoxy]ethoxy] ethanamine
61166-00-5	1,2-bis (3-Hydroxyphenoxy) ethane
104-66-5	Ethylene glycol diphenyl ether
3753-05-7	1,2-bis (4-Carboxyphenoxy) ethane
22616-31-5	Benzyldiisobutyl [2-(2-phenoxyethoxy)ethyl] ammonium chloride

(Continued)

Table E–14 (Continued).—Miscellaneous glycol ethers

CAS number	Name
14417-67-5	1,2-bis (Pyridinomethoxy) ethane dichloride
17418-59-6	1-Amino-4-hydroxy-2-(2-phenoxyethoxy) anthraquinone
41312-86-1	1,4-Diamino-2-chloro-3-(2-phenoxyethoxy) anthraquinone
63833-78-3	5-[(2-Cyano-4-nitrophenyl) azo]-6-[2-hydroxyethyl) amino]-4-methyl-2-[[3-(2-phenoxyethoxy) propyl] amino]-3-pyridinecarbonitrile
63281-10-7	5-[[2-Chloro-4-(methylsulfonyl) phenyl] azo]-4-methyl-2,6-bis [[3-(2-phenoxyethoxy) propyl] amino]-3-pyridinecarbonitrile
63281-05-0	4-Methyl-2,6-bis [[3-(2-phenoxyethoxy) propyl] amino]-5-[[4-(phenylazo) phenyl] azo]-3-pyridinecarbonitrile
63281-03-8	5-[[2-Chloro-4-(phenylzap) phenyl] azo]-4-methyl-2,6-bis[[3-(2-phenoxyethoxy) propyl] amino]-3-pyridinecarbonitrile
68299-27-4	Nonabromomonochloro-1,2-diphenoxyethane
121-54-0	p-Diisobutyl(phenoxyethoxy) ethyl] dimethylbenzylammonium chloride
61262-53-1	1,1'- [1,2-Ethanediylbis (oxy)] bis [2,3,4,5,6-pentabromo-benzene
23421-22-9	4,4"-[Oxybis(ethyleneoxy)]bis [2-hydroxy benzophenone]
37853-59-1	1,2-bis(2,4,6-Tribromophenoxy) ethane
67923-87-2	2-[2-[2-(Octylphenoxy) ethoxy] ethoxy] ethanesulfonic acid, sodium salt
72953-52-7	1-Amino-2-[2-(bromophenoxy) ethoxy]-4-hydroxyanthraquinone
72953-51-61	1-Amino-2-[2-(dibromophenoxy) ethoxy] -4-hydroxyanthraquinone

APPENDIX F

BACKGROUND OF METHODS USED FOR ANALYSIS OF EAA and MAA IN URINE

Smallwood et al. [1984]* developed a method for analyzing the glycol ether metabolites EAA and MAA in urine. The method was based on (1) methylene chloride extraction of "spiked" acidified human urine, (2) pentafluorobenzyl bromide (PFBB) derivitization, and (3) gas chromatography analysis using flame ionization detection (FID). Urine (1 ml) was adjusted to pH 2 with HCl and extracted three times with methylene chloride. Phase transfer catalysis (a combination of ion-pair extraction and fluoroanhydride derivitization) was done by adding alkaline tetrabutylammonium hydrogen sulfate and PFBB to the methylene chloride extract. The mixture was rotated for 2 hr. Gas chromatography was employed to analyze 5 μl of the methylene chloride layer (bottom layer) using FID and a 6 ft × 1/4 in (4-mm id) glass column (packed with 1.95% QF-1 and 1.5% OV-17 on 80/100 mesh Supelcoport). Detection limits for MAA and EAA were 11.4 and 5.0 mg/liter of urine, respectively. Average recoveries (and relative standard deviations) were 78% (0.17) for MAA and 91% (0.14) for EAA.

Groeseneken et al. [1986a] developed a method for determining MAA and EAA in urine based on lyophilization of urine samples followed by derivitization with diazomethane. After adjustment of urine specimens to pH 8 to 8.5 with KOH, 1 ml of urine and 50 μg of 2-furonic acid (FA) (internal standard) were added, and the sample was lyophilized. The dry residue was redissolved in 1 ml methylene chloride with added HCl and derivitized with diazomethane in methylene chloride. Gas chromatographic analysis using FID was performed on a fused silica capillary column (CP WAX 57 CB, 25 m × 0.33 mm id) with a split ratio of 10:1. The detection limits of MAA and EAA were 0.15 and 0.07 mg/liter of urine, respectively. Mean recoveries of MAA, EAA, and FA added to "blank" urine samples were 31.4%, 62.5%, and 58.4%, respectively; the recoveries of MAA and EAA were well correlated with those of the internal standard. Day-to-day variability for MAA and EAA was 6.0% and 6.4%, respectively; the corresponding within-day variability was 6.2% and 8.9%.

*See References beginning on page 262.

Smallwood et al. [1988] developed and validated a method for analysis of EAA in urine. Two ml of urine, along with potassium carbonate, tetrabutylammonium hydrogen sulfate, methylene chloride, and PFBB were added to a screw-top culture tube. After 2 hr of mixing on a rotator at 60 rpm, the tube was heated for 20 min in a 50°C water bath. Additional mixing at room temperature, removal of the upper aqueous layer, and washing of the lower methylene chloride layers with distilled water removed unreacted reagents. The methylene chloride extract was dried with anhydrous sodium sulfate and loaded into an autosampler vial. Automated gas chromatographic analysis using FID was conducted with the use of a 6 ft × 4 mm id glass column packed with 4% SE-30 and 6% OV-210 on 100/120 mesh Chromosorb WHP. Standards were prepared in pooled urine. The analytical range for EAA was 5 to 100 mg/liter of urine; the limit of detection was 4 mg/liter; and the limit of quantitation was 7 mg/liter. Within-day variation was 0.5% to 1.8%, and day-to-day variation was 3.0% to 4.7%. Sample stability was confirmed for at least 8 months when specimens were stored at −20°C. The authors stated that the method could also be used for MAA and butoxyacetic acid (BAA) in urine. Preliminary data were presented in the paper indicating that the technique has the potential for assessing EGEE exposure in shipyard painters who use paints containing EGEE.

Groeseneken et al. [1989b] observed that MAA appeared in the chromatogram of control subjects not exposed to EGME. Further investigation revealed that the diazomethane procedure was producing MAA by reacting with the hydroxyl group of naturally occurring glycolic acid. Groeseneken et al. [1989b] further evaluated the existing methods for determining alkoxyacetic acids and concluded that the phase transfer catalysis procedures had the required specificity, without the production of artifacts, but lacked sufficient sensitivity to detect these metabolites at low occupational exposure concentrations. On the other hand, the methods utilizing diazomethane derivitization had the required sensitivity but lacked the specificity. Therefore, Groeseneken et al. [1989a] developed an improved method that combined the best attributes of the two basic existing methods.

The procedure developed by Groeseneken et al. [1989b] was described as follows. Urine was adjusted to pH 7; 1-ml aliquots were placed in small vials with 3-chloropropionic acid (internal standard) and lyophilized overnight. The dry residue was redissolved in methanol containing PFBB, and the vials were capped. The vials were heated at 90°C for 3 hr. After cooling, sample cleanup was done by adding distilled water and extracting the penta-fluorobenzyl-esters (PFB-esters) with methylene chloride. The methylene chloride extract was analyzed by gas chromatography using FID. A fused silica capillary column was used (CP Sil 5, 25 m × 0.32 mm id, 0.21 μm film thickness) with a split ratio of 5:1. Temperature programming was employed. All PFB-esters showed baseline resolution; retention times of 6.53 min (MAA), 7.77 min (EAA), and 8.59 min (internal standard) were observed. A typical gas chromatographic run, including cool-down and equilibration times, required about 30 min.

Optimization studies were done for reagent concentrations as well as for urinary pH and reaction time. After correction for the partial solubility of methylene chloride in the 50:50 methanol:urine phase, recoveries of alkoxyacetic acids from urine averaged 95.0% (MAA), 94.8% (EAA), and 95.1% (BAA). The yield for the derivitization reaction averaged 99.5%

(MAA) and 101.8% (EAA). Standard curves were set up for urine and were linear over the range of 0.1 to 200 mg/liter. The limit of detection, at a signal-to-noise ratio of 5, for the two acids was 0.03 mg/liter. Precision of the method, calculated from triplicate injections of 40 urine samples, averaged 3.5% (RSD), ranging from 1.1% at 25 mg/liter to 20% at 0.1 mg/liter.

NIOSH has not validated the Groeseneken et al. methods [1986a, 1989b].

APPENDIX G

GUIDELINES FOR BIOLOGICAL MONITORING

G.1 Monitoring

The frequency of biological monitoring should be tied to work practices and the use of the glycol ethers. Dermal absorption of glycol ethers can be significant. Compliance with the NIOSH RELs without a biological monitoring evaluation may not protect workers from the potential adverse effects of glycol ethers.

Urine samples should be evaluated for alkoxyacetic acid metabolites using the method of Groeseneken et al. [1989b]* or an equivalent method. Expression of results as milligrams of metabolite per gram of creatinine (mg/g creatinine) is suggested.

Factors that may affect the urinary levels of EAA and MAA include ethanol consumption (which lowers urinary metabolite levels) and dermal contact, heavy work, and nonoccupational exposures (all of which raise urinary levels).

Urine sample collection times are specific for the individual glycol ethers:

- EGEE and EGEEA: Urine samples should be collected at the beginning of the shift on the last working day of the workweek. This specimen would represent the integrated weekly exposure (dermal and inhalation).
- EGME and EGMEA: Urine samples should be collected preshift on the first day of the workweek following a typical workweek of exposure. This specimen would reflect the integrated exposure (dermal and inhalation) from the previous week.

Measurable concentrations of EAA or MAA in the urine are an indication of uptake of the respective glycol ethers by either inhalation or skin exposure. The concentrations reflect nonoccupational as well as occupational exposure and are not likely to correlate with the NIOSH RELs. If concentrations of EAA and MAA exceed the estimated guidelines below, then exposure to glycol ethers has occurred, but not necessarily at concentrations above the NIOSH RELs. A thorough industrial hygiene evaluation, with specific emphasis on possible dermal absorption, should be conducted to determine the source of exposure. The following guidelines are suggested until better documented guidelines are developed.

*See References beginning on page 262.

1. The presence of EAA in urine specimens (collected as specified) above a concentration of approximately 5 mg EAA/g creatinine is evidence for a single EGEE and/or EGEEA inhalation exposure corresponding to an 8-hr exposure to 0.5 ppm EGEE and/or EGEEA at 60 W of exercise. This value was extrapolated from 4-hr experimental exposures at 5 ppm at 60-W workload to an 8-hr exposure at 0.5 ppm at 60-W workload [Groeseneken et al. 1986c, 1987b] using the principle of superposition [Gibaldi and Perrier 1982].

2. The presence of MAA in urine specimens (collected as specified) above a concentration of approximately 1 μg/ml (equivalent to approximately 0.8 mg/g creatinine) is evidence of inhalation-only exposure to EGME and/or EGMEA. This value was extrapolated from 4-hr laboratory exposures at 5.1 ppm EGME at rest to 8-hr exposure to 0.5 ppm at 60-W workload [Groeseneken et al. 1989a]. The excretion of MAA was relatively constant 4 hr after the end of a 4-hr exposure. Therefore, doubling the urinary EAA concentration after a 4-hr exposure is a reasonable estimate of urinary values following an 8-hr exposure (based on Figure 1 [Groesenken et al. 1989a]). Extrapolation to 0.1 ppm may produce MAA levels below the detection limit of the method. There are no data on occupational exposures, but based on EGEE data and on the strong possibility of concurrent dermal absorption of EGME, concentrations of MAA may be higher than 0.8 mg/g creatinine in urine specimens collected from workers.

G.2 Justification For Recommendations

Biological monitoring for glycol ether exposure is recommended, even though no validated guidelines can be provided as to the relationship between airborne exposure to glycol ethers and the alkoxyacetic acid urinary metabolites. The alkoxyacetic acid metabolites (EAA and MAA) are not only an index of exposure or uptake of EGEE or EGME by the worker, but they are also an index of potential adverse health effects from these glycol ethers.

Dermal absorption may be a major route of exposure to EGME and EGEE and their respective acetates. The potential exists for absorption of glycol ether vapors through wet skin.

The influence of workload is significant for inhalation exposure. Doubling the workload results in twice the uptake of the glycol ethers.

APPENDIX H

MEDICAL ASPECTS OF WEARING RESPIRATORS*

In recommending medical evaluation criteria for respirator use, one should apply rigorous decision-making principles [Halperin et al. 1986];† tests used should be chosen for operating characteristics such as sensitivity, specificity, and predictive value. Unfortunately, many knowledge gaps exist in this area. The problem is complicated by the large variety of respirators, their conditions of use, and individual differences in the physiologic and psychologic responses to them. The following guidelines are intended primarily to assist the physician in developing medical evaluation criteria for respirator use.

H.1 BACKGROUND INFORMATION

Brief descriptions of the health effects associated with wearing respirators are summarized below. More detailed analyses of the data are available in recent reviews by James [1977] and Raven et al. [1979].

H.1.1 Pulmonary Effects

In general, the added inspiratory and expiratory resistances and dead space of most respirators cause an increase in tidal volume and a decrease in respiratory rate and ventilation (including a small decrease in alveolar ventilation). These respirator effects have usually been small both among healthy individuals and, in limited studies, among individuals with impaired lung function [Gee et al. 1968; Altose et al. 1977; Raven et al. 1981; Hodous et al. 1983; Hodous et al. 1986]. This generalization is applicable to most respirators when resistances (particularly expiratory resistance) are low [Bentley et al. 1973; Love et al. 1977]. Although most studies report minimal physiologic effects during submaximal exercise, the resistances commonly lead to reduced endurance and reduced maximal exercise performance [Craig et al. 1970; Raven et al. 1977; Stemler and Craig 1977; Myhre et al. 1979; Deno et al. 1981]. The dead space of a respirator (reflecting the amount of expired air that must be rebreathed before fresh air is obtained) tends to cause increased ventilation. At least one study has shown substantially increased ventilation with a full-face respirator, a type that can have a large effective dead space [James et al. 1984]. However, the net effect of a respirator's added resistances and dead space is usually a small decrease in ventilation [Craig

*Adapted from NIOSH Respiratory Decision Logic [NIOSH 1987b].
†References for Appendix H are at the end of this Appendix.

et al. 1970; Hermansen et al. 1972; Raven et al. 1977; Stemler and Craig 1977; Deno et al. 1981; Hodous et al. 1983].

The potential for adverse effects, particularly decreased cardiac output, from the positive pressure feature of some respirators has been reported [Meyer et al. 1975]. However, several recent studies suggest that this is not a practical concern, at least not in healthy individuals [Bjurstedt et al. 1979; Arborelius et al. 1983; Dahlback and Balldin 1984].

Theoretically, the increased fluctuations in thoracic pressure caused by breathing with a respirator might constitute an increased risk to subjects with a history of spontaneous pneumothorax. Few data are available in this area. While an individual is using a negative-pressure respirator with relatively high resistance during very heavy exercise, the usual maximal-peak negative oral pressure during inhalation is about 15 to 17 cm of water [Dahlback and Balldin 1984]. Similarly, the usual maximal-peak positive oral pressure during exhalation is about 15 to 17 cm of water, which might occur with a respirator in a positive-pressure mode, again during very heavy exercise [Dahlback and Balldin 1984]. By comparison, maximal positive pressures such as those during a vigorous cough can generate 200 cm of water pressure [Black and Hyatt 1969]. The normal maximal negative pleural pressure at full inspiration is -40 cm of water [Bates et al. 1971], and normal subjects can generate -80 to -160 cm of negative water pressure [Black and Hyatt 1969]. Thus vigorous exercise with a respirator does alter pleural pressures, but the risk of barotrauma is substantially less with exercise than with coughing.

In some asthmatics, an asthmatic attack may be exacerbated or induced by a variety of factors including exercise, cold air, and stress, all of which may be associated with wearing a respirator. Although most asthmatics who are able to control their condition should not have problems with respirators, a physician's judgment and a field trial may be needed in selected cases.

H.1.2 Cardiac Effects

The added work of breathing from respirators is small and could not be detected in several studies [Gee et al. 1968; Hodous et al. 1983]. A typical respirator might double the work of breathing (from 3% to 6% of the total oxygen consumption), but this is probably not of clinical significance [Gee et al. 1968]. In concordance with this view, several other studies indicated that at the same workloads heart rate does not change with the wearing of a respirator [Raven et al. 1982; Harber et al. 1982; Hodous et al. 1983; Arborelius et al. 1983; Petsonk et al. 1983].

In contrast, the added cardiac stress due to the weight of a heavy respirator may be considerable. A self-contained breathing apparatus (SCBA) may weigh up to 35 lb. Heavier respirators can reduce maximum external workloads by 20% and similarly increase heart rate at a given submaximal workload [Raven et al. 1977]. In addition, it should be noted that many uses of SCBA (e.g., for firefighting and hazardous waste site work) also necessitate the wearing of 10 to 25 lb of protective clothing. Raven et al. [1982] found

statistically significant higher systolic and/or diastolic blood pressures during exercise for persons wearing respirators. Arborelius et al. [1983] did not find significant differences for persons wearing respirators during exercise.

H.1.3 Body Temperature Effects

Proper regulation of body temperature is primarily of concern with the closed circuit SCBA that produces oxygen via an exothermic chemical reaction. Inspired air within these respirators may reach 120°F (49°C), thus depriving the wearer of a minor cooling mechanism and causing discomfort. Obviously this can be more of a problem with heavy exercise and when ambient conditions and/or protective clothing further reduce the body's ability to lose heat. The increase in heart rate because of increasing temperature represents an additional cardiac stress.

Closed-circuit breathing units of any type have the potential for causing heat stress since warm expired gases (after exothermic carbon dioxide removal with or without oxygen addition) are rebreathed. Respirators with large dead spaces also have this potential problem, again because of partial rebreathing of warmed expired air [James et al. 1984].

H.1.4 Sensory Effects

Respirators may reduce visual fields, decrease voice clarity and loudness, and decrease hearing ability. Besides the potential for reduced productivity, these effects may result in reduced industrial safety. These factors may also contribute to a general feeling of stress [Morgan 1983a].

H.1.5 Psychologic Effects

This important topic is discussed in recent reviews by Morgan [Morgan 1983a, 1983b]. There is little doubt that virtually everyone suffers some discomfort when wearing a respirator. The large variability and the subjective nature of the psychophysiologic aspects of wearing a respirator, however, make studies and specific recommendations difficult. Fit testing obviously serves an important additional function by providing a trial to determine if the wearer can psychologically tolerate the respirator. The great majority of workers can tolerate respirators, and experience in wearing them aids in this tolerance [Morgan 1983b]. However, some individuals are likely to remain psychologically unfit for wearing respirators.

H.1.6 Local Irritation Effects

Allergic skin reactions may occur occasionally from wearing a respirator, and skin occlusion may cause irritation or exacerbation of preexisting conditions such as pseudofolliculitis barbae. Facial discomfort from the pressure of the mask may occur, particularly when the fit is unsatisfactory.

H.1.7 Miscellaneous Health Effects

In addition to the health effects (described above) associated with wearing respirators, specific groups of respirator wearers may be affected by the following factors:

a. Perforated tympanic membrane

Although inhalation of toxic materials through a perforated tympanic membrane (ear drum) is possible, recent evidence indicates that the airflow would be minimal and rarely if ever of clinical importance [Cantekin et al. 1979; Ronk and White 1985]. In highly toxic or unknown atmospheres, use of positive pressure respirators should ensure adequate protection [Ronk and White 1985].

b. Contact lenses

Contact lenses are generally not recommended for use with respirators, although little documented evidence exists to support this viewpoint [daRoza and Weaver 1985]. Several possible reasons for this recommendation are noted below:

(1) Corneal irritation or abrasion

Corneal irritation or abrasion might occur with the exposure. This would, of course, be a problem primarily with quarter- and half-face masks, especially with particulate exposures. However, exposures could occur with full-face respirators because of leaks or inadvisable removal of the respirator for any reason. Although corneal irritation or abrasion might also occur without contact lenses, their presence is known to substantially increase this risk.

(2) Loss or misplacement of a contact lens

The loss or misplacement of a contact lens by an individual wearing a respirator might prompt the wearer to remove the respirator, thereby resulting in exposure to the hazard as well as to the potential problems noted above.

(3) Eye irritation from respirator airflow

The constant airflow of some respirators, such as powered air-purifying respirators (PAPR's) or continuous flow air-line respirators, might irritate the eyes of a contact lens wearer.

H.2 SUGGESTED MEDICAL EVALUATION AND CRITERIA FOR RESPIRATOR USE

The following NIOSH recommendations allow latitude for the physician in determining a medical evaluation for a specific situation. More specific guidelines may become available as knowledge increases regarding human stresses from the complex interactions of worker

health status, respirator usage, and job tasks. Although some of the following recommendations should be part of any medical evaluation of workers who wear respirators, others are applicable for specific situations.

- A physician should determine fitness to wear a respirator by considering the worker's health, the type of respirator, and the conditions of respirator use.

The recommendation above leaves the final decision of an individual's fitness to wear a respirator to the person who is best qualified to evaluate the multiple clinical and other variables. Much of the clinical and other data could be gathered by other personnel. It should be emphasized that the clinical examination alone is only one part of the fitness determination. Collaboration with foremen, industrial hygienists, and others may often be needed to better assess the work conditions and other factors that affect an individual's fitness to wear a respirator.

- A medical history and at least a limited physical examination are recommended.

The medical history and physical examination should emphasize the evaluation of the cardiopulmonary system and should elicit any history of respirator use. The history is an important tool in medical diagnosis and can be used to detect most problems that might require further evaluation. Objectives of the physical examination should be to confirm the clinical impression based on the history and to detect important medical conditions (such as hypertension) that may be essentially asymptomatic.

- Although chest X-ray and/or spirometry may be medically indicated in some fitness determinations, these should not be routinely performed.

In most cases, the hazardous situations requiring the wearing of respirators will also mandate periodic chest X-rays and/or spirometry for exposed workers. When such information is available, it should be used in the determination of fitness to wear respirators.

Data from routine chest X-rays and spirometry are not recommended solely for determining if a respirator should be worn. In most cases, with an essentially normal clinical examination (history and physical), these data are unlikely to influence the respirator fitness determination; additionally, the X-ray would be an unnecessary source of radiation exposure to the worker. Chest X-rays in general do not accurately reflect a person's cardiopulmonary physiologic status, and limited studies suggest that mild to moderate impairment detected by spirometry would not preclude the wearing of respirators in most cases. Thus it is recommended that chest X-rays and/or spirometry be done only when clinically indicated.

- The recommended periodicity of medical fitness determinations varies according to several factors but could be as infrequent as every 5 years.

Federal or other applicable regulations shall be followed regarding the frequency of respirator fitness determinations. The guidelines for most work conditions for which respirators are required are shown in Table H-1.

Table H-1.—Suggested frequency of medical fitness determinations*

Type of working conditions	Worker age (yr)		
	<35	35 to 45	>45
Most work conditions requiring respirators	Every 5 yr	Every 2 yr	1-2 yr
Strenuous working conditions with a SCBA†	Every 3 yr	Every 18 mo	Annually

*Interim testing would be needed if changes in health status occur.
†SCBA = self-contained breathing apparatus.

These guidelines are similar to those recommended by ANSI, which recommends annual determinations after age 45 [ANSI 1984]. The more frequent examinations with advancing age relate to the increased prevalence of most diseases in older people. More frequent examinations are recommended for individuals performing strenuous work involving the use of a SCBA. These guidelines are based on clinical judgment and, like the other recommendations in this section, should be adjusted as clinically indicated.

- The respirator wearer should be observed during a trial period to evaluate potential physiological problems.

In addition to considering the physical effects of wearing respirators, the physician should determine if wearing a given respirator would cause extreme anxiety or claustrophobic reaction in the individual. This could be done during training while the worker is wearing the respirator and is engaged in some exercise that approximates the actual work situation.

Present OSHA regulations state that a worker should be provided the opportunity to wear the respirator "in normal air for a long familiarity period . . ." [29 CFR* 1910.134(e)(5)]. This trial period should also be used to evaluate the ability and tolerance of the worker to wear the respirator [Harber 1984]. This trial period need not be associated with respirator fit testing and should not compromise the effectiveness of the vital fit testing procedure.

- Examining physicians should realize that the main stress of heavy exercise while using a respirator is usually on the cardiovascular system and that heavy respirators (e.g., SCBA) can substantially increase this stress. Accordingly, physicians may want to consider exercise stress tests with electrocardiographic monitoring when heavy respirators are used, when cardiovascular risk factors are present, or when extremely stressful conditions are expected.

*Code of Federal Regulations. See CFR in references.

Some respirators may weigh up to 35 lb and may increase workloads by 20%. Although a lower activity level could compensate for this added stress [Manning and Griggs 1983], a lower activity level might not always be possible. Physicians should also be aware of other added stresses, such as heavy protective clothing and intense ambient heat, that would increase the worker's cardiac demand. As an extreme example, fire fighters who use a SCBA inside burning buildings may work at maximal exercise levels under life-threatening conditions. In such cases, the detection of occult cardiac disease, which might manifest itself during heavy stress, may be important. Some authors have either recommended stress testing [Kilbom 1980] or at least its consideration in the fitness determination [ANSI 1984]. Kilbom [1980] has recommended stress testing at 5-yr intervals for fire fighters below age 40 who use SCBA and at 2-yr intervals for those aged 40 to 50. He further suggested that firemen over age 50 not be allowed to wear SCBA.

Exercise stress testing has not been recommended for medical screening for coronary artery disease in the general population [Weiner et al. 1979; Epstein 1979]. It has an estimated sensitivity and specificity of 78% and 69%, respectively, when the disease is defined by coronary angiography [Weiner et al. 1979; Nicklin and Balaban 1984]. In a recent 6-yr prospective study, stress testing to determine the potential for heart attacks indicated a positive predictive value of 27% when the prevalence of disease was 3.5% [Giagnoni et al. 1983; Folli 1984]. Although stress testing has limited effectiveness in medical screening, it could detect individuals who may not be able to complete the heavy exercise required in some jobs.

A definitive recommendation regarding exercise stress testing cannot be made at this time. Further research may determine whether this is a useful tool in selected circumstances.

- An important concept is that "general work limitations and restrictions identified for other work activities also shall apply for respirator use" [ANSI 1984].

In many cases, if a worker is physically able to do an assigned job while not wearing a respirator, the worker will in most situations not be at increased risk when performing the same job while wearing a respirator.

- Because of the variability in the types of respirators, work conditions, and workers' health status, many employers may wish to designate categories of fitness to wear respirators, thereby excluding some workers from strenuous work situations involving the wearing of respirators.

Depending on the various circumstances, several permissible categories of respirator usage are possible. One conceivable scheme would consist of three overall categories: full respirator use, no respirator use, and limited respirator use including "escape only" respirators. The latter category excludes heavy respirators and strenuous work conditions. Before identifying the conditions that would be used to classify workers into various categories, it is critical that the physician be aware that these conditions have not been validated and are presented only for consideration. The physician should modify the use of these conditions based on actual experience, further research, and individual worker sensitivities. He may

also wish to consider the following conditions in selecting or permitting the use of respirators:

- History of spontaneous pneumothorax
- Claustrophobia/anxiety reaction
- Use of contact lenses (for some respirators)
- Moderate or severe pulmonary disease
- Angina pectoris, significant arrhythmias, recent myocardial infarction
- Symptomatic or uncontrolled hypertension, and
- Advanced age

Wearing a respirator would probably not play a significant role in causing lung damage such as pneumothorax. However, without good evidence that wearing a respirator would not cause such lung damage, the physician would be prudent to prohibit the individual with a history of spontaneous pneumothorax from wearing a respirator.

Moderate lung disease is defined by the Intermountain Thoracic Society [Kanner and Morris 1975] as being present when the following conditions exist—a forced expiratory volume in 1 sec (FEV_1) divided by the forced vital capacity (FVC) (i.e., FEV_1/FVC) of 0.45 to 0.60, or an FVC of 51% to 65% of the predicted FVC value. Similar arbitrary limits could be set for age and hypertension. It would seem more reasonable, however, to combine several risk factors into an overall estimate of fitness to wear respirators under certain conditions. Here the judgment and clinical experience of the physician are needed. Many impaired workers would even be able to work safely while wearing respirators if they could control their own work pace, including having sufficient time to rest.

H.3 CONCLUSION

Individual judgment is needed to determine the factors affecting an individual's fitness to wear a respirator. Although many of the preceding guidelines are based on limited evidence, they should provide a useful starting point for a respirator fitness screening program. Further research is needed to validate these and other recommendations currently in use. Of particular interest would be laboratory studies involving physiologically impaired individuals and field studies conducted under actual day-to-day work conditions.

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