NIOSH

Criteria For A Recommended Standard

Occupational Exposure to Ethylene Glycol Monobutyl Ether and Ethylene Glycol Monobutyl Ether Acetate

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

CDC
CENTERS FOR DISEASE CONTROL

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Division of Standards Development and Technology Transfer
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FOREWORD

In the Occupational Safety and Health Act of 1970 (Public Law 91-596), Congress declared that its purpose was to assure, insofar as possible, safe and healthful working conditions for every working man and woman and to preserve our human resources. The Act authorizes the National Institute for Occupational Safety and Health (NIOSH) to develop and establish recommended occupational safety and health standards and to develop criteria that will assure that no employee will suffer diminished health, functional capacity, or life expectancy as a result of his or her work experience. By means of criteria documents, NIOSH communicates these recommended standards to regulatory agencies (including the Occupational Safety and Health Administration [OSHA] and the Mine Safety and Health Administration [MSHA]) and to others in the community of occupational safety and health.

Criteria documents provide the scientific basis for new 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. In addition to transmitting these documents to the Department of Labor, NIOSH also distributes them to health professionals in academic institutions, industry, organized labor, public interest groups, and other government agencies.

This criteria document reviews available information about the adverse health effects associated with exposure to ethylene glycol monobutyl ether (EGBE) and ethylene glycol monobutyl ether acetate (EGBEA). The results of studies in animals have clearly demonstrated dose-related adverse effects on the central nervous system, the hematopoietic tissues, the blood, the kidneys, and the liver in several species by different routes of administration. Limited data from humans also indicate the risk of adverse effects on the central nervous and hematopoietic tissues, the blood, and the kidneys. Because limited data are available from studies in humans, NIOSH bases its recommended exposure limits (RELs) for EGBE and EGBEA on data from studies in animals. The data were adjusted to allow for uncertainties in the extrapolation from animals to humans.

NIOSH 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 monobutyl ether (EGBE) and its acetate, ethylene glycol monobutyl ether acetate (EGBEA). Criteria are also provided for eliminating or minimizing the risks encountered by workers during the manufacture and use of EGBE and EGBEA. These criteria include recommendations for preventing dermal contact, sampling and analytical methods, medical monitoring, biological monitoring, engineering controls and work practices, and protective clothing and equipment.

In humans and animals, the principal health effects of exposure to EGBE and EGBEA involve the blood and hematopoietic system, the central nervous system (CNS), the kidneys, and the liver. No evidence indicates that EGBE or EGBEA causes reproductive or developmental toxicity.

In animals, CNS, liver, and kidney effects occur at higher EGBE exposures than hematotoxic effects. Thus limiting exposures to prevent hematotoxic effects will also prevent CNS, kidney, and liver effects. Because limited data are available from studies in humans, NIOSH bases its recommended exposure limits for EGBE on data from studies in animals. The data were adjusted to allow for uncertainties in the extrapolation from animals to humans. Because any effects of EGBEA are likely to occur after this compound is metabolized to EGBE, the same REL is recommended for EGBEA.

The National Institute for Occupational Safety and Health (NIOSH) therefore recommends that exposure to EGBE and EGBEA in the workplace be limited to 5 parts per million parts of air (5 ppm). Dermal contact is prohibited because EGBE and EGBEA are readily absorbed through the skin.

CONTENTS

ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
BAA	butoxyacetic acid
Cal OSHA	California Occupational Safety and Health Administration
CAS	Chemical Abstracts Service
cc	cubic centimeter
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CNS	central nervous system
EAA	ethoxyacetic acid
EC_{50}	concentration that allows 50% cell formation
EGBE	ethylene glycol monobutyl ether
EGBEA	ethylene glycol monobutyl ether acetate
EGEE	ethylene glycol monoethyl ether
EGEEA	ethylene glycol monoethyl ether acetate
FR	Federal Register
g.d.	gestation day
Hb	hemoglobin
Hct	hematocrit
i.v.	intravenous
kg	kilogram
L	liter
LC_{50}	lethal concentration for 50% of the exposed animals
LD_{50}	lethal dose for 50% of the exposed animals
L/min	liter per minute

LOAEL	lowest observable adverse effect level
m.a.c.	maximum allowable concentration
MCHb	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean cell volume
mg	milligram
mg/m^3	milligrams per cubic meter
mM	millimolar
mmol	millimole
MSDS	material safety data sheet
MSHA	Mine Safety and Health Administration
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
PEL	permissible exposure limit
ppm	parts per million parts of air
REL	recommended exposure limit
RBC	erythrocyte or red blood cell
RTECS	Registry of Toxic Effects of Chemical Substances
s.c.	subcutaneous
STEL	short-term exposure limit
TLV®	threshold limit value
TSCAPP	Toxic Substances Control Act Plant and Production
TWA	time-weighted average
UCC	Union Carbide Corporation

UDS	unscheduled DNA synthesis
µmol	micromole
USITC	United States International Trade Commission
W	watt
WBC	white blood cell

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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, Michigan 48214

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

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

Mr. Walter Lypka
Graphic Communications
International Union
1900 L Street, N.W.
Washington, D.C. 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, D.C. 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, Pennsylvania 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, D.C. 20037

Dr. Laura Welch
George Washington University
Department of Medicine,
Occupational Medicine Program
6th Floor
2150 Pennsylvania Avenue, N.W.
Washington, D.C. 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, Utah 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
Ohio 45433-6573

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

1 RECOMMENDATIONS FOR STANDARDS

The National Institute for Occupational Safety and Health (NIOSH) recommends that worker exposure to ethylene glycol monobutyl ether (EGBE) and ethylene glycol monobutyl ether acetate (EGBEA) be controlled in the workplace by complying with the provisions presented in Chapter 1 of this document. 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. Adherence to these recommendations should prevent or greatly reduce the risk of adverse effects on exposed workers.

Because environmental concentrations of contaminants vary from day to day, a time-weighted average (TWA) exposure that is below the NIOSH recommended exposure limit (REL) on a given day does not necessarily indicate that exposure on other days will also be below the REL. If a worker's TWA exposure during a workshift is one-half or more of the REL, it is probable that exposures will exceed the REL on other days. Therefore an "action level"* of one-half the REL should be adopted to ensure adequate protection of workers.

SECTION 1.1 RECOMMENDED EXPOSURE LIMITS FOR EGBE AND EGBEA

1.1.1 Exposure

Exposure to EGBE and EGBEA in the workplace shall be controlled so that workers are not exposed to concentrations greater than 5 parts per million parts of air (5 ppm) (24 mg EGBE/m^3 or 33 mg EGBEA/m^3).

Dermal contact shall be prohibited because EGBE and EGBEA are readily absorbed through the skin.

1.1.2 Sampling and Analysis

Workplace air samples shall be collected and analyzed for EGBE as described in the *NIOSH Manual of Analytical Methods*, Method No. 1403 [NIOSH 1984] (see Appendix A); this method may be adapted for EGBEA as well. OSHA Method No. 83 [OSHA 1990] is also recommended for sampling and analysis of EGBE and EGBEA.

*In this recommended standard for EGBE and EGBEA, the "action level" is the concentration at which exposure monitoring and medical monitoring should be initiated.

SECTION 1.2 EXPOSURE MONITORING

Exposure monitoring shall be conducted as specified in Sections 1.2.1, 1.2.2, and 1.2.3. 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 EGBE or EGBEA may occur, the employer shall conduct initial industrial hygiene surveys to determine their magnitude by using personal sampling techniques for an entire workshift. The employer shall keep records of these surveys. If the employer concludes that exposures to EGBE and EGBEA are below 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 EGBE and EGBEA. The employer shall also look for, evaluate, and record the potential for skin exposure.

1.2.2 Personal Monitoring

If workers are exposed to EGBE or EGBEA at or above the action level (one-half the REL), a program of personal monitoring shall be instituted to identify and measure or calculate the exposure of each worker occupationally exposed to airborne EGBE and EGBEA (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 EGBE and EGBEA 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 shall be collected to characterize each worker's exposure during each workshift (see Section 8.8). Although not all workers must be monitored, sufficient 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 deciding about sampling locations, times, and frequencies.

If a worker is found to be exposed to EGBE or EGBEA below the REL but at or above the action level, the exposure of that worker shall be monitored at least once every 6 months or as otherwise indicated by a professional industrial hygienist. If a worker is found to be exposed to EGBE or EGBEA above the REL, the worker must wear a respirator for protection until adequate engineering controls 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 shall be instituted; if concentrations of EGBE and EGBEA below the action level are noted after two semiannual consecutive surveys, sampling can be conducted annually.

1.2.3 Biological Monitoring

Measurement of urinary butoxyacetic acid (BAA), the metabolite of EGBE and EGBEA, may help characterize occupational EGBE and EGBEA exposures when the potential exists for airborne concentrations at the REL, or for skin contact from accidental exposure or breakdown of chemical protective clothing (see Section 8.6.1). Guidelines for biological monitoring are presented in Appendix D.

SECTION 1.3 MEDICAL MONITORING

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

- The requirements of the applicable standard
- An estimate of the worker's potential exposure to EGBE or EGBEA, including any available workplace sampling results
- 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 EGBE or EGBEA at or above the action level, or who have the potential for skin exposure.
- 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 without loss of pay or other cost to the workers, and at a reasonable time and place.

1.3.2 Preplacement Medical Examinations

Preplacement medical examinations shall include at least the following:

- A comprehensive medical and work history that emphasizes identification of existing medical conditions (e.g., those affecting the blood, 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 blood, hematopoietic and central nervous systems, skin, liver, and kidneys

- A judgment about 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 EGBE or EGBEA at or above the action level, and to workers with the potential for skin exposure. These examinations shall include at least the following:

- An update of medical and work histories
- A medical examination and tests giving special attention to the hematopoietic and central nervous systems, blood, skin, liver, and kidneys
- Urinary monitoring, which may serve as a useful adjunct to environmental monitoring because it indicates both airborne and dermal exposures (see Section 1.2.3)

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 EGBE or EGBEA 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 EGBE and EGBEA shall be posted in readily visible positions in work areas and at entrances to work areas or building enclosures where exposures may exceed the REL and where skin exposures may occur (see Figure 1-2).

If respirators and personal protective clothing are needed when there is the possibility of skin exposure and airborne exposure at or above the REL 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:

Respiratory Protection And Protective Clothing Required In This Area

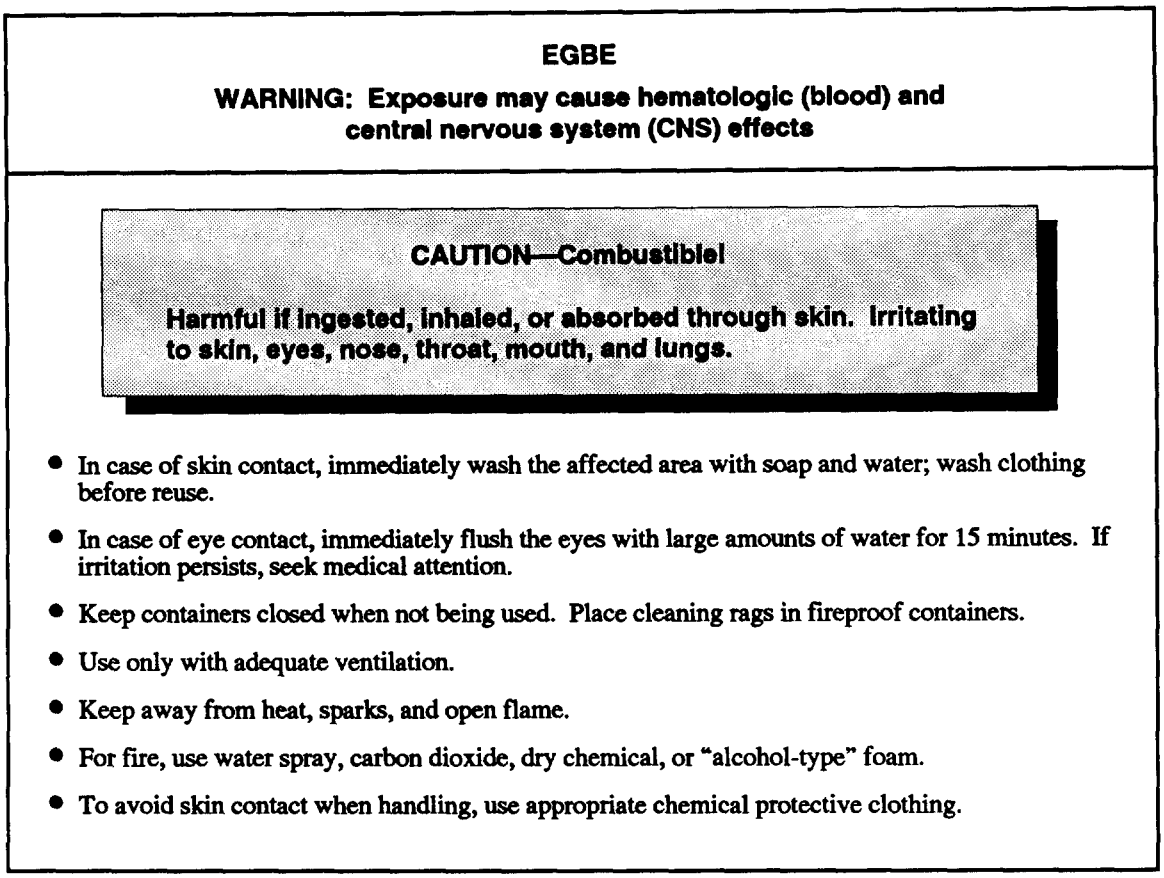

Figure 1–1. Example of a container label identifying the glycol ether and listing information about its effects on human health and emergency procedures.

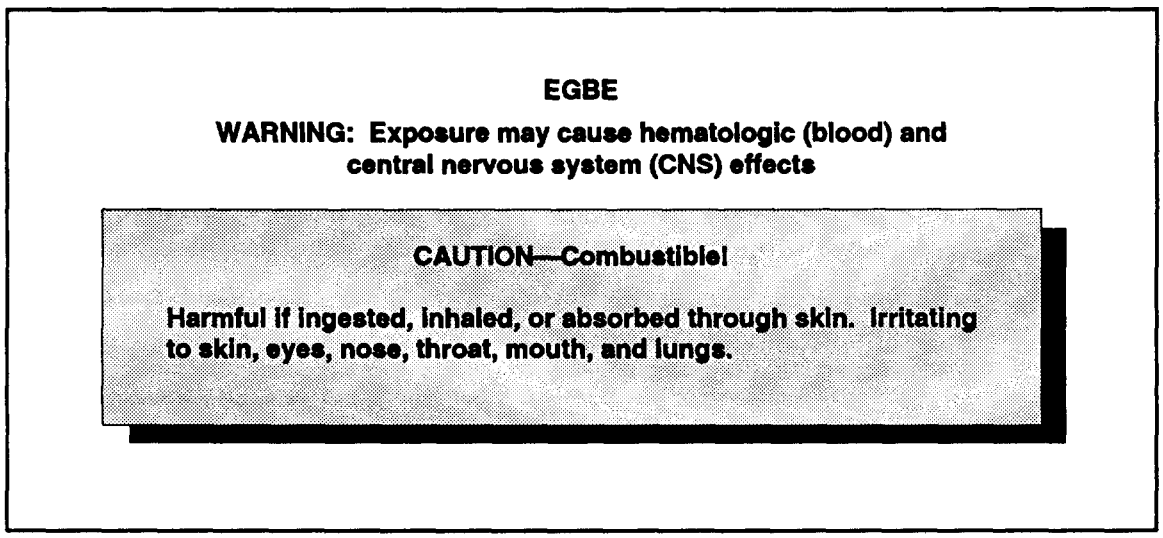

Figure 1–2. Example of a sign containing information about the health effects of EGBE .

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 EGBE and EGBEA below the REL and to prevent skin and eye contact. When protective clothing and equipment are needed, they shall be provided by the employer.

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 EGBE or EGBEA 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 skin exposure to EGBE or EGBEA 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 EGBE or EGBEA shall be cleaned before reuse. Anyone who handles contaminated clothing or is responsible for its cleaning shall be informed about the hazards of these glycol ethers and the proper precautions for their safe handling and use.

- The employer shall ensure that all personal protective clothing and equipment is inspected regularly and maintained in a clean and satisfactory working condition.

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 EGBE and EGBEA are presented in Tables 1-1 and 1-2, respectively.

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

Table 1-1.—NIOSH recommended respiratory protection for EGBE

Condition	Minimum respiratory protection*
50 ppm or less [10 × REL]	Any air-purifying respirator equipped with organic vapor cartridges,† or
	Any supplied-air respirator equipped with a half-mask†
125 ppm or less [25 × REL]	Any powered, air-purifying respirator equipped with a loose-fitting hood or helmet and an organic vapor cartridge or canister, or
	Any supplied-air respirator operated in a continuous-flow mode†
250 ppm or less [50 × REL]	Any air-purifying, full-facepiece respirator equipped with organic vapor cartridges or canister, or
	Any supplied-air respirator with a full facepiece, or
	Any self-contained breathing apparatus with a full facepiece, or
	Any powered, air-purifying respirator equipped with a tight-fitting facepiece and organic vapor cartridges or canister
700 ppm or less	Any supplied-air respirator equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode
Greater than 700 ppm	Any self-contained breathing apparatus equipped with a full facepiece and 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- or MSHA-approved equipment shall be used.
†If eye irritation occurs, a respirator equipped with full facepiece, helmet, or hood shall be used.

Table 1-2.—NIOSH recommended respiratory protection for EGBEA

Condition	Minimum respiratory protection*
50 ppm or less [10 × REL]	Any air-purifying respirator equipped with a half-mask†
125 ppm or less [25 × REL]	Any powered, air-purifying respirator equipped with an organic vapor cartridge or canister,† or
	Any supplied-air respirator equipped with a hood or helmet and operated in a continuous-flow mode
250 ppm or less [50 × REL]	Any supplied-air respirator with a full facepiece, or
	Any self-contained breathing apparatus with a full facepiece, or
	Any powered, air-purifying respirator equipped with a tight-fitting facepiece and organic vapor cartridges or canister
700 ppm or less	Any supplied-air respirator equipped with a full facepiece and operated in a pressure-demand or other positive-pressure mode
Greater than 700 ppm	Any 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- or MSHA-approved equipment shall be used.
†If eye irritation occurs, a respirator equipped with full facepiece, helmet, or hood shall be used.

- 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 medical status of the respirator user should be reviewed at least annually or as recommended by the physician responsible for the physical examination. See Appendix E for additional information on the medical aspects of wearing respirators.

- The employer shall be responsible for establishing and maintaining a respiratory protection program as summarized below:*

  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.

  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 on 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].

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

SECTION 1.6 INFORMING WORKERS ABOUT THE HAZARDS OF EGBE AND EGBEA

1.6.1 Hazard Communication

All workers who are assigned to areas where airborne exposures to EGBE or EGBEA are at or above the action level or who have the potential for skin exposure 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 EGBE and EGBEA. Workers shall be made aware of possible central nervous system (CNS) and hematologic effects of exposure to EGBE and EGBEA.

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 EGBE or EGBEA 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 the advantages of worker participation in these surveillance programs. The employer shall maintain a written plan of these training and surveillance 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 EGBE or EGBEA exposures may occur during spills or emergencies shall be trained in proper emergency and evacuation procedures.

1.6.3 File of Written Hazard Information

Required information shall be recorded on the material safety data sheet (MSDS) shown in Appendix B, 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 when needed to maintain exposure to airborne EGBE or EGBEA within the limits prescribed in Section 1.1.

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 EGBE or EGBEA 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 EGBE or EGBEA 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 EGBE or EGBEA.

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 EGBE and EGBEA are handled or used.
- Transportation and use of EGBE and EGBEA shall comply with all applicable local, State, and Federal regulations.
- EGBE and EGBEA 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.

- EGBE and EGBEA 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 EGBE and EGBEA containers and systems. Adequate ventilation shall be provided to minimize exposures of such workers to airborne EGBE or EGBEA.

- EGBE and EGBEA 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 EGBE and EGBEA 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 such as 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 EGBE or EGBEA shall be thoroughly ventilated, inspected, and tested for oxygen deficiency and for airborne concentrations of these compounds. Every effort shall be made to prevent the inadvertent release of hazardous amounts of EGBE or EGBEA into confined spaces where work is in progress. EGBE or EGBEA supply lines shall be disconnected or blocked off before such work begins.

- No worker shall enter a confined space without an entry large enough to admit a worker wearing 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 EGBE and EGBEA below the REL, to keep the concentration of other contaminants below toxic or dangerous levels, and to prevent oxygen deficiency.

- If the concentration of EGBE or EGBEA in the confined space exceeds the REL, 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 EGBE or EGBEA. 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 EGBE or EGBEA:

  — 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.

  — The EGBE and EGBEA shall be contained and absorbed with vermiculite, sand, or paper towels.

  — 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 pyrolyzed in a suitable combustion chamber.

  — Contaminated absorbent 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 EGBE or EGBEA is likely. If EGBE or

EGBEA 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 EGBE or EGBEA 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

EGBE and EGBEA 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 (U.S. Environmental Protection Agency), State, and local regulations, or it shall be disposed of in a licensed hazardous waste landfill.

SECTION 1.8 SANITATION AND HYGIENE

1.8.1 Food, Cosmetics, and Tobacco

The following shall be prohibited in areas where EGBE or EGBEA 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 EGBE or EGBEA—chemicals that may cause adverse hematologic (blood) and 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 local, State, and Federal regulations.

1.8.5 Showering and Changing Facilities

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

SECTION 1.9 RECORDKEEPING

1.9.1 Exposure Monitoring

The employer shall establish and maintain an accurate record of all exposure measurements required in Section 1.8 of this document. 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 of this document. Pertinent medical records (i.e., the physician's written statement, the results of medical examinations and tests, medical complaints, etc.) shall be retained in the medical files of all workers subject to airborne concentrations of EGBE or EGBEA in the workplace at or above the action level. 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 and 1.3 of this document for at least the following periods:

- 30 years for exposure monitoring records, and
- 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, upon request, 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

The employer shall comply with the requirements for the transfer of records as set forth in 29 CFR 1910.20(h), Transfer of Records.

2 INTRODUCTION

2.1 PURPOSE

This document presents the criteria and recommended standards necessary to prevent health impairment from exposure to EGBE and EGBEA—two solvents used primarily in surface coatings. The principal signs and symptoms of acute overexposure to these compounds are irritation of the eyes, nose, and throat; drowsiness; nausea; shaking; and weakness. Repeated exposure may damage the bone marrow, blood cells, kidneys, and liver. The document was developed in response to Section 20(a)(3) of the Occupational Safety and Health (OSH) Act of 1970 [29 USC 1900 (1970)]. In this act, NIOSH is charged with developing criteria for toxic materials and harmful physical agents to describe 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 the National Institute for Occupational Safety and Health (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 EGBE and EGBEA apply only to workplace exposures arising from the processing, manufacturing, handling, and use of EGBE and EGBEA. 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 EGBE and EGBEA. 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 assesses the hazards associated with occupational exposure to EGBE and EGBEA. Chapter 1 presents the recommended standard and describes its requirements. Chapter 3 gives information about the chemical and physical properties of EGBE and EGBEA, 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, 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

EGBE and EGBEA 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 (butyl) moiety and R_2 either H or acetate.

EGBE is also known as butyl Cellosolve®, 2-butoxyethanol (2-BE), Dowanol EB®, Jeffersol EB®, Ektasolve EB®, or butyl Oxitol®. The chemical formula for this organic compound is $C_4H_9OCH_2CH_2OH$. EGBE is a colorless liquid with a mild ether odor; the odor threshold is 0.10 ppm [Amoore and Hautala 1983]. This compound is miscible in water and is soluble in most organic solvents.

EGBEA, the acetate ester of EGBE, is also known as butyl Cellosolve® acetate, 2-butoxyethyl acetate (2-BEA), Ektasolve EB® acetate, or butyl glycol acetate. This organic compound has the chemical formula $C_4H_9OCH_2CH_2OCOCH_3$. EGBEA is a colorless liquid with a fruity odor [Sax and Lewis 1987]. The compound is only slightly soluble in water, but it is soluble in hydrocarbons and organic solvents. Other chemical and physical properties are listed in Table 3-1.

3.2 PRODUCTION METHODS AND USES

EGBE is usually produced by a reaction of ethylene oxide with butyl alcohol, but it may also be made by the direct alkylation of ethylene glycol with an agent such as dibutyl 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. EGBEA is prepared by esterifying EGBE with acetic acid, acetic acid anhydride, or acetic acid chloride.

EGBE is widely used as a solvent in surface coatings such as spray lacquers, quick-dry lacquers, enamels, varnishes, varnish removers, and latex paint [Leaf 1985; Sax and Lewis 1987]. In surface coatings, it imparts blush resistance, gloss, and good flow-out [Carpenter et al. 1956]. EGBE is also used as a coupling agent in metal cleaning formulas and household cleaners, as an intermediate in EGBEA production, and as a component in herbicides and automotive brake fluids [Leaf 1985]. Table 3-2 presents production figures for EGBE an EGBEA.

Table 3-1.—Chemical and physical properties of EGBE and EGBEA*

Property	EGBE	EGBEA
RTECS† accession number	KJ8575000	KJ8925000
CAS§ registry number	111-76-2	112-07-2
Molecular formula	$C_6H_{14}O_2$	$C_8H_{16}O_3$
Molecular weight	118.2	160.2
Specific gravity at 25°/4°C	0.898	0.940
Evaporation rate (butyl acetate = 1.00)	0.1	0.03
Boiling point (°C)	170.8	192.2
Freezing point (°C)	-77	-63.5
Vapor pressure (mm Hg at 25°C)	0.88	<0.98
Refractive index	1.417	1.414
Flash point (°C), closed cup	62	71
Autoignition temperature (°C)	238	340
Flammability limits (vol. % in air)	1.10-12.7	0.88-8.54
Water solubility (% by weight)	Miscible	1.5
Vapor density (air = 1)	4.1	5.5
ppm in saturated air (25°C)	1,200	<1,300
mg/m^3 at 25°C, 760 mm Hg**	4.83	6.55
ppm at 25°C, 760 mm Hg††	0.21	0.15

*Adapted from Rowe and Wolf [1982], UCC [1985], and NFPA [1987].
†Registry of Toxic Effects of Chemical Substances [NIOSH 1987c].
§Chemical Abstracts Service.
**Equals 1 ppm.
††Equals 1 mg/m^3.

Table 3-2.—U.S. production of EGBE and EGBEA*

Compound	Production (lb)	Latest year data was available
EGBE	302,979,000	1986
EGBEA	11,000,000	1977

*Source: TSCAPP [1977] and USITC [1986].

EGBEA is primarily used as a retarder solvent* for nitrocellulose lacquer and epoxy and acrylic enamels; it is also a film-coalescing aid for polyvinyl acetate latex, and it may be used in some ink and spot remover formulations [Leaf 1985; Sax and Lewis 1987].

3.3 NUMBER OF WORKERS POTENTIALLY EXPOSED

The National Occupational Exposure Survey (NOES) [NIOSH 1983] estimates that during the period 1981-83, 1,680,768 workers were occupationally exposed to EGBE and 123,911 workers were occupationally exposed to EGBEA. Among industries labeled by the four-digit Standard Industrial Code (SIC), 375 were identified as having workers potentially exposed to EGBE, and 104 were identified as having workers potentially exposed to EGBEA. NOES identified 222 occupations as having workers potentially exposed to EGBE, and 62 occupations as having workers potentially exposed to EGBEA. Table 3-3 presents the six industries and the six occupations with the most workers potentially exposed to EGBE and EGBEA.

Table 3-4 presents representative information about the occurrence of airborne EGBE or EGBEA in the workplace. The limited data collected at facilities in the United States indicate that most exposures to EGBE or EGBEA are below 7 ppm. The highest exposures for EGBE and EGBEA occurred at separate silk-screening facilities (see Table 3-4). In contrast to these data, EGBE exposures in a Belgian study of various industrial operations [Veulemans et al. 1987b] ranged from 0.04 to 367.2 ppm, and exposures to EGBEA ranged from 0.70 to 4.04 ppm (see Table 3-5).

*Retarder solvents are active, slow-evaporating solvents that ensure smooth film-forming and are generally used in concentrations of 1% to 5% in coating formulations.

Table 3–3.—Six industries and six occupations with the most workers potentially exposed to EGBE and EGBEA*

Compound and industry	Workers exposed		Compound and occupation	Workers exposed	
	Number	% of total		Number	% of total
EGBE:†			EGBE:†		
General medical and surgical hospitals	191,619	11.4	Janitors and cleaners	344,743	20.5
Building maintenance services	166,790	9.9	Printing machine operators	88,017	5.2
Commercial printing, lithographic	57,127	3.4	Machine operators, not specified	81,594	4.9
Gasoline service stations	35,126	2.1	Miscellaneous machine operators	56,698	3.4
Certificated air transportation	31,713	1.9	Painting and paint spraying machine operators	52,252	3.1
Electric services	31,457	1.87	Automobile mechanics	51,925	3.08
EGBEA:§			EGBEA:§		
Wood household furniture	14,864	12.0	Assemblers	17,558	14.2
Oil and gas field services	12,988	10.5	Painting and paint spraying machine operators	13,920	11.2
Heavy construction	5,341	4.3	Janitors and cleaners	12,529	10.1
Commercial printing, letterpress	5,147	4.2	Mining machine operators	8,072	6.5
Women's and misses' outerwear	4,442	3.6	Printing machine operators	6,054	4.9
Motor vehicles and car bodies	4,376	3.5	Secretaries	5,306	4.3

*Taken from NIOSH [1983].
†Total workers exposed to EGBE = 1,680,768.
§Total workers exposed to EGBE = 123,911.

Table 3–4.—Occupational exposures to EGBE and EGBEA by work site or process

Glycol ether	Work site or process	Reference	Number and type of samples	Concentration (ppm)	
				Range	Average
EGBE	Silk-screening	Boiano [1983]	6 BZ*	1.1–5.4	3.5
	Silk screeners	Baker et al. [1985]	16 BZ	†	6.8
	Spray painters	Baker et al [1985]	5 BZ	†	2.6
	Hospital housekeeping	Apol and Cone [1983]	4 BZ	ND§	ND
	Coating process	Bryant [1978]	4 area	ND	ND
	Printing	Apol [1981]	7 BZ	1–2	1.8
		Lewis and Thoburn [1981]	3 BZ	<0.04–0.5%	0.18
	Scrubbing of floor	Apol and Johnson [1979]	1 BZ	1.6	1.6
	Manufacture of electrical resistors	Gilles and Philblin [1976]	2 BZ	ND	ND
			2 area	ND	ND
EGBEA	Silk screening	Boiano et al. [1983]	6 BZ	0.8–3.9	2.5
	Printing	Salisbury [1983]	4 BZ	ND–0.8	0.3
			4 area	ND–0.5	0.2

*Breathing zone.
†Data not presented.
§None detected.

Table 3-5.—Concentration of EGBE and EGBEA measured in various industrial operations* (ppm)

Operation	EGBE		EGBEA	
	Geometric mean	Range	Geometric mean	Range
Printing	0.85	0.31-3.7	1.94	0.70-4.04
Painting	3.9	0.71-19.5	---	---
Car repair	1.23	---	---	---
Miscellaneous	1.77	0.04-367.2†	1.62	1.36-1.8

*Table adapted from Veulemans et al. [1987b].
†Concentration recorded in a mirror-manufacturing plant.

4 EFFECTS OF EXPOSURE

4.1 EFFECTS ON HUMANS

4.1.1 Case Studies

A case of severe poisoning from massive ingestion of EGBE has been described by Rambourg-Schepens et al. [1988]. In a suicide attempt, a 50-year-old woman ingested 250 to 500 ml of a window cleaner containing 12% EGBE. When admitted to the hospital 12 hr later, the woman was comatose with no response to painful stimuli; she ventilated poorly and was placed under mechanical ventilation. Metabolic acidosis, hypokalemia (an abnormally small amount of potassium in the blood), a rise in serum creatinine level, hemoglobinuria, and oxaluria were observed. The hemoglobinuria was paralleled by a progressive erythropenia (a deficiency in the number of red blood cells). The clinical status of the woman improved gradually, and she was discharged on the 10th day.

Gijsenbergh et al. [1989] described a suicide attempt by a 23-year-old woman who ingested about 500 ml of a window-cleaning agent that contained EGBE and a small quantity of alcohol (the percentage of each compound was not presented). When admitted to the hospital 1 hr after ingesting the substance, the woman was comatose and suffering from hypotension. She subsequently developed severe metabolic acidosis. Routine laboratory blood examination revealed no abnormalities. The woman recovered after forced diuresis and hemodialysis.

NIOSH conducted a health hazard evaluation in 1983 to evaluate worker exposure to two solvent cleaners—an image remover and a paint remover used in a silk screening process [Boiano 1983]. A silk screener using the image remover was monitored for exposure to ethylene glycol monoethyl ether acetate (EGEEA) and cyclohexanone, and a worker using the paint remover was monitored for a variety of organic solvents, one of which was EGBEA. Although the workers were primarily exposed by inhalation, they also may have been exposed by skin absorption because personal protective equipment was not always worn. The workers complained of headaches, lethargy, sinus problems, nausea, and heartburn. When the workers were away from work, their symptoms improved. Measurement of the silk screener's airborne exposures to EGBEA indicated that the TWA exposures ranged from 0.8 to 3.9 ppm, with a short-term excursion to 5.3 ppm; however, absorption through the skin may have contributed to the workers' overall exposure. Boiano [1983] concluded that a health hazard from exposures to airborne solvent mixtures did not exist at this facility.

4.1.2 Experimental Exposure

Two men and six rats were exposed simultaneously in a 1,250-cubic-ft room to 113 ppm EGBE for 4 hr [Carpenter et al. 1956]. Symptoms of the men included nasal and eye irritation, disagreeable metallic taste, occasional belching, and a slight increase in nasal mucous discharge. Although erythrocyte osmotic fragility did not change for the men, it rose appreciably for the rats.

In a second experiment about a year later, the same two men and one woman were exposed to 195 ppm EGBE for two 4-hr periods, separated by a 30-min recess for lunch [Carpenter et al. 1956]. Exposure took place in a 6 1/2-ft cube (7,900 liters). The responses of all three subjects included immediate irritation of the nose and throat, followed by eye irritation and disturbed taste. The woman also developed a headache that lasted about 24 hr. Erythrocyte osmotic fragility did not change. However, increased osmotic fragility was found in vitro with the human erythrocytes. Therefore, increased osmotic fragility would be expected after inhalation of EGBE at concentrations higher than 200 ppm (approximate). Erythrocyte osmotic fragility increased steadily in three female rats concurrently exposed. Concentrations of butoxyacetic acid (BAA), demonstrated as a metabolite of EGBE (see Section 4.2), were determined in urine samples collected during the 24-hr period following exposure. The woman and one of the men excreted considerable amounts of BAA (300 mg and 175 mg, respectively) in the 24-hr period following exposure, but the other man excreted only trace amounts of the metabolite. The three subjects agreed that 195 ppm EGBE caused discomfort when breathed continually.

In a third study, four subjects—two men and two women (including the man who had participated in the second study and had excreted only trace amounts of BAA)—were exposed to 100 ppm EGBE for 8 hr. Following this exposure, all four subjects excreted significant amounts of BAA in their urine (75 to 250 mg). Other effects of exposure included vomiting and headaches; there was no effect on the osmotic fragility of erythrocytes [Carpenter et al. 1956].

4.2 METABOLISM, UPTAKE, AND ELIMINATION

4.2.1 Research Studies

Carpenter et al. [1956] postulated that EGBE is oxidized to BAA in mammals. The authors verified this postulate with the identification of BAA in the urine of various animal species (dog, rabbit, rat, and guinea pig) exposed to EGBE vapor. The data (excluding that on the dogs) suggested that a correlation existed between the EGBE vapor concentration and urinary BAA [Carpenter et al. 1956]. Although BAA was not identified in the blood of the dogs, rats, or guinea pigs, it was found in the blood of the rabbits 4 hr after i.v. administration of EGBE, and in the urine collected during the 24 hr after injection. The authors [Carpenter et al. 1956] suggested that EGBE was present in the blood at a concentration too low for detection by the analytical method used.

Jonsson and Steen [1978] exposed male albino rats to 414 ppm EGBE for 1 hr, and then collected urine for 20 hr. Gas chromatographic analysis of organic acids in urine after EGBE exposure was conducted. Gas chromatography retention time and mass spectrum of the EGBE metabolite were the same as that of synthetic BAA.

Johanson et al. [1986] exposed seven male volunteers to 20 ppm EGBE for 2 hr during light physical exercise on a bicycle ergometer. Expired air was collected at regular time intervals to estimate respiratory uptake of EGBE. Blood and urine samples were collected and analyzed for EGBE and BAA. The respiratory uptake of EGBE averaged 57% of the inspired amount. The concentration of EGBE in the blood reached a plateau of 7.4 micromoles (μmol)/liter (1 ppm volume/volume) within 1 to 2 hr and could no longer be detected in the blood 2 to 4 hr after exposure. The elimination half-time was 40 min, mean residence time was 42 min, total blood clearance time was 1.2 liters/min, and steady-state volume of distribution was 54 liters. Less than 0.03% of the total uptake of EGBE was excreted in the urine, whereas urinary excretion as BAA ranged from 17% to 55%.

Johanson et al. [1988] studied the percutaneous uptake of EGBE in five healthy males (see Section 5.4.5.1). The subjects kept two or four fingers immersed in undiluted EGBE for 2 hr. Blood samples were collected from the unexposed hand before, during, and up to 4 hr after the EGBE-exposure and analyzed for EGBE by gas chromatography. Urine samples were collected for 24 hr and analyzed for BAA by gas chromatography. The authors concluded that detection of EGBE in the blood of all subjects was indicative of systemic uptake of EGBE through the skin in vivo. The percutaneous uptake varied from 127 to 1,891 μmol/subject. The acid metabolite BAA was found in the urine. Urinary excretion peaked 3 hr after exposure and then declined with an average half-life of 3.1 hr. The accumulated excretion of BAA ranged from 8.7 to 313 μmol, corresponding to 2.5% to 39% of the uptake. The authors concluded that their study clearly showed that EGBE is absorbed through human skin in vivo and enters the systemic circulation. A comparison of dermal uptake rate with inhalatory uptake suggested that both skin and respiratory uptake should be considered when workers are exposed to EGBE. Both studies by Johanson et al. [1986, 1988] are assessed and discussed under biological monitoring in Section 5.4.

A lack of data exists concerning the metabolism of EGBEA. However, reports in the literature have identified ethoxyacetic acid (EAA) as the metabolite of both ethylene glycol monoethyl ether (EGEE) and its acetate (EGEEA) [Jonsson et al. 1982; Cheever et al. 1984; Groeseneken et al. 1986c; Groeseneken et al. 1987a]. The findings confirmed that EGEEA is first converted to EGEE by hydrolysis of the ester moiety [Elam 1980] and then passes through the same pathway as EGEE to EAA. By analogy to EGEE and EGEEA, it is reasonable to assume that EGBEA is first hydrolyzed to EGBE and then oxidized to BAA [Carpenter et al. 1956; Jonsson and Steen 1978].

4.2.2 Summary of Studies on Metabolism, Uptake, and Elimination

Carpenter et al. [1956] identified BAA in the urine of various animal species exposed to EGBE vapor. Analysis of organic acids in urine after EGBE exposure of rats revealed the presence of BAA [Jonsson and Steen 1978].

Exposure of male volunteers to EGBE vapors during light physical exercise resulted in 57% respiratory uptake of inspired EGBE [Johanson et al. 1986]. Less than 0.03% of the total uptake of EGBE was excreted unchanged in urine, and urinary BAA excretion ranged from 17% to 55% of the EGBE absorbed. Percutaneous exposure of male volunteers to EGBE resulted in systemic uptake of EGBE through the skin in vivo, and BAA was found in the urine [Johanson et al. 1988]. A comparison of dermal and respiratory uptake suggested that both routes of exposure should be considered when workers are exposed to EGBE [Johanson et al. 1988].

The metabolite of EGBEA has not been identified. However, by analogy to EGEEA, which is converted to EGEE and then to EAA [Jonsson et al. 1982; Cheever et al. 1984; Groeseneken et al. 1986c; Groeseneken et al. 1987a], it is logical to assume that EGBEA is metabolized to EGBE and then to BAA.

4.3 EFFECTS ON ANIMALS

Kidney, hematologic, and central nervous system (CNS) effects have been observed in experimental animals exposed to EGBE and EGBEA.

4.3.1 Acute Toxicity

Many experiments have been performed to investigate the acute toxicity of glycol ethers in animals. These investigations have 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, and injection). A summary of the available data by animal species is presented in Table 4-1, and more detailed information is given in Table 4-2.

4.3.1.1 Oral Administration

When rabbits were dosed by a single gavage with 890 or 1,780 mg EGBE/kg, death occurred within 30 or 22 hr [Gross 1943]. Sluggishness, ruffling of coats, prostration, and narcosis occurred after oral administration of lethal concentrations of EGBE to male and female rats (2,400 and 2,500 mg/kg, respectively) [Carpenter et al. 1956]. Necropsies revealed congested or hemorrhaged lungs, mottled livers, congested kidneys, and hemoglobinuria. When EGBEA was administered by gastric intubation to male and female Wistar rats (3,000 and 2,400 mg/kg, respectively), hypertrophic and bloody kidneys were observed at necropsy [Truhaut et al. 1979].

4.3.1.2 Inhalation Exposure

Werner et al. [1943c] demonstrated an adverse effect of EGBE on the hematopoietic system. Single 7-hr exposures of White-Swiss mice to EGBE (390 to 1,210 ppm) caused marked follicular phagocytosis in the spleen, congestion of the cavernous veins of the spleen, and hemoglobinuria. The usual sign of toxic action was dyspnea.

Table 4–1.—Lethal doses or concentrations of glycol ethers*

Species and sex	LD_{50}* oral (mg/kg)		EGBE LD_{50} i.v. (mg/kg)	LD_{50} dermal (mg/kg)		LC_{50}* inhalation (ppm)	
	EGBE	EGBEA		EGBE	EGBEA	EGBE	EGBEA
Rat:							
Male	2,400	3,000	---	---	---	486 (4 hr)	---
	---	7,000	---	---	---	---	---
Female	2,500	2,400	---	---	---	450 (4 hr)	---
Unspecified	---	---	380	---	---	---	---
Rabbit:							
Male	320	---	---	404 to 502	1,500	---	---
Unspecified	---	---	500	---	1,500	---	---
Guinea pig:							
Male and female	1,200	---	---	---	---	---	---
Mouse:							
Male	1,200	---	---	---	---	---	---
Female	---	---	---	---	---	---	---
Unspecified	---	---	1,100	---	---	700 (7 hr)	---

*Abbreviations: LD_{50} = mean lethal dose; LC_{50} = mean lethal concentration.

Table 4–2.—Acute toxicity of EGBE and EGBEA

Species	Route of administration and dose	Observed effects	Compound studied and reference
			EGBE:
Rat	Tail vein injection: LD_{50},* 380 mg/kg	Death	Carpenter et al. 1956
Mouse	Tail vein injection: LD_{50}, 1,100 mg/kg	Death	Carpenter et al. 1956
Rabbit	Ear vein injection: LD_{50}, 500 mg/kg	Death	Carpenter et al. 1956
Rabbit	Subcutaneous:		Gross 1943
	180 mg/kg	Kidney inflammation	
	360 mg/kg	Death	
	2,700 mg/kg	Respiratory paralysis, death	
Cat	Subcutaneous: 1,800 mg/kg	Kidney injury, death	Gross 1943
Rabbit	Oral: 900 or 1,800 mg/kg	Death	Gross 1943
Rabbit	Oral: LD_{50}, 320 mg/kg	Death	Carpenter et al. 1956
Mouse	Oral: LD_{50}, 1,200 mg/kg	Death	Carpenter et al. 1956
Guinea pig	Oral: LD_{50}, 1,200 mg/kg	Death	Carpenter et al. 1956
Rat (M)	Oral: LD_{50}, 2,400 mg/kg	Congested lungs and kidneys, hemoglobinuria, mottled livers	Carpenter et al. 1956
Rat (F)	Oral: LD_{50}, 2,500 mg/kg	Congested lungs and kidneys, hemoglobinuria, mottled livers	Carpenter et al. 1956

(Continued)

*Abbreviations: LC_{50} = mean lethal concentration; LD_{50} = mean lethal dose.

Table 4–2 (Continued).—Acute toxicity of EGBE and EGBEA

Species	Route of administration and dose	Observed effects	Compound studied and reference
			EGBE:
Cat	Inhalation: 518 ppm, 8 hr/day for 8 or 9 days	Death, kidney inflammation	Gross 1943
Guinea pig	Inhalation: 518 ppm, 8 hr/day for 8 or 9 days	Death, kidney inflammation	Gross 1943
Mouse	Inhalation: LC_{50}*, 700 ppm for 7 hr	Hemoglobinuria, splenic lesions	Werner et al. 1943c
Rat (M)	Inhalation: LC_{50}, 486 ppm for 4 hr	Enlarged kidneys, blood in bladders	Dodd et al. 1983
Rat (F)	Inhalation: LC_{50}, 450 ppm for 4 hr	Enlarged kidneys, blood in bladders	Dodd et al. 1983
Rabbit	Dermal: LD_{50}, 404 to 502 mg/kg	Congested kidneys, hemoglobinuria, pale livers, enlarged spleens	Carpenter et al. 1956
			EGBEA:
Rat (M)	Oral: LD_{50}, 7,000 mg/kg	Death	Smyth et al. 1962
Rat (M)	Oral: LD_{50}, 3,000 mg/kg ± 300 mg/kg	Bloody and hypertrophic kidneys	Truhaut et al. 1979
Rat (F)	Oral: LD_{50}, 2,400 mg/kg ± 200 mg/kg	Bloody and hypertrophic kidneys	Truhaut et al. 1979
Rabbit (M)	Dermal: LD_{50}, 1,500 mg/kg	Death	Smyth et al. 1962
Rabbit	Dermal: LD_{50}, 1,500 mg/kg	Bloody and hypertrophic kidneys	Truhaut et al. 1979

Inhalation exposures of groups of female rats to 62 ppm EGBE for 4 hr resulted in increased osmotic fragility of rat erythrocytes [Carpenter et al. 1956].

Single 4-hr exposures of male and female Fischer 344 rats to EGBE (486 ppm and 450 ppm, respectively) caused hematuria; enlarged and discolored kidneys were observed at autopsy [Dodd et al. 1983].

4.3.1.3. Dermal Exposure

The percutaneous toxicity of EGBE and EGBEA has been investigated in the rabbit [Carpenter et al. 1956; Truhaut et al. 1979]. Toxic effects on the kidneys were seen consistently. Male albino New Zealand rabbits were immobilized during 24 hr of skin contact with undiluted EGBE (0.48 to 0.64 ml/kg); they were observed for 14 days thereafter [Carpenter et al. 1956]. Autopsy of the rabbits revealed congestion of the kidneys, hemoglobinuria, pale livers, and engorged spleens. Truhaut et al. [1979] exposed rabbits to 7.5 to 23.5 g EGBEA/kg for 24 hr using an occluded bandage technique. Bloody kidneys were found at necropsy; histologic examination revealed necrotizing, hemorrhagic, atrophic, acute, tubular nephrosis with occasional glomerular lesions.

4.3.1.4 Subcutaneous Administration

Gross [1943] administered single subcutaneous (s.c.) injections of varying doses of EGBE to 13 rabbits. At 180 mg/kg, a slight, temporary, kidney inflammation was noted. Doses of 360 to 1,800 mg/kg caused death within 20 to 72 hr from kidney inflammation, and a dose of 2,700 mg/kg caused death within 2 hr from respiratory paralysis. A cat injected s.c. with 900 mg EGBE/kg did not show signs of illness; a second cat received 1,800 mg EGBE/kg s.c. and died 3 days later with signs of kidney injury.

4.3.1.5 Summary of Acute Toxicity

The acute toxicity of EGBE and EGBEA has been investigated in a number of experiments with a variety of species and routes of exposure. Animals exhibited inactivity, weakness, and dyspnea. Autopsies revealed congested lungs and kidneys [Carpenter et al. 1956; Truhaut et al. 1979]. The principal effect exerted by these compounds was damage to the kidneys [Gross 1943; Dodd et al. 1983], which included extreme tubular necrosis and degeneration. Additional adverse effects included increased osmotic fragility of erythrocytes and damaged spleens [Werner et al. 1943c; Carpenter et al. 1956; Truhaut et al. 1979]. The acute toxic effects of EGBE and EGBEA are summarized in Table 4-2.

4.3.2 Hematologic Effects

EGBE and EGBEA have been shown to have adverse hematologic effects. These effects include increased osmotic fragility and decreased levels of hemoglobin (Hb), hematocrit (Hct), platelets, red blood cells (RBCs), white blood cells (WBCs), and mean cell volume (MCV).

In an early investigation [von Oettingen and Jirouche 1931], the hemolytic action of EGBE was studied by adding 1 cc of EGBE to 5-cc suspensions of dog or beef blood corpuscles in Ringer solution. The investigators reported that hemolysis occurred in the presence of EGBE.

4.3.2.1 Oral Administration

In a study by Nagano et al. [1979], male JCL-ICR mice were treated orally with 500 or 1,000 mg EGBE/kg per day, 5 days/wk for 5 wk. Although EGBE exerted no effect on WBC counts, MCV, or Hb levels, it significantly reduced RBC counts at doses of both 500 mg EGBE/kg per day ($P<0.05$) and 1,000 mg EGBE/kg per day ($P<0.01$).

EGBE-induced hematotoxicity in rats is age-dependent, with older rats more susceptible to EGBE treatment than young rats [Ghanayem et al. 1987]. EGBE (0, 125, or 500 mg/kg) was administered orally to young (4- to 5-week-old) and adult (9- to 13-week-old) male F344 rats (≥5 rats/group). No significant hematologic effects were observed in the younger rats at any time intervals (2, 4, 8, 24, and 48 hr) investigated in the group receiving 125 mg EGBE/kg. However, a significant decrease ($P\leq0.05$) in RBCs, Hct, and Hb was detected in the adult rats 8 and 24 hr after oral administration of 125 mg EGBE/kg. Free Hb concentrations in plasma were significantly increased ($P\leq0.05$) in adult rats 8 hr after oral administration of 125 mg EGBE/kg; there was no effect on free Hb concentrations in plasma of young rats. Twenty-four hours after dosing, free Hb concentrations in plasma of older rats were comparable with those in untreated control rats [Ghanayem et al. 1987].

Decreases in RBCs, Hb, and Hct were accompanied by a significant ($P\leq0.05$) dose-dependent increase in the free Hb concentrations of both age groups treated with 500 mg EGBE/kg [Ghanayem et al. 1987]. The authors state that a gradual recovery from hematotoxicity was observed after 48 hr in both of these groups.

Hemoglobinuria secondary to the hemolytic effect of EGBE was also observed. Table 4-3 demonstrates the incidence of hemoglobinuria in rats of various ages treated orally with various doses of EGBE.

Table 4-3.—Incidence of hemoglobinuria in rats of various ages administered EGBE by gavage*

	Dose (mg EGBE/kg)†				
Age of rats	**32**	**63**	**125**	**250**	**500**
4-5 wk	0/6	0/6	1/11	6/6	12/12
9-13 wk	0/6	0/6	12/12	6/6	12/12
5-6 mo	0/6	6/6	6/6	ND§	ND
16 mo	6/6	6/6	6/6	ND	ND

*Adapted from Ghanayem et al. [1987].
†EGBE was administered in water at a dose volume of 5 ml/kg.
§Not done.

A 100% incidence of hemoglobinuria was detected in 16-month-old rats treated with 32 mg EGBE/kg, but no effect was observed in rats younger than 16 months treated with the same dosage. A dose of 125 mg EGBE/kg caused 100% incidence of hemoglobinuria in all rats older than 4 to 5 weeks and a 9% incidence in 4- to 5-wk-old rats.

Histopathologic evaluation of tissues from rats of various ages examined 24 hr after EGBE administration demonstrated that EGBE caused dose- and age-dependent liver and kidney changes. These histopathologic changes exhibited signs of regression when examined 48 hr after EGBE-dosing.

The results presented in this report clearly demonstrate that a direct relationship exists between toxicity of EGBE and the age of the rats [Ghanayem et al. 1987]. Older rats are more susceptible than younger rats to hematotoxicity and liver/kidney damage caused by EGBE. Severe acute hemolytic anemia was evidenced by a decrease in circulating RBCs, an increase in the concentration of free Hb in plasma, and the development of hemoglobinuria. Ghanayem et al. [1987] state that the greater susceptibility of older rats to EGBE-induced toxicity may be caused by (1) a longer half-life of its metabolite butoxyacetic acid (BAA) in older rats compared with younger rats and (2) an enhanced ability of younger rats to degrade BAA to CO_2 and/or excrete BAA in the urine.

Grant et al. [1985] exposed male F344 rats (24 per group) orally to 500 or 1,000 mg EGBE/kg per day for 4 consecutive days. Six animals from each group were bled from a lateral caudal vein and then sacrificed and necropsied 1, 4, 8, and 22 days after the last EGBE treatment. EGBE caused pronounced dose-dependent effects on circulating RBCs and WBCs. Reduced erythrocyte counts, reduced Hct and Hb levels, and elevated MCV, reticulocyte counts, and mean cell hemoglobin concentration (MCHC) ($P<0.001$) were noted at the end of treatment in animals dosed with 1,000 mg EGBE/kg per day. Most of these alterations in the RBCs disappeared over the 22-day recovery period, although the MCV and MCHC values were slightly elevated at day 22. In the high-dose EGBE group (1,000 mg/kg per day), leukocyte counts were also depressed on day 1 ($P<0.001$); this was principally because of reduced numbers of circulating lymphocytes. Although the leukocyte numbers gradually increased, they did not reach control levels by the end of the recovery period. These effects on RBCs and WBCs were also observed in the group receiving 500 mg EGBE/kg per day, although the severity of the changes was less marked.

EGBE was administered by gavage to groups of 10 male rats at doses of 0, 222, 443, or 885 mg/kg per day, 5 days/wk for 6 wk [Krasavage 1986]. At termination, the animals were sacrificed and blood was collected for hematologic and serum chemistry determinations. During the treatment period, two rats in the high-dose group and one rat in the intermediate dose group died. All the other animals survived to termination. The principal effect of EGBE was on the RBC. Hb and RBC levels were significantly reduced at all doses ($P\leq0.05$), and MCHC was statistically lower ($P<0.05$) than the control at the high and intermediate doses. Statistically significant increases were noted for mean cell hemoglobin (MCHb) at all doses and for MCV at the high and intermediate doses. Hct and WBC counts were unaffected.

4.3.2.2 Inhalation

In two separate inhalation studies, Wistar-derived rats [Werner et al. 1943a] and dogs of an unspecified strain [Werner et al. 1943b] were exposed to EGBE, and the effects on hematologic parameters were examined. In the rat study, 23 animals per group were exposed to 0, 135, or 320 ppm EGBE for 7 hr/day, 5 days per wk over a 5-wk period; the animals were sacrificed 3 wk after termination of exposure. Hematologic examinations were made before, during, and after the 5 wk of exposure; they consisted of RBC and WBC counts, differential counts, reticulocyte counts, and Hb estimations. No statistical analysis was presented. The authors [Werner et al. 1943a] concluded that exposure of rats to 320 ppm EGBE resulted in an increased percentage of circulating immature granulocytes, a decrease in Hb concentration and RBC count, and an increase in the reticulocyte count. These hematologic changes were not severe and were reversed 3 wk after discontinuing exposure. There was no effect on the WBC population.

In the second inhalation study [Werner et al. 1943b], groups of 2 dogs were exposed to 0 or 415 ppm EGBE for 7 hr/day, 5 days/wk during a 12-wk period. Animals were sacrificed 5 wk after discontinuing exposure. Hematologic determinations were again made before, during, and after the exposure period. No statistical analysis was presented. The authors [Werner et al. 1943b] concluded that exposure of dogs to EGBE vapors resulted in (1) decreased Hb concentration and RBC count, and (2) increased hypochromia, polychromatophilia, and microcystosis, as shown by the RBC. These hematologic changes were not severe and were reversed 5 wk after exposure ceased [Werner et al. 1943b].

Carpenter et al. [1956] also studied the hemolytic effects exerted by the inhalation of EGBE vapors on various animal species. No statistical evaluations were presented. Exposure to 62 ppm EGBE for 4 hr caused significant osmotic fragility of erythrocytes in six female Carworth-Wistar rats. Groups of 15 rats of both sexes and 10 male guinea pigs (strains not specified) inhaled various concentrations of EGBE, 7 hr/day, 5 days/wk for 30 days. Erythrocyte osmotic fragility was found in rats immediately after a single 7-hr exposure to 107 ppm or higher (203, 314, or 432 ppm EGBE) and after 30 daily 7-hr exposures to 54 ppm EGBE. Osmotic fragility values for females usually exceeded those for the males. In almost all cases, these high fragility values returned to normal after the rats rested overnight. No effect was exerted on the osmotic fragility of guinea pig erythrocytes at the concentrations tested (54, 107, 203, 376, or 494 ppm EGBE). The authors [Carpenter et al. 1956] also exposed groups of 10 male C_3H mice to 100, 200, or 400 ppm EGBE for 7 hr/day over 30-, 60-, or 90-day periods. Increased erythrocyte osmotic fragility occurred at all concentrations. The increase was as great after the first exposure as it was after the 89th exposure. In all instances, erythrocyte osmotic fragility was normal after a 17-hr rest.

Repeated exposure of one male and one female basenji dog to 385 ppm EGBE caused increased RBC osmotic fragility in both dogs, but a significant reduction in RBC count and Hb level occurred only in the male [Carpenter et al. 1956]. The female dog died after eight exposures. When one male and one female basenji from the same litter were exposed to 200 ppm EGBE for 7 hr/day over a 31-day period, RBC osmotic fragility increased slightly in both dogs. WBC counts doubled in the male, and the RBC count and Hb level fell slightly

in the female. When one male and one female wire-haired terrier from the same litter were exposed to 100 ppm EGBE for 7 hr/day over a 90-day period, a transitory doubling of WBC counts occurred in both dogs midway in the 90-day period. At the end of the exposure period, the female's WBC count returned to the preexposure level, but the male's remained 50% higher. The Hct level of the male also dropped by 8.5%.

In another part of the study by Carpenter et al. [1956], two monkeys were exposed to 100 ppm EGBE for 7 hr/day, 5 days/wk over a 90-day period. RBC osmotic fragility rose on several occasions, higher in the female than in the male, but returned to normal at the end of the exposure period. RBC counts also fell briefly but returned to normal. In addition, a rhesus monkey inhaled 210 ppm EGBE for 7 hr/day, 5 days/wk over a 30-day period. RBC osmotic fragility rose after the fourth exposure but returned to normal overnight. At the end of the exposure period, the RBC count and Hb level had been reduced to one-half the initial values.

Dodd et al. [1983] conducted inhalation studies with Fischer 344 rats of both sexes. In these studies, 8 animals per group were exposed to 0, 20, 86, or 245 ppm EGBE during a 9-day period, or 16 animals per group were exposed to 0, 5, 25, or 77 ppm EGBE during a 90-day period. For the 9-day study, the rats were exposed for 6 hr/day during 5 consecutive days, followed by 2 days of nonexposure and 4 consecutive days of exposure. For the 90-day study, rats were exposed for 6 hr/day, 5 days/wk over a 13-wk period. All blood samples for hematologic measurements were obtained on the day before sacrifice.

In the 9-day study, both sexes of the group exposed to 245 ppm EGBE had significantly depressed RBC counts ($P<0.001$), Hb levels ($P<0.001$), and MCHC ($P<0.01$). These rats also had a significant increase ($P<0.001$ in all cases) in MCV, nucleated RBC, reticulocytes, and (in males only) lymphocytes ($P<0.001$). Following a 14-day postexposure period, a substantial recovery of the affected erythroid parameters was observed; however, statistically significant differences from controls were still present for the males (i.e., RBC count [$P<0.01$], MCV [$P<0.001$], and MCHb [$P<0.001$]). During the 14-day postexposure recovery period, the WBC count, which had been elevated ($P<0.001$) in males, returned to control values. There was a significant but less profound effect on erythroid parameters in both sexes of the group exposed to 86 ppm EGBE. In male rats, Hb concentration was reduced relative to that of the controls ($P<0.01$); in female rats, Hb concentration ($P<0.001$) and MCHC ($P<0.01$) were reduced, and Hct ($P<0.01$) and MCV ($P<0.05$) were increased.

In the 90-day study, after 6 wk of the exposure regimen, the authors concluded that the female rats exposed to 77 ppm EGBE had slight but statistically significant decreases in RBC counts ($P<0.01$) and Hb levels (statistics not reported) accompanied by an increase in MCHb 11% above the values for controls ($P<0.001$). At the end of the study, these effects had either decreased or returned to the ranges of the control values. The only significant hematologic finding for male rats in the group exposed to 77 ppm EGBE was a 5% decrease in RBC count after 66 EGBE exposures (statistics not given).

In a later study by Tyl et al. [1984], Fischer 344 rats and New Zealand white rabbits were exposed to EGBE vapors (25 to 200 ppm) on g.d. 6 through 15 (rats) or 6 through 18 (rabbits).

Blood samples were collected before sacrifice. Hematologic determinations in rats exposed to EGBE indicated no alterations in RBC osmotic fragility, but there were significant reductions in RBC count, and significant increases in Hb and Hct at 200 ppm ($P<0.001$). RBC count was also reduced at 100 ppm ($P<0.001$). In rats exposed to 100 and 200 ppm EGBE, MCV and MCHb were significantly increased relative to those of the controls ($P<0.001$). In addition, the MCHC was reduced significantly at 100 ppm EGBE ($P<0.01$) and 200 ppm EGBE ($P<0.001$) relative to that of the controls. Hematologic determinations in rabbits exposed to EGBE revealed no apparent exposure-related effects. Statistically significant increases in Hb concentration and Hct were observed at 100 ppm ($P<0.01$) but not at 200 ppm EGBE.

Truhaut et al. [1979] carried out inhalation studies of EGBEA using groups of 10 Wistar rats of both sexes and 4 New Zealand rabbits, two of each sex. Exposure of rats and rabbits to 400 ppm EGBEA for 4 hr resulted in slight and transient hemoglobinuria and/or hematuria only in rabbits, but this effect did not last more than 24 to 48 hr. Exposure of rats (10 male and 10 female) and rabbits (2 male and 2 female) to 400 ppm EGBEA for 4 hr/day, 5 days/wk over a 1-month period resulted in hemoglobinuria and/or hematuria (slight in rats, more pronounced in rabbits) from the second week of exposure onward. RBC counts and Hb concentrations were normal during the first 3 weeks, then decreased slightly in two of four rabbits, and severely in the two others. These latter two rabbits died during the fourth week. Administration of 100 ppm EGBEA for 4 hr/day, 5 days/wk over a 10-month period to rats and rabbits of both sexes had no effect on hematologic parameters.

4.3.2.3 Dermal Exposure

Percutaneous treatment by Truhaut et al. [1979] of New Zealand rabbits of both sexes with a single application of 1,500 mg/kg EGBEA resulted in RBC counts and Hb levels that were 20% to 25% of the control value (statistics not given). These values returned to normal after 8 to 14 days.

Bartnik et al. [1987] applied a single dose of 260, 320, 375, or 500 mg EGBE/kg to the shaved dorsal skin of groups of three female rats; they also applied 200 mg/kg EGBE to the shaved dorsal skin of six female rats. Blood was collected retroorbitally six hr after dosing. Test animals were then sacrificed by carbon dioxide asphyxiation, and blood samples were taken immediately by cardiac puncture. Preliminary test results indicated that 500 mg EGBE/kg caused adverse effects such as an increase in mean cell volume, a lowered erythrocyte count and Hb level, and hemoglobinuria within 6 hr of dosing. No adverse effects were caused by 200 mg EGBE/kg. EGBE at doses of 260, 320, 375, and 500 mg/kg produced the effects described above in at least some animals in each group, but there was no discernible dose-response relationship. Bartnik et al. [1987] attributed this result to inherent biologic variation in percutaneous absorption and hemolytic susceptibility of erythrocytes, and to the small number of animals per group.

4.3.2.4 In Vitro Exposure

Bartnik et al. [1987] also examined the effects of EGBE and BAA on human and rat erythrocytes. Human erythrocytes were isolated from the blood of healthy adult male donors

(number unspecified) and rat erythrocytes were collected from four adult male Wistar rats. Under in vitro conditions, 175, 200, 225, and 250 millimoles (mmol) EGBE/liter induced complete lysis of rat erythrocytes, and 200, 225, and 250 mmol EGBE/liter induced complete lysis of human erythrocytes. At a concentration of 3.75 to 7.5 mmol/liter, BAA caused complete lysis of rat erythrocytes but failed to cause lysis of human erythrocytes. These results indicate that the rat may be more susceptible than humans to the effects of EGBE [Bartnik et al. 1987] (see Tables 4-4 and 4-5).

Ghanayem [1989] examined the effect of EGBE and its metabolite BAA on whole blood collected by cardiac puncture from male F344 rats. The addition of 5 or 10 mM EGBE to whole blood exerted no effect on Hct levels and rat erythrocytes, whereas 20 mM EGBE caused a significant reduction in Hct along with significant hemolysis ($P \leq 0.05$). The addition of 0.5 or 1 mM BAA to rat erythrocytes caused a time- and concentration-dependent increase in Hct followed by hemolysis, while adding 2 mM BAA caused a faster time-dependent increase in Hct. The Hct level reached its maximum after 2 hr followed by nearly complete hemolysis after 4 hr. Ghanayem [1989] also examined the effect of BAA (0.5, 1, 2, 4, 8 mM) on human blood obtained from healthy young male and female volunteers. No significant changes in Hct or hemolysis occurred at BAA concentrations of 4 mM and below. However, at 8 mM BAA there was a slight but significant increase in Hct ($P \leq 0.05$), followed by slight but significant hemolysis ($P < 0.05$) of human erythrocytes.

4.3.2.5 Summary of Hematologic Effects

Early investigators [von Oettingen and Jirouche 1931] demonstrated the hemolytic activity of EGBE in vitro. In later studies, adverse hematologic effects of EGBE were shown in a variety of species by various exposure routes (i.e., oral, inhalation, dermal). These effects included decreased RBC, Hb, and Hct levels [Werner et al. 1943a,b; Carpenter et al. 1956; Nagano et al. 1979; Dodd et al. 1983; Grant et al. 1985; Tyl et al. 1984; Bartnik et al. 1987; Ghanayem et al. 1987]; the responses were transitory and their severity was dose-dependent. In addition Ghanayem et al. [1987] demonstrated that EGBE-induced hematotoxicity in rats is age-dependent, with older rats more susceptible than younger rats. In the study by Carpenter et al. [1956], exposure to EGBE vapors induced a transitory increase in RBC osmotic fragility in mice, rats, and monkeys. Although inhalation of EGBE vapors caused an increase in WBC levels [Dodd et al. 1983], oral EGBE exposure reduced WBC levels in a dose-dependent manner [Grant et al. 1985]. Exposure of rats and rabbits to EGBEA vapors caused slight hematuria and hemoglobinuria [Truhaut et al. 1979]. Under in vitro conditions, 200, 225, and 250 mmol EGBE/liter induced complete lysis of human erythrocytes [Bartnik et al. 1987]. At a concentration of 3.75 to 7.5 mmol/liter, BAA caused complete lysis of rat erythrocytes [Bartnik et al. 1987]; 8 mM BAA caused a slight but statistically significant lysis of human erythrocytes [Ghanayem 1989]. Studies of the hematologic effects of EGBE and EGBEA are summarized in Table 4-6.

4.3.3 Reproductive Effects in Males

A number of experimental animal studies have demonstrated that EGBE does not exert adverse effects on the male reproductive system.

Table 4–4.—Percentage hemolysis of human and rat erythrocytes by EGBE[*, †, §]

BE (mmol/liter)	15 min		30 min		45 min		60 min		120 min		180 min	
	R[**]	H[††]	R	H	R	H	R	H	R	H	R	H
100	[§§]	---	---	---	---	---	---	---	---	---	---	---
125	---	---	---	---	---	---	---	---	10.8	---	64.4	---
150	---	---	---	---	---	---	8.2	---	62.8	3.4	92.2	11
175	---	---	6.2	---	41.4	---	91.1	2.1	100	23.4	100	89.5
200	5.4	---	100	---	100	2.8	100	8.8	100	100	100	100
225	96.4	---	100	14.8	100	89.5	100	100	100	100	100	100
250	200	8.6	100	100	100	100	100	100	100	100	100	100

[*]Source: Bartnik et al. [1987].
[†]Data are mean values of up to three measurements, as percentage of total hemolysis (100%) induced by Saponion.
[§]Final erythrocyte concentration = 1%.
[**]R = rat erythrocytes.
[††]H = human erythrocytes.
[§§]No hemolysis.

Table 4–5.—Percentage hemolysis of human and rat erythrocytes by BAA[*, †, §]

BAA (mmol/liter)	15 min		30 min		45 min		60 min		120 min		180 min	
	R[**]	H[††]	R	H	R	H	R	H	R	H	R	H
1.25	§§	---	---	---	---	---	---	---	6.9	---	25.0	---
2.50	---	---	---	---	4.0	---	20.0	---	79.3	---	95.0	---
3.75	---	---	---	---	17.9	---	49.7	---	86.2	---	100	---
5.0	---	---	13.0	---	59.7	---	88.3	---	100	---	100	---
6.25	---	---	17.4	---	59.9	---	89.0	---	100	---	100	---
7.5	---	---	25.0	---	69.2	---	100	---	100	---	100	---
10	n.m.[***]	---	n.m.	---	n.m.	---	n.m.	---	n.m.	---	n.m.	---
15	n.m.	---	n.m.	---	n.m.	---	n.m.	---	n.m.	---	n.m.	---

[*]Source: Bartnik et al. [1987].
[†]Data are mean values of up to three measurements, as percentage of total hemolysis (100%) induced by Saponion.
[§]Final erythrocyte concentration = 1%.
[**]R = rat erythrocytes.
[††]H = human erythrocytes.
[§§]No hemolysis.
[***]Not measured.

Table 4–6.—Hematologic effects of EGBE and EGBEA

Species and sex	Route of administration and dose	Observed effects	Compound studied and reference
			EGBE:
	In vitro RBC (beef blood)	Hemolysis	von Oettingen and Jirouche 1931
Mouse (M)*	Oral: 500 or 1,000 mg/kg per day, 5 days/wk for 5 wk	Reduced RBC counts (500 and 1,000 mg/kg per day)	Nagano et al. 1979
Rat (M) 4–5 wk old	Oral: 125 or 500 mg/kg (single dose)	No effect (125 mg/kg); reduced RBCs, Hb, Hct (500 mg/kg)	Ghanayem et al. 1987
Rat (M) 9–13 wk old		Reduced RBCs, Hb, and Hct (125 and 500 mg/kg)	
Rat (M)	Oral: 500 or 1,000 mg/kg per day for 4 consecutive days	Reduce RBC and WBC counts, Hct and Hb levels; increased MCV, reticulocyte counts and MCHC (1,000 mg/kg per day; same effects but less severe in 500 mg/kg per day group	Grant et al. 1985
Rat (M)	Oral: 222, 443, or 885 mg/kg per day, 5 days/wk for 6 wk	Reduced Hb and RBC count (all doses); decreased MCHC (443 or 885 mg/kg per day); increased MCHb (all doses)	Krasavage 1986
Rat	Inhalation: 135 or 320 ppm, 7 hr/day, 5 days/wk for 5 wk	Increased circulating, immature granulocytes; decreased Hb and RBC count; increased reticulocyte count (320 ppm); effects for 5 wk are reversible	Werner et al. 1943a
Dog	Inhalation: 415 ppm, 7 hr/day, 5 days/wk for 12 wk	Decreased Hb and RBC count; increased hypochromia, polychromatophilia and microcystosis; changes are reversible	Werner et al. 1943b
Rat (F)†	Inhalation: 62 ppm for 4 hr	Increased osmotic fragility	Carpenter et al. 1956
Rat (M, F)	Inhalation: 107, 203, 314, or 432 ppm for 7 hr	Increased osmotic fragility	Carpenter et al. 1956
	Inhalation: 54 ppm, 7 hr/day, 5 days/wk for 30 days	Increased osmotic fragility	Carpenter et al. 1956

(Continued)

*Male.
†Female.

Table 4–6 (Continued).—Hematologic effects of EGBE and EGBEA

Species and sex	Route of administration and dose	Observed effects	Compound studied and reference
Guinea Pig (M, F)	Inhalation: 54, 107, 203, 376, or 494 ppm, 7 hr/day, 5 days/wk for 30 days	No effect on osmotic fragility	Carpenter et al. 1956
Mouse (M)	Inhalation: 100, 200, or 400 ppm, 7 hr/day for 30, 60, or 90 days	Increased osmotic fragility	Carpenter et al. 1956
Dog (F)	Inhalation: 385 ppm (8 exposures)	Death; increased osmotic fragility	Carpenter et al. 1956
Dog (M)	Inhalation: 385 ppm (28 exposures)	Death; increased osmotic fragility, decreased Hb and RBC counts	Carpenter et al. 1956
Dog (M)	Inhalation: 200 ppm, 7 hr/day for 31 days	Slightly increased osmotic fragility, increased WBC count	Carpenter et al. 1956
Dog (F)	Inhalation: 200 ppm, 7 hr/day for 31 days	Slightly increased osmotic fragility, decreased Hb and RBC counts	Carpenter et al. 1956
Dog (M, F)	Inhalation: 100 ppm, 7 hr/day for 90 days	Transitory increase in WBC; female's WBC returned to pre-exposure level, but males remained 50% higher; decrease Hct in male	Carpenter et al. 1956
Monkey (M, F)	Inhalation: 100 ppm, 7 hr/day for 90 days	Transitory increase in osmotic fragility and decrease in RBC counts	Carpenter et al. 1956
Monkey	Inhalation: 210 ppm, 7 hr/day, for 30 days	Reduced Hb and RBC count; transitory increase in osmotic fragility	Carpenter et al. 1956
Rat (M, F)	Inhalation: 0, 20, 86, or 245 ppm, 6 hr/day for 9 days	Reduced RBC counts, Hb levels, MCHC; increases in MCV, nucleated erythrocytes, reticulocytes, and (in males only) lymphocytes (245 ppm); reduced Hb in males (86 ppm); reduced Hb and MCHb, and increased Hct and MCV in females (86 ppm)	Dodd et al. 1983
	Inhalation: 0, 5, 25, or 77 ppm, 6 hr/day for 90 days	Decreased RBC counts and Hb, and increased MCHb in females (77 ppm); 5% decrease in RBC counts in males (77 ppm)	Dodd et al. 1983

(Continued)

Table 4–6 (Continued).—Hematologic effects of EGBE and EGBEA

Species and sex	Route of administration and dose	Observed effects	Compound studied and reference
Rat (F)	Inhalation: 25, 50, 100, or 200 ppm, 6 hr/day, g.d. 6-15	Reduced RBC count (100, 200 ppm); increased Hb and Hct (200 ppm); increased MCV and MCHb, reduced MCHC (100 and 200 ppm)	Tyl et al. 1984
Rabbit (F)	Inhalation: 25, 50, 100, or 200 ppm, 6 hr/day, g.d. 6-18	No effects	Tyl et al. 1984
Rat (F)	Dermal: 200, 260, 320, 375 or 500 mg/kg	Increased MCV, decreased RBC and Hb, hemoglobinuria (500 mg/kg)	Bartnik et al. 1987
Rat (M) Man (M)	In vitro: 100, 125, 150, 175, 200, 225, or 250 mmol/liter added to blood cultures	Complete hemolysis of rat erythrocytes (175-250 mmol/liter). Complete hemolysis of human erythrocytes (200-250 mmol/liter).	Bartnik et al. 1987
Man (M)	In vitro: 5, 10, or 20 mm added to human blood	Decrease in Hct followed by hemolysis (20 mM)	Ghanayem 1989
			EGBEA:
Rat (M, F)	Inhalation: 400 ppm for 4 hr	No effect	Truhaut et al. 1979
Rabbit (M, F)	Inhalation: 400 ppm for 4 hr	Transient hemoglobinuria and hematuria	Truhaut et al. 1979
Rat (M, F)	Inhalation: 400 ppm, 4 hr/day, 5 d/wk for 1 mo	Slight hematuria and hemoglobinuria	Truhaut et al. 1979
Rabbit (M, F)	Inhalation: 400 ppm, 4 hr/ day, 5 d/wk for 1 mo	Hematuria and hemoglobinuria; severe decrease in RBC counts and Hb in 2 out of 4 rabbits	Truhaut et al. 1979
Rat (M, F)	Inhalation: 100 ppm, 4 hr/day, 5 d/wk for 10 mo	No effects	Truhaut et al. 1979
Rabbit	Inhalation: 100 ppm, 4 hr/day, 5 d/wk for 10 mo	No effects	Truhaut et al. 1979
	Dermal: 1,500 mg/kg	Reduced RBC counts and Hb levels	Truhaut et al. 1979

4.3.3.1 Oral Administration

In a study by Nagano et al. [1979], groups of five JCL-ICR male mice were treated orally with various doses of EGBE (500, 1,000, or 2,000 mg/kg per day, 5 days/wk for 5 wk). The mice treated with 2,000 mg EGBE/kg died. The day after the final administration of EGBE, the remaining mice were sacrificed and dissected. Weight of the testes was not significantly affected by treatment with EGBE.

Krasavage [1986] administered EGBE by gavage to groups of 10 male rats at doses of 0, 222, 443, or 885 mg/kg per day, 5 days/wk for 6 wk. The animals were sacrificed at the end of the exposure period. Organs were removed, weighed, and examined histopathologically. No adverse effects on the testes were observed.

Foster et al. [1987] exposed groups of six male Alpk/AP (Wistar-derived) rats to single oral doses (174, 434, or 868 mg/kg) of BAA, the metabolite of EGBE (see Section 4.2), to determine the initial target for testicular toxicity. Rats were sacrificed on days 1, 2, 4, and 14 after treatment. No testicular damage was induced by BAA at any dose for any length of exposure, but rats receiving the high dose of BAA did show evidence of hematuria throughout the study. The addition of 5 mM BAA to Sertoli male germ cell culture systems did not produce any specific changes in testicular cell populations.

4.3.3.2 Inhalation

In an inhalation study by Doe [1984], male Alpk/Ap Wistar-derived rats were exposed to 800 ppm EGBE for 3 hr; the rats were then observed throughout the next 14 days. The animals were sacrificed on day 15 and subjected to gross macroscopic postmortem examination, which included the weighing of the testes. EGBE had no effect on testicular weights.

4.3.3.3 Summary of Reproductive Effects in Males

Studies using EGBE [Nagano et al. 1979; Doe 1984; Krasavage 1986] and BAA [Foster et al. 1987], the metabolite of EGBE (see Section 4.2), have demonstrated no adverse effects on the male reproductive system. No studies exist for EGBEA. However, because EGBEA would be metabolized to EGBE (see Section 4.2), it would also be expected to cause no reproductive effects.

4.3.4 Effects on the Female Reproductive System and the Embryo

The following studies in animals have been conducted to investigate the effects of EGBE on the female reproductive system and the embryo.

4.3.4.1 Oral Administration

Schuler et al. [1984] exposed CD-1 mice orally to 4,000 mg EGBE/kg once per day on g.d. 7 through 14. This treatment resulted in 20% maternal mortality and in 77% viable litters, which differed significantly from 100% viability in the control group ($P<0.05$).

4.3.4.2 Inhalation

In an inhalation study, Nelson et al. [1984] exposed Sprague-Dawley rats on g.d. 7 through 15 to 150 or 200 ppm EGBE for 7 hr/day. The investigators had reduced the doses from 250 and 500 ppm EGBE because of maternal toxicity. Three of four nonpregnant rats exposed to 500 ppm EGBE for 6.5 hr died within 36 hr after termination of EGBE exposure; of three nonpregnant rats exposed to 250 ppm EGBE for 7 hr, one died within 18 hr after exposure ended, and a second died 2 days after exposure. Some hematuria was observed on the first day of exposure in the group exposed to 200 ppm EGBE. No other adverse effects were observed in the dams or the pups in either treatment group. The number of resorptions, fetal weights, and incidence of malformations did not differ from the controls.

Tyl et al. [1984] examined the effects of EGBE administered via inhalation to Fischer 344 rats and New Zealand white rabbits. The animals were exposed to 0, 25, 50, 100, or 200 ppm EGBE, 6 hr/day, on g.d. 6 through 15 (rats) or g.d. 6 through 18 (rabbits). Rats were then sacrificed on g.d. 21 and rabbits on g.d. 29. In rats, the pregnancy rate was equivalent across all groups. A significant increase occurred in the number of totally resorbed litters at 200 ppm EGBE relative to controls ($P<0.01$). Maternal toxicity in rats was indicated by reductions in body weight on g.d. 9, 12, 15, and 21 at 200 ppm EGBE, and by reduced body weight gain on (1) g.d. 6 through 15 at 100 ppm EGBE ($P<0.05$) and (2) g.d. 6 through 15 and 6 through 21 at 200 ppm EGBE ($P<0.001$).

When rats were exposed to 200 ppm EGBE, the number of viable implants ($P<0.001$) and the percentage of live fetuses ($P<0.01$) per litter were reduced relative to controls [Tyl et al. 1984]. However, treatment with EGBE resulted in no statistically significant increases in the incidence of external, visceral, skeletal, or total malformations. Evidence of retarded skeletal ossification was seen at 100 and 200 ppm EGBE. At 100 and 200 ppm EGBE, a significant increase ($P<0.05$) occurred in the number of litters containing one or more fetuses with unossified or poorly ossified skeletal elements.

Significant reductions in maternal body weight, gravid uterine weight, and numbers of total implants and viable implants were noted at 200 ppm EGBE relative to controls ($P<0.05$). No statistically significant increases in the number of fetuses or litters with malformations were observed in any treatment group. Two significant variations were seen in rabbit fetuses. At 200 ppm EGBE, there was a significant reduction in unossified sternebrae and in rudimentary rib ($P<0.05$). The occurrence of unossified skeletal elements in both rats and rabbits was considered an indication of delayed development. None of the observations indicated abnormal development in rats or rabbits exposed to EGBE in this study [Tyl et al. 1984].

4.3.4.3 Dermal Exposure

Hardin et al. [1984] applied EGBE to the skin of pregnant Sprague-Dawley rats to investigate its potential for developmental toxicity. Four daily doses of 106 mg EGBE (total daily dose of 424 mg) were applied to shaved interscapular skin of rats on g.d. 7 through 16. No maternal, embryotoxic, fetotoxic, or teratogenic effects were detected in litters of the EGBE-exposed dams.

4.3.4.4 In Vitro

The in vitro culture system of Yonemoto et al. [1984] was used by Rawlings et al. [1985] to study the mechanism of teratogenicity of EGBE. Conceptuses were explanted from pregnant Wistar-Porton rats at the embryonic age of 9.5 days and cultured for 48 hr with 2 or 5 mmol BAA/liter. 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. BAA at the 5mM concentration had an adverse effect on all parameters except crown-rump length. BAA produced statistically significant reductions in somite number ($P<0.01$), head length ($P<0.01$), yolk sac diameter ($P<0.05$), and protein content of the embryo ($P<0.05$). No statistically significant reductions in growth parameters were seen at the 2-mM level. Irregularity of the neural suture line was seen in 29% of the embryos exposed to 5 mM BAA. BAA-exposed embryos also showed abnormal otic and somite development. None of the observations indicated abnormal development.

4.3.4.5 Summary of Reproductive Effects in Females

The preceding studies demonstrated that EGBE administered by a variety of routes in a variety of species did not have teratogenic effects on litters of EGBE-exposed dams [Schuler et al. 1984; Tyl et al. 1984; Nelson et al. 1984; Hardin et al. 1984]. Signs of maternal toxicity included decreased body weight and body weight gain [Tyl et al. 1984]. At the maternal LD_{20} (lethal dose for 20% of the test animals), EGBE induced fetal death [Schuler et al. 1984]. BAA, the metabolite of EGBE (see Section 4.2), did not adversely affect fetal development in vitro [Rawlings et al. 1985].

No studies are reported for EGBEA. However, because it would be metabolized to EGBE (see Section 4.2), it would also be expected to cause no effects on the female reproductive system and the embryo. Table 4-7 summarizes the studies of reproductive and developmental effects of EGBE.

4.3.5 Carcinogenicity

Prechronic carcinogenicity studies of EGBE are currently in progress [NTP 1988].

4.3.6 Mutagenicity

A limited number of studies concerning the potential mutagenicity of EGBE have been performed. Most of these involved tests with microorganisms or mammalian cell cultures in vitro. EGBE does not appear to be mutagenic. No data are available concerning the mutagenicity of EGBEA.

EGBE was tested for mutagenic activity by using an assay of unscheduled DNA synthesis (UDS) in rat primary hepatocytes; total radioactivity was measured by scintillation counting [McGregor 1984]. In this study, EGBE was tested at concentrations up to 0.1% of the culture medium for 2 hr. The results suggested that EGBE might be inhibiting UDS, but further

Table 4–7.—Reproductive and developmental effects of EGBE and BAA

Species and sex	Route of administration and dose	Observed effects	Compound studied and reference
			EGBE:
Mouse (M)*	Oral: 500, 1,000, or 2,000 mg/kg per day, 5 day/wk for 5 wk	No testicular effects	Nagano et al. 1979
Mouse (F)†	Oral: 4,000 mg/kg per day on g. d. 7–14	20% maternal mortality, 23% nonviable litters	Schuler et al. 1984
Mouse (M)	Oral: 222, 443, or 885 mg/kg per day, 5 day/wk for 6 wk	No testicular effects	Krasavage 1986
Rat (F)	Inhalation: 25, 50, 100, or 200 ppm, 6 hr/day on g. d. 6–15; sacrificed on g. d. 21	Increase in number of litters resorbed, reduced maternal body weight and body weight gain, reduced live fetuses (200 ppm), retarded skeletal ossification (100, 200 ppm)	Tyl et al. 1984
Rabbit (F)	Inhalation: 25, 50, 100, or 200 ppm, 6 hr/day on g. d. 6–18; sacrificed on g. d. 29	Reduced maternal body weight and gravid uterine weight (200 pm), reduced numbers of total viable implants (200 pm), two skeletal variations (200 ppm)	Tyl et al. 1984
Rat (F)	Inhalation: 250 or 500 ppm, 7 hr/day on g. d. 7–15	Death	Nelson et al. 1984
	Inhalation: 150 or 200 ppm, 7 hr/day on g. d. 7–15	Hematuria (200 ppm)	Nelson et al. 1984
Rat (M)	Inhalation: 800 ppm for 3 hr	Hematuria; no testicular effects	Doe 1984
Rat (F)	Dermal: 0.9 mmol, 4 times/day on g. d. 7–16	No effects on offspring	Hardin et al. 1984
	Dermal: 2.7 mmol, 4 times/day on g. d. 7–16	Hematuria, death of 10/11 treated rats	Truhaut et al. 1979
			BAA:
Rat (M)	Oral: single dose of 174, 434, or 868 mg/kg	No testicular effects	Foster et al. 1987
	In vitro: 2 or 5 mmol/liter	No effect on embryonic development	Rawlings et al. 1985

*Male.
†Female.

testing is needed to confirm this possibility. McGregor [1984] also examined the ability of EGBE to induce point mutations in vitro. EGBE was not mutagenic at the HGPRT locus of Chinese hamster ovary (CHO) cells in either the presence or absence of rat S9 mix at concentrations up to 1% of the culture medium for 5 hr, followed by a 7-day expression period. Data from the McGregor [1984] study are presented in Table 4-8.

4.3.7 Cytotoxicity

The in vitro cytotoxicity of EGBE and BAA was 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 before 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. EGBE was cytotoxic (EC_{50} = 0.05 mmol/ml or 6.9 mg/ml). The EC_{50} for BAA was 0.04 mmol/ml (5.3 mg/ml).

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 1983]. The effects of EGBE 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, EGBE was able to block metabolic cooperation in vitro.

Table 4-8.—Mutagenic effects

Type of test	Compound	Test species	Results	Reference
Mammalian in vitro unscheduled DNA syntheis	EGBE	CHO cells with and without rat S9 mix	No response	McGregor 1984
Mammalian in vitro point mutations	EGBE	CHO cells, HGRPT locus, with and without rat S9 mix	No response	McGregor 1984

5 HAZARD IDENTIFICATION

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

5.1 ENVIRONMENTAL SAMPLING

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

5.2 ANALYTICAL METHODS

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

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

5.3 MEDICAL MONITORING

EGBE and EGBEA have been shown to have adverse effects on the central nervous, hematopoietic, and renal systems in humans and animals; furthermore, exposure to these glycol ethers may impair liver function. Preplacement and periodic medical examinations should therefore be instituted for workers who may be exposed to EGBE and EGBEA. Medical monitoring should include the following:

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

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

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

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

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

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

- Periodic medical examinations. The aforementioned medical examinations should be performed annually for all workers occupationally exposed to EGBE and EGBEA at or above the action levels, especially those who have the potential for significant skin exposure.

5.4 BIOLOGICAL MONITORING

Biological monitoring may be a useful adjunct to environmental monitoring in assessing worker exposure to EGBE and EGBEA. Biological monitoring takes into account the influence of workload and percutaneous absorption.

5.4.1 Justification for Biological Monitoring

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

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

Metabolism studies in animals (described in Section 4.2) demonstrated that EGBE is metabolized to its corresponding alkoxyacetic acid, BAA, which is excreted in the urine. This urinary metabolite has been shown to produce hematologic toxicity in rats [Bartnik et al. 1987; Ghanayem 1989]. Thus measurement of this metabolite can be viewed as an indicator of potential health effects as well as an assessment of total uptake through inhalation and dermal absorption.

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

5.4.2 Selection of Monitoring Medium

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

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

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

- BAA exerts hematologic toxicity and may reflect the concentration of the "active agent" at the target sites.
- The elimination half-life of EGBE (4 to 7 hr) reflects the integrated exposure over a workday [Johanson et al. 1986, 1988; Van Vlem 1987].
- Collection of urine samples is a noninvasive procedure.

5.4.3 Limitations of Biological Monitoring

Limitations and possible sources of error exist in the biological monitoring of the acid metabolite of EGBE and EGBEA. Biological monitoring primarily assesses uptake and not exposure concentration. In addition to the lack of well designed field evaluations of workers exposed to EGBE and EGBEA, the following factors limit the use of biological monitoring to assess exposure [Johanson 1988]:

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

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

5.4.4 Correlation of EGBE Uptake with BAA Excretion

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

5.4.5 Assessment of Biological Monitoring Results in Various Studies

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 5-2.—Summary of EGBE exposure studies

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

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

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

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

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

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

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

5.4.6 Method for Analyzing Urinary BAA

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

5.4.7 Summary

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

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

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

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

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

6 OTHER STANDARDS AND RECOMMENDATIONS

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

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

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

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

Federal Register. See Fed. Reg. in references.

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

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

[*]Data from ECETOC [1985].

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

[§]ACGIH deleted the STEL in 1987.

[**]Values are subject to change.

[††]No exposure limit has been established.

7 ASSESSMENT OF EFFECTS

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

7.1 CORRELATION OF EXPOSURE AND EFFECTS

7.1.1 EGBE

7.1.1.1 Studies in Humans

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

7.1.1.2 Studies in Animals

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

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

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

(continued)

See footnote at end of table.

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

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

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

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

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

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

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

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

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

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

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

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

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

7.1.2 EGBEA

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

7.2 BASIS FOR THE RECOMMENDED STANDARD FOR EGBE AND EGBEA

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 7-2.—Data for rat inhalation study

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

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

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

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

The values in this equation were rounded to obtain 44.9.

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 labeling 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. Any chemical that is determined to be a carcinogen must be listed if it is present in quantities of 0.1% or greater. Ingredients present in concentrations of less than 1% must also be listed if there is evidence that the PEL may be exceeded or if it 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 EGBE or EGBEA is 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 EGBE and EGBEA should be stored in a cool, dry, well ventilated location away from any area containing a fire hazard. Outside or detached storage is preferred. EGBE and EGBEA 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 EGBE and EGBEA, 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 EGBE and EGBEA. The employer should make handwashing facilities available and encourage the workers to use them before eating, smoking, using the toilet, or leaving the work site. 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 carried uncovered, smoked, or chewed 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 EGBE and EGBEA. The following procedures are recommended in the event of an EGBE or EGBEA spill [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 EGBE and EGBEA. Depending on the process, warning signs may 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 work site to inform other workers of the 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 EGBE or EGBEA. 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 EGBE or EGBEA 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 EGBE and EGBEA in the workplace. Achieving and maintaining reduced concentrations of airborne EGBE and EGBEA depend on adequate engineering controls such as 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 EGBE and EGBEA 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 measured 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

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 EGBE and EGBEA. The personal protective equipment (PPE) ensemble is dictated by the worker's potential exposure to EGBE or EGBEA and ranges from gloves to encapsulating suits. The following materials have good but varied resistance to EGBE [Forsberg and Mandorf 1989]:

Material	*Breakthrough time (hr)*
Butyl rubber, Saranex®,	> 8
Polyethylene/ethylene vinyl alcohol laminate	> 4

To evaluate the use of these materials with EGBEA, 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.

Any chemical-resistant clothing that is used should be periodically evaluated to determine its effectiveness in preventing dermal contact. Safety showers and eye wash stations should be located close to operations that involve EGBE and EGBEA.

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 work shift 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 EGBE and EGBEA 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 EGBE and EGBEA 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. NIOSH's *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 EGBE or EGBEA 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 minutes) may also be used to determine the average exposure concentration.

When the potential for exposure to EGBE or EGBEA 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 EGBE or EGBEA concentrations that are below the REL but at or above the action level (one-half of 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 REL for EGBE or EGBEA, 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 a week apart indicate that the workers' exposure no longer exceeds the REL.

When workers' exposures are greater than the action level but less than the REL, sampling should be conducted after 6 months; if EGBE or EGBEA concentrations are lower than the action level 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 EGBE and EGBEA 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 BAA for any worker exposed to unknown concentrations of EGBE or EGBEA during a spill or emergency (see Appendix D).

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 independent or interactive adverse effects on the worker's health (including exacerbation of preexisting health problems and nonoccupational risk factors such as tobacco use), and (b) potentially hazardous characteristics of the work site (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 EGBE and EGBEA. 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 reexamine organ systems at risk to note changes from the previous examination.

8.10 BIOLOGICAL MONITORING

The urinary concentration of BAA (the metabolite of EGBE and EGBEA) may be a useful biological indicator of worker exposure to EGBE and EGBEA. 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 D.

Biological monitoring is suggested when the potential exists for exposure to airborne EGBE or EGBEA at or above the REL, or for skin contact resulting from accidental exposure or breakdown of chemical protective clothing (see Section 8.6.1). Monitoring of urinary BAA (see Appendix D) should be made available to any worker exposed to unknown concentrations of EGBE or EGBEA during a spill or other emergency. In the absence of skin exposure, a urinary BAA concentration of 60 mg/g creatinine approximates the concentration that would result from exposure to the REL for EGBE or EGBEA (5 ppm) during an 8-hr work shift. If a worker's urinary BAA suggests exposure to EGBE or EGBEA above the REL, 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 health effects from occupational exposure to EGBE or EGBEA:

- Investigations should be conducted in workplaces where exposures have been maintained below the current standards. Evaluations should be made of the relationship of exposure concentrations to urinary metabolite concentrations and toxic effects on the hematopoietic system.
- Evaluations should be made to correlate dermal absorption of EGBE or EGBEA with concentrations of the urinary metabolite in populations exposed to these compounds.
- Additional data should be collected to determine actual concentrations of EGBE and EGBEA in the workplace.
- Physiologically based pharmacokinetic models should be prepared and validated to predict NOAELs for EGBE and EGBEA in humans and animals.
- A device should be developed to measure dermal exposure.
- Additional studies should be conducted to investigate EGBE and EGBEA for carcinogenicity and mutagenicity.
- Studies should be conducted to determine the effect of mixed solvent exposure on the metabolism of EGBE to BAA.

APPENDIX A

METHODS FOR SAMPLING AND ANALYSIS OF EGBE AND EGBEA IN AIR*

A.1 GENERAL REQUIREMENTS FOR SAMPLING

The air samples collected represent the air a worker breathes while performing each job or 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.

NIOSH METHOD NO. 1403 FOR 2-BUTOXYETHANOL

FORMULA: Table 1 — ALCOHOLS IV

METHOD: 1403

M.W.: Table 1 — ISSUED: 2/15/84

OSHA/NIOSH/ACGIH: Table 1 — PROPERTIES: Table 1

COMPOUND and SYNONYM:
(1) 2-Methoxyethanol: [Methyl Cellosolve; CAS #109-86-4];
(2) 2-Ethoxyethanol: [Cellosolve; CAS #110-80-5]; and
(3) 2-Butoxyethanol: [Butyl Cellosolve; CAS #111-76-21].

SAMPLING

SAMPLER: SOLID SORBENT TUBE (coconut shell charcoal, 100 mg/50 mg)

FLOW RATE: 0.01 to 0.05 L/min

	(1) & (3)	(2)
VOL-MIN:	1 L	1 L
-MAX:	10 L	6 L

SHIPMENT: routine

SAMPLE STABILITY: store in freezer; analyze as soon as possible

BLANKS: 2 to 10 field blanks per set

ACCURACY

RANGE STUDIED: see EVALUATION OF METHOD

BIAS: not significant [1,2]

OVERALL PRECISION (s_r): see EVALUATION OF METHOD

MEASUREMENT

TECHNIQUE: GAS CHROMATOGRAPHY, FID

ANALYTE: compounds above

DESORPTION: 1 mL 5% methanol in CH_2Cl_2

INJECTION VOLUME: 5 μL

TEMPERATURE-INJECTION: 200°C
-DETECTOR: 250-300°C
-COLUMN: (1) 95°C;
(2) 140°C;
(3) 145°C

CARRIER GAS: N_2 or He, 30 mL/min

COLUMN: glass, 3 m x 2 mm ID, 10% SP-1000 on 80/100 mesh Chromosorb WHP, or equivalent

CALIBRATION: solutions of analyte in eluent with internal standard

RANGE AND PRECISION: see EVALUATION OF METHOD

ESTIMATED LOD: 0.01 to 0.02 mg per sample [3]

ALCOHOLS IV METHOD: 1403

APPLICABILITY: This method may be used to determine two or more analytes simultaneously by varying GC conditions (e.g., temperature programming).

INTERFERENCES: High humidity reduces sampling capacity. The methods were validated using a 3 m x 3 mm stainless steel column packed with 10% FFAP on Chromosorb W-AW; other columns with equal or better resolution (e.g., capillary) may be used. Less volatile compounds may displace more volatile compounds on the charcoal.

OTHER METHODS: This method combines and replaces Methods S79 [4], S361 [5], and S76 [4].

REAGENTS:

1. Eluent: methylene chloride with 5% (v/v) methanol and 0.2% (v/v) 1-heptanol, 0.1% (v/v) ethyl benzene or other suitable internal standard.
2. Analyte.
3. Nitrogen, purified.
4. Hydrogen, prepurified.
5. Air, compressed, filtered.

EQUIPMENT:

1. Sampler: glass tube, 7 cm long, 6 mm OD, 4 mm ID, flame-sealed ends, containing two sections of activated (600°C) coconut shell charcoal (front=100 mg; back=50 mg) separated by a 2-mm urethane foam plug. A silylated glass wool plug precedes the front section and a 3-mm urethane foam plug follows the back section. Pressure drop across the tube at 1 L/min airflow must be less than 3.4 kPa. Tubes are commercially available.
2. Personal sampling pump, 0.01 to 0.05 L/min, with flexible connecting tubing.
3. Gas chromatograph, FID, integrator and column (page 1403-1).
4. Vials, glass, 2-mL, PTFE-lined crimp caps.
5. Syringe, 10-μL, readable to 0.1 μL.

SPECIAL PRECAUTIONS: None.

SAMPLING:

1. Calibrate each personal sampling pump with a representative sampler in line.
2. Break the ends of the sampler immediately before sampling. Attach sampler to personal sampling pump with flexible tubing.
3. Sample at an accurately known flow rate between 0.01 and 0.05 L/min for a total sample size of 1 to 10 L (2-methoxyethanol and 2-butoxyethanol) or 1 to 6 L (2-ethoxyethanol). NOTE: Maximum flow rate for 2-methoxyethanol and 2-butoxyethanol is 0.2 L/min.
4. Cap the samplers with plastic (not rubber) caps and pack securely for shipment.

SAMPLE PREPARATION:

5. Place the front and back sorbent sections of the sampler tube in separate vials. Discard the glass wool and foam plugs.
6. Add 1.0 mL eluent to each vial. Attach crimp cap to each vial.
7. Allow to stand 30 min with occasional agitation.

CALIBRATION AND QUALITY CONTROL:

8. Calibrate daily with at least five working standards over the range 0.02 to 8 mg analyte per sample.
   a. Add known amounts of analyte to eluent in 10-mL volumetric flasks and dilute to the mark.
   b. Analyze together with samples and blanks (steps 11 and 12).
   c. Prepare calibration graph (ratio of peak area of analyte to peak area of internal standard vs. mg analyte).
9. Determine desorption efficiency (DE) at least once for each batch of charcoal used for sampling in the calibration range (step 8). Prepare three tubes at each of five levels plus three media blanks.
   a. Remove and discard back sorbent section of a media blank sampler.
   b. Inject a known amount of analyte directly onto front sorbent section with a microliter syringe.
   c. Cap the tube. Allow to stand overnight.
   d. Desorb (steps 5 through 7) and analyze together with working standards (steps 11 and 12).
   e. Prepare a graph of DE vs. mg analyte recovered.
10. Analyze three quality control blind spikes and three analyst spikes to insure that the calibration graph and DE graph are in control.

MEASUREMENT:

11. Set gas chromatograph according to manufacturer's recommendations and to conditions given on page 1403-1. Inject sample aliquot manually using solvent flush technique or with autosampler.

NOTE: If peak area is above the linear range of the working standards, dilute with eluent, reanalyze and apply the appropriate dilution factor in calculations.

12. Measure peak area. Divide the peak area of analyte by the peak area of internal standard on the same chromatogram.

CALCULATIONS:

13. Determine the mass, mg (corrected for DE) of analyte found in the sample front (W_f) and back (W_b) sorbent sections, and in the average media blank front (B_f) and back (B_b) sorbent sections.
    NOTE: If $W_b > W_f/10$, report breakthrough and possible sample loss.
14. Calculate concentration, C, of analyte in the air volume sampled, V (L):

$$C = \frac{(W_f + W_b - B_f - B_b) \cdot 10^3}{V}, \text{ mg/m}^3$$

EVALUATION OF METHOD:

Methods S79 (2-methoxyethanol), S361 (2-ethoxyethanol) and S76 (2-butoxy-ethanol) were issued on February 14, 1975 [4], March 17, 1978 [5], and February 14, 1975 [4], and validated using, respectively, 50-, 6- and 10-L air samples of atmospheres generated by calibrated syringe drive. Precision and recovery were as shown below, representing non-significant bias in each method:

Overall method	Precision (S_r)	Recovery (%)	Range studied		Breakthrough @ 2 × OSHA	Measurement	
			mg/m³	mg per sample		Avg. DE	Precision (S_r)
S79 [1,4]	0.068	93	44 to 160	2 to 8	128 L*	0.98	0.008
S361 [2,5,6]	0.059	107	340 to 1460	2 to 7	>10 L**	1.02	0.009
S76 [1,4]	0.060	92	124 to 490	1 to 5	>44 L*	0.99	0.009

*Dry air.
**90% RH.

REFERENCES

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2. Backup Data, S361, available as "Ten NIOSH Analytical Methods, Set 6," Order No. PB 288-629 from NTIS, Springfield, VA 22161.
3. User check, UBTL, NIOSH Sequence #3990-Z [unpublished, November 3, 1983].
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5. Ibid, V. 5, S361, U.S. Department of Health, Education, and Welfare, Publ. (NIOSH) 79-141 [1979].

6. NIOSH Research Report, Development and Validation of Methods for Sampling and Analysis of Workplace Toxic Substances, U.S. Dept. of Health and Human Services Publ. (NIOSH) 80-133 [1980].

METHOD REVISED BY: George Williamson, NIOSH/DPSE; methods originally validated under NIOSH Contracts 99-74-45 and 210-76-0123.

Table 1.—General information

Compound	Exposure limits (ppm) OSHA	NIOSH	ACGIH	Formula	mg/m^3 = 1 ppm @ NTP	M.W.	Density @ 20°C (g/mL)	BP (°C)	VP @ 20°C, kPa (mm Hg)
2-Methoxyethanol	25	Lowest feasible	25 (skin)	$HOCH_2CH_2OCH_3$; $C_3H_8O_2$	3.11	76.09	0.966	124	0.8 (6)
2-Ethoxyethanol	20	Lowest feasible	100 (skin)	$HOCH_2CH_2OCH_2CH_3$; $C_4H_{10}O_2$	3.68	90.12	0.931	135	0.5 (4)
2-Butoxyethanol	50	---	25 (skin)	$HOCH_2CH_2O(CH_2)_3\ CH_3$; $C_6H_{14}O_2$	4.83	118.17	0.902	171	0.08 (0.6)

OSHA METHOD NO. 83 FOR 2-BUTOXYETHANOL (BUTYL CELLOSOLVE) AND 2-BUTOXYETHYL ACETATE (BUTYL CELLOSOLVE ACETATE)*

Method no.:	83	
Matrix:	Air	
Procedure:	Samples are collected by drawing air through standard size coconut shell charcoal tubes. The charcoal is desorbed with a 95/5 (v/v) methylene chloride/methanol solution and the desorbate is analyzed by gas chromatography using a flame ionization detector.	
Recommended air volume and sampling rate:	48 L at 0.1 L/min	
	2-butoxyethanol	2-butoxyethyl acetate
Target concentration:	5 ppm (24 mg/m^3)	5 ppm (33 mg/m^3)
Reliable quantitation limit:	31 ppb (150 μg/m^3)	24 ppb (157 μg/m^3)
Standard error of estimate at target concentration: (Section 4.7.)	5.2%	5.5%
Special requirement:	Samples for 2-butoxyethyl acetate should be stored at 0°C or colder to reduce hydrolysis. Reduced temperature shipment of samples to the laboratory is not necessary.	
Status of method:	Evaluated method. This method has been subjected to the established evaluation procedures of the Organic Methods Evaluation Branch.	
Date: May 1990	Chemist: Carl J. Elskamp	

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

*Reprinted from OSHA [1990].

1. General Discussion

1.1. Background

1.1.1. History

Methodologies to determine airborne concentrations of 2-methoxyethanol (methyl Cellosolve), 2-methoxyethyl acetate (methyl Cellosolve acetate), 2-ethoxyethanol (Cellosolve), and 2-ethoxyethyl acetate (Cellosolve acetate) have previously been evaluated by the OSHA Laboratory at two different target concentrations (OSHA Method 53, Ref. 5.1 and OSHA Method 79, Ref. 5.2). These two methods were based on work done by NIOSH where samples are collected by drawing air through coconut shell charcoal and are analyzed by GC after desorption of the charcoal with 95/5 (v/v) methylene chloride/methanol (Ref. 5.3). The NIOSH method also included an evaluation of 2-butoxyethanol at a range of 124 to 490 mg/m^3 for 10-L air samples. NIOSH has no evaluated method for 2-butoxyethyl acetate.

OSHA has adopted a PEL of 25 ppm for 2-butoxyethanol (Ref. 5.4) and currently has no PEL for 2-butoxyethyl acetate. NIOSH is considering issuing recommendations to lower the PEL for 2-butoxyethanol and to establish a PEL at about the same recommended concentration for 2-butoxyethyl acetate, thus a target concentration of 5 ppm was chosen for both analytes in this evaluation. A number of modifications were made to OSHA Method 79 for this evaluation. Although an RTx-Volatiles (Restek Corp.) capillary column is acceptable for analysis of 2-butoxyethanol, there was less peak-tailing when a Nukol (Supelco, Inc.) capillary column was used. There is no significant peak-tailing for 2-butoxyethyl acetate on either of these columns. In OSHA Method 79, solid anhydrous magnesium sulfate was added to the desorption vials for 2-methoxyethanol and 2-ethoxyethanol samples to improve desorption efficiency. This was found to be unnecessary for 2-butoxyethanol samples.

To ascertain the validity of this method at higher concentrations, the collection efficiency of charcoal sampling tubes was confirmed at 50 ppm for each analyte. The stability and desorption efficiency of the analytes should not be affected at these higher loadings.

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

The effects of overexposure to 2-butoxyethanol and 2-butoxyethyl acetate are similar. Inhalation of vapors may be irritating to the respiratory tract and may cause nausea, headaches, vomiting, dizziness, drowsiness, and unconsciousness. The liquid is readily absorbed through the skin and may cause irritation to the skin and eyes. Ingestion may cause nausea, vomiting,

headaches, dizziness, and gastrointestinal irritation. Chronic overexposure may damage the kidneys, liver, and blood (Ref. 5.5).

1.1.3. Workplace exposure

2-Butoxyethanol is used as a solvent for nitrocellulose, natural and synthetic resins, soluble oils, lacquers, varnishes and enamels. It is also used in textile dyeing and printing, in the treatment of leather, in the production of plasticizers, as a stabilizer in metal cleaners and household cleaners, and in hydraulic fluids, insecticides, herbicides and rust removers (Ref. 5.6).

2-Butoxyethyl acetate is used as a high-boiling solvent for nitrocellulose lacquers, epoxy resins, and multicolor lacquers. It is also used as a film coalescing aid for polyvinyl acetate latex (Ref. 5.7).

1.1.4. Physical properties (Ref. 5.6 unless otherwise noted)

chemical formula:

2-butoxyethanol: $CH_3CH_2CH_2CH_2OCH_2CH_2OH$

2-butoxyethyl acetate: $CH_3CH_2CH_2CH_2OCH_2CH_2OOCCH_3$

	2-Butoxyethanol	2-Butoxyethyl acetate
CAS no.:	111-76-2	112-07-2
mol wt:	118.17	160.21
bp at 101.3 kPa, °C:	171.2	192
appearance:	colorless liquid	colorless liquid
sp gr at 20/20°C:	0.9022 (Ref. 5.8)	0.9422
vp at 20°C, Pa:	101	33-40
vapor density, air=1:	4.1	5.5
flash point, °C		
open cup: (Ref. 5.8)	69.4	87.8
closed cup: (Ref. 5.8)	60.0	73.9
autoignition temp., °C	244	340
odor:	mild	pleasant, sweet, fruity
odor threshold, ppm:	approx. 0.4	0.1 (absolute perception limit) 0.35-0.48 (recognition)
explosive limits, %		
lower:	1.1	0.88
upper	10.1	8.54
solubility:	soluble in water, alcohol, ether	moderately soluble (1 g per 100 g at 20°C) in water, soluble in hydrocarbons and other organic solvents

synonyms and trade names:

2-butoxyethanol:

ethylene glycol monobutyl ether; ethylene glycol n-butyl ether; butyl Cellosolve

2-butoxyethyl acetate:

ethylene glycol monobutyl ether acetate; 2-butoxyethanol acetate; acetic acid, 2-butoxyethyl ester; ethylene glycol butyl ether acetate; Ektasolve EB Acetate; butyl Cellosolve acetate

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

1.2. Limit defining parameters

1.2.1. Detection limit of the analytical procedure

The detection limits of the analytical procedure are 0.12 and 0.13 ng per injection (1.0-μL injection with a 58:1 split) for 2-butoxyethanol and 2-butoxyethyl acetate 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 7.22 and 7.54 μg per sample for 2-butoxyethanol and 2-butoxyethyl acetate 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 31 ppb (150 $\mu g/m^3$) and 24 ppb (157 $\mu g/m^3$) for 2-butoxyethanol and 2-butoxyethyl acetate 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.

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 both analytes (Section 4.4).

1.2.5. Recovery

The recovery of 2-butoxyethanol and 2-butoxyethyl acetate from samples used in a 15-day storage test remained above 98 and 86% respectively when the samples were stored at ambient temperatures (Section 4.5, from regression lines shown in Figures 4.5.1.2 and 4.5.2.2).

1.2.6. Precision (analytical procedure)

The pooled coefficients of variation obtained from replicate injections of analytical standards at 0.5, 1 and 2 times the target concentrations are 0.004 and 0.002 for 2-butoxyethanol and 2-butoxyethyl acetate 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 $\pm$10.1 and $\pm$10.8% for 2-butoxyethanol and 2-butoxyethyl acetate respectively. These include an additional $\pm$5% for pump error. The overall procedure must provide results at the target concentration that are $\pm$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 8 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 quantitate certain co-collected solvent vapors using this method because most other common solvents which are collected on charcoal are normally analyzed after desorption with carbon disulfide and may exhibit unacceptably low desorption efficiencies when 95/5 (v/v) methylene chloride/methanol is used.

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. x 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. It is desirable to utilize sampling tube holders that have protective covers to shield the employee from the sharp, jagged end of the sampling tube. Position the tube so that sampled air passes through the 100-mg section first.

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

2.3.4. To avoid channeling, place the sampling tube vertically 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 a list of any other solvents being used in the sampling area.

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

2.4. Sampler capacity

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 analytes by monitoring the effluent from sampling tubes containing only the 100-mg section of charcoal while sampling at 0.1 L/min from atmospheres containing 50 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 more than 8 h (>48 L).

2.5. Desorption efficiency

2.5.1. The average desorption efficiencies of 2-butoxyethanol and 2-butoxyethyl acetate from SKC Inc. Lot 120 charcoal are 99.0 and 101.5% respectively over the range of 0.5 to 2 times the target concentrations (Section 4.9.).

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

2.5.3. Desorption efficiencies should be periodically confirmed because they may change slightly due to variations in charcoal and operator technique.

2.6. Recommended air volume and sampling rate

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

2.6.2. For short-term samples, the recommended air volume is 15 L collected at 1.0 L/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 99 ppb (478 $\mu g/m^3$) for 2-butoxyethanol when 15 L is sampled.

2.7. Interferences (sampling)

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

2.7.2. Other solvents used in the sampling area should be reported to the laboratory as potential interferences.

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. Use sampling tube holders with protective covers if possible.

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 30-m × 0.25-mm i.d. (0.25-μm film), fused silica Nukol column (Catalog Number 2-4107M, Supelco, Inc., 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 Waters 860 Networking Computer 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-Butoxyethanol and 2-butoxyethyl acetate, reagent grade. Aldrich Lot 01604KT 2-butoxyethanol and Lot 01106KP 2-butoxyethyl acetate were used in this evaluation.

3.2.2. Methylene chloride, chromatographic grade. American Burdick and Jackson Lot AQ553 was used in this evaluation.

3.2.3. Methanol, chromatographic grade. American Burdick and Jackson Lot AW106 was used in this evaluation.

3.2.4. A suitable internal standard, reagent grade. Aldrich Lot 01601HT 2-ethyl-1-hexanol was used in this evaluation.

3.2.5. The desorption solvent consists of methylene chloride/methanol, 95/5 (v/v) containing an internal standard at a concentration of 1.5 mL/L.

3.2.6. GC grade nitrogen, air, and hydrogen.

3.3. Standard preparation

3.3.1. Prepare concentrated stock standards by diluting the pure analytes with methylene chloride. 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 2-butoxyethanol, dilute 3.0 mL of pure 2-butoxyethanol (sp gr = 0.9022) to 10.0 mL with methylene chloride. This stock solution would contain 270.7 μg/μL. A working standard of 1137 μg/sample is prepared by injecting 4.2 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. Add 1.0 mL of desorption solvent to each vial using the same dispenser as used for preparation of standards.

3.4.3. Immediately cap the vials and shake them periodically for about 30 min before analysis.

3.5. Analysis

3.5.1. GC conditions

column:	30-m x 0.25-mm i.d. fused silica, Nukol, 0.25-μm film	
injection volume:	1.0 μL (with a 58:1 split)	
zone temperatures:	column—90°C injector—150°C detector—200°C	
gas flows:	hydrogen (carrier)— (83 kPa head pressure) nitrogen (makeup)— hydrogen (flame)— air—	1.7 mL/min 20 mL/min 65 mL/min 315 mL/min
retention times:	2-butoxyethanol— 2-butoxyethyl acetate— (2-ethyl-1-hexanol—	7.55 min 9.75 min 5 min)
chromatogram:	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 produces a flame ionization detector response and has a similar retention time as the analyte or internal standard is a potential interference. Any potential interferences reported to the laboratory by the industrial hygienist 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.

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

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

where 24.46 = molar volume (L) at 25°C and 101.3 kPa (760 mmHg)
molecular weight = 118.17 for 2-butoxyethanol
160.21 for 2-butoxyethyl acetate

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 58:1 split) was used in the determination of the detection limits of the analytical procedure. The detection limits of 0.12 and 0.13 ng were determined by making injections of 7.22 and 7.54 ng/μL standards for 2-butoxyethanol and 2-butoxyethyl acetate, respectively. These amounts were judged to produce peaks with heights approximately 5 times the baseline noise. A chromatogram of such an injection is shown in Figure 4.1.

4.2. Detection limit of the overall procedure

Six samples for each analyte were prepared by injecting 7.22 µg of 2-butoxyethanol and 7.54 µg of 2-butoxyethyl acetate into the 100-mg section of charcoal tubes. The detection limits of the overall procedure correspond to air concentrations of 31 ppb (150 µg/m^3) and 24 ppb (157 µg/m^3) for 2-butoxyethanol and 2-butoxyethyl acetate, respectively. The results are given in Tables 4.2.1 and 4.2.2.

Table 4.2.1
Detection Limit of Overall Procedure
for 2-Butoxyethanol

Sample no.	µg spiked	µg recovered
1	7.22	6.87
2	7.22	7.03
3	7.22	7.49
4	7.22	7.36
5	7.22	6.98
6	7.22	7.16

Table 4.2.2
Detection Limit of Overall Procedure
for 2-Butoxyethyl Acetate

Sample no.	µg spiked	µg recovered
1	7.54	8.57
2	7.54	8.51
3	7.54	7.76
4	7.54	7.58
5	7.54	7.72
6	7.54	7.34

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 7.22 µg of 2-butoxyethanol and 7.54 µg of 2-butoxyethyl acetate into the 100-mg section of charcoal tubes. These amounts

correspond to air concentrations of 31 ppb (150 $\mu g/m^3$) and 24 ppb (157 $\mu g/m^3$) for 2-butoxyethanol and 2-butoxyethyl acetate, respectively. The results are given in Tables 4.3.1 and 4.3.2.

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

Sample no.	Percent recovered	Statistics
1	95.2	$\overline{X}$ = 99.0
2	97.4	
3	103.7	
4	101.9	SD = 3.25
5	96.7	Precision = (1.96) (±3.25)
6	99.2	= ±6.37

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

Sample no.	Percent recovered	Statistics
1	113.7	$\overline{X}$ = 105.0
2	112.9	
3	102.9	
4	100.5	SD = 6.74
5	102.4	Precision = (1.96) (±6.76)
6	97.3	= ±13.2

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 and 4.4.2 and Figures 4.4.1 and 4.4.2. The response is linear for both analytes with slopes (in ISTD-corrected area counts per micrograms of analyte per sample) of 226.3 and 219.6 for 2-butoxyethanol and 2-butoxyethyl acetate, respectively.

Table 4.4.1
Instrument Response to 2-Butoxyethanol

× target concn	0.5×	1×	2×
µg/sample	568.9	1138	2276
ppm	2.45	4.91	9.81
Area counts	130013	265338	511143
	130843	264851	511543
	130236	266530	510113
	130759	264206	507834
	130483	266271	508070
	130198	265353	514955
$\overline{X}$	130422	265425	510610

Table 4.4.2
Instrument Response to 2-Butoxyethyl Acetate

× target concn	0.5×	1×	2×
µg/sample	791.3	1583	3165
ppm	2.52	5.03	10.07
Area counts	174117	355187	690704
	174715	355740	688825
	173817	355966	690567
	173654	355907	690419
	173498	355731	693114
	173516	354933	692883
$\overline{X}$	173886	355577	691085

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-h 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 L/min (12-L samples). For each set of 36 samples for each analyte, six samples were analyzed immediately after generation, fifteen were stored in a refrigerator at 0°C, and fifteen were stored in a closed drawer at ambient temperatures of 20–28°C. Six samples, three from refrigerated and three

from ambient storage, were analyzed at intervals over a period of fifteen days. The results are given in Tables 4.5.1 and 4.5.2 and shown graphically in Figures 4.5.1.1, 4.5.1.2, 4.5.2.1 and 4.5.2.2. The loss of analyte on the 2-butoxyethyl acetate samples was due to hydrolysis of the ester to 2-butoxyethanol and acetic acid. This was supported by the fact that amounts of 2-butoxyethanol were found on these samples which corresponded to the loss of 2-butoxyethyl acetate. The loss of analyte in this study after 15 days was about 3% for refrigerated storage and about 10% for ambient storage. If possible, stored 2-butoxyethyl acetate samples should be refrigerated to reduce hydrolysis.

Table 4.5.1
Storage Test for 2-Butoxyethanol

Storage time (days)	% recovery (refrigerated)			% recovery (ambient)		
0	98.5	96.9	98.0	98.5	96.9	98.0
0	97.7	98.2	98.4	97.7	98.2	98.4
2	99.7	99.7	99.2	99.5	98.9	99.7
6	97.9	98.3	99.0	97.5	98.2	99.0
8	95.5	96.0	96.2	95.2	96.4	96.3
13	100.3	100.2	100.8	98.4	99.4	100.0
15	99.1	99.0	100.0	98.2	99.6	98.2

Table 4.5.2
Storage Test for 2-Butoxyethyl Acetate

Storage time (days)	% recovery (refrigerated)			% recovery (ambient)		
0	99.2	98.6	98.9	99.2	98.6	98.9
0	97.7	94.0	99.4	97.7	94.0	99.4
2	98.6	96.4	98.6	93.2	96.5	95.8
6	97.5	97.1	97.9	91.6	86.7	92.4
8	96.0	96.5	97.7	89.3	90.1	90.9
13	97.4	95.1	97.1	88.2	85.2	90.0
15	97.2	93.1	96.8	87.0	89.7	89.1

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 and 4.6.2. These tables are based on the data presented in Section 4.4.

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

× target concn	0.5×	1×	2×
µg/sample	568.9	1138	2276
ppm	2.45	4.91	9.81
SD (area counts)	330.6	867.7	2624
CV	0.0025	0.0033	0.0051

$\overline{CV}$ = 0.004

Table 4.6.2
Precision of the Analytical Procedure
for 2-Butoxyethyl Acetate
(Based on Table 4.4.2)

× target concn	0.5×	1×	2×
µg/sample	791.3	1583	3165
ppm	2.52	5.03	10.07
SD (area counts)	466.2	418.9	1632
CV	0.0027	0.0012	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
Y_{obs} = observed % recovery at a given time
Y_{est} = 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 5.2% and 5.5% for 2-butoxyethanol and 2-butoxyethyl acetate 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 ±10.1% and ±10.8% for 2-butoxyethanol and 2-butoxyethyl acetate respectively. The SEE and precision of the overall procedure for each analyte were obtained from Figures 4.5.1.2 and 4.5.2.2 for 2-butoxyethanol and 2-butoxyethyl acetate, respectively.

4.8 Reproducibility

Six samples for each analyte, collected from controlled test atmospheres (at about 80% R.H., 24–28°C, 86–88 kPa) containing the analytes at about 4 times the target concentrations, were analyzed by a chemist unassociated with this evaluation. The samples were generated by drawing the test atmospheres through sampling tubes for 60 min at approximately 0.2 L/min. The samples were stored in a refrigerator for 8 days before being analyzed. The results are presented in Tables 4.8.1 and 4.8.2.

Table 4.8.1
Reproducibility for 2-Butoxyethanol

Sample no.	µg found	µg expected	% found	% deviation
1	1008	1090	92.5	-7.5
2	992.6	1073	92.5	-7.5
3	994.5	1073	92.7	-7.3
4	993.2	1063	93.4	-6.6
5	1007	1091	92.3	-7.7
6	1036	1104	93.8	-6.2

Table 4.8.2
Reproducibility for 2-Butoxyethyl Acetate

Sample no.	µg found	µg expected	% found	% deviation
1	1347	1396	96.5	-3.5
2	1337	1372	97.4	-2.6
3	1315	1371	95.9	-4.1
4	1318	1361	96.8	-3.2
5	1364	1373	99.3	-0.7
6	1380	1414	97.6	-2.4

4.9. Desorption efficiency

The desorption efficiency for each analyte was determined by injecting microliter amounts of stock standards onto the front section of charcoal tubes. Eighteen samples were prepared, six samples for each concentration level listed in the following table.

Table 4.9
Desorption Efficiency Data

Analyte	2-Butoxyethanol			2-Butoxyethyl acetate		
× target concn	0.5×	1×	2×	0.5×	1×	2×
µg/sample	568.9	1138	2276	791.3	1583	3165
ppm	2.45	4.91	9.81	2.52	5.03	10.07
Desorption	99.0	99.4	99.9	101.6	100.6	102.2
efficiency, %	98.7	99.1	99.1	101.6	101.7	101.8
	100.4	98.5	98.4	101.9	101.4	101.3
	99.2	98.9	99.0	101.5	101.2	102.2
	98.5	98.0	99.2	101.4	100.9	101.7
	99.1	98.2	99.3	101.1	100.9	102.4
$\overline{X}$	99.2	98.7	99.2	101.5	101.1	101.9
$\overline{X}$		99.0			101.5	

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

Sample no.	% desorption after 24 h	
	2-Butoxyethanol	2-Butoxyethyl acetate
1	101.8	103.4
2	102.7	103.8
3	102.7	103.8
4	101.7	103.8
5	101.0	103.6
6	100.7	103.4
$\overline{X}$	101.8	103.6

4.11. Chromatograms

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

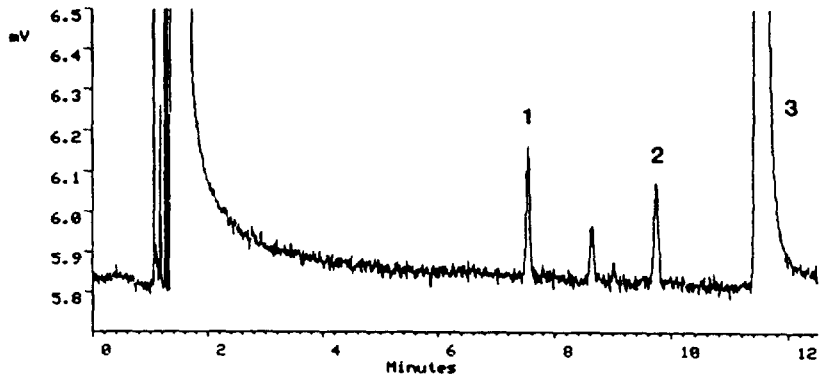

Figure 4.1. Detection limit chromatogram. Key: (1) 2-butoxyethanol, (2) 2-butoxyethyl acetate, (3) 2-ethyl-1-hexanol.

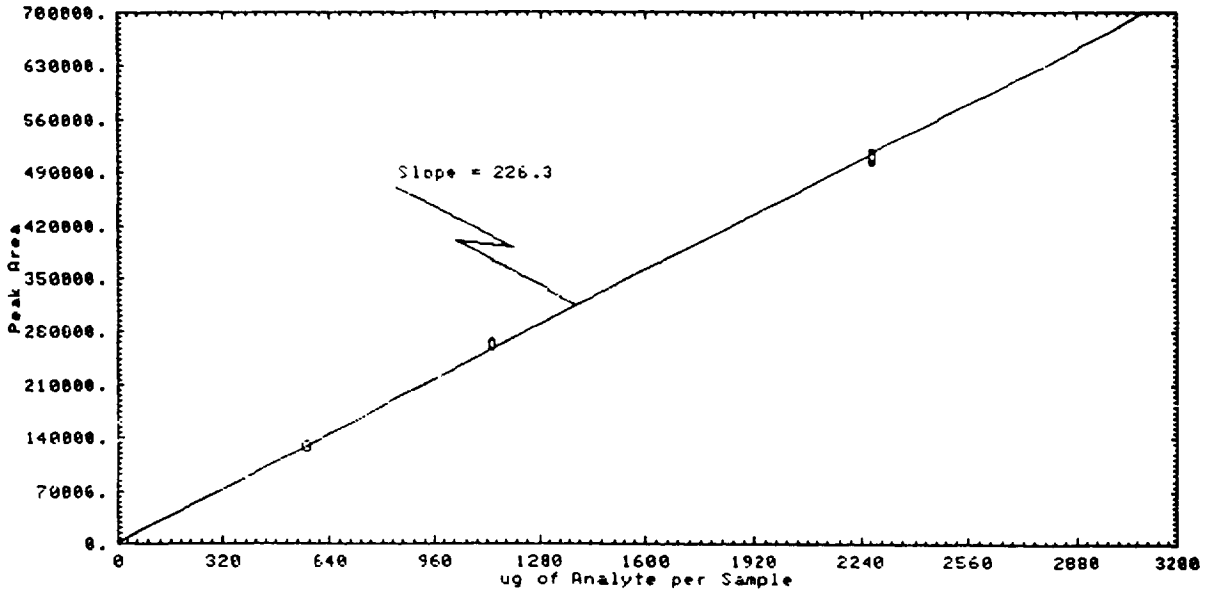

Figure 4.4.1. Instrument response to 2-butoxyethanol.

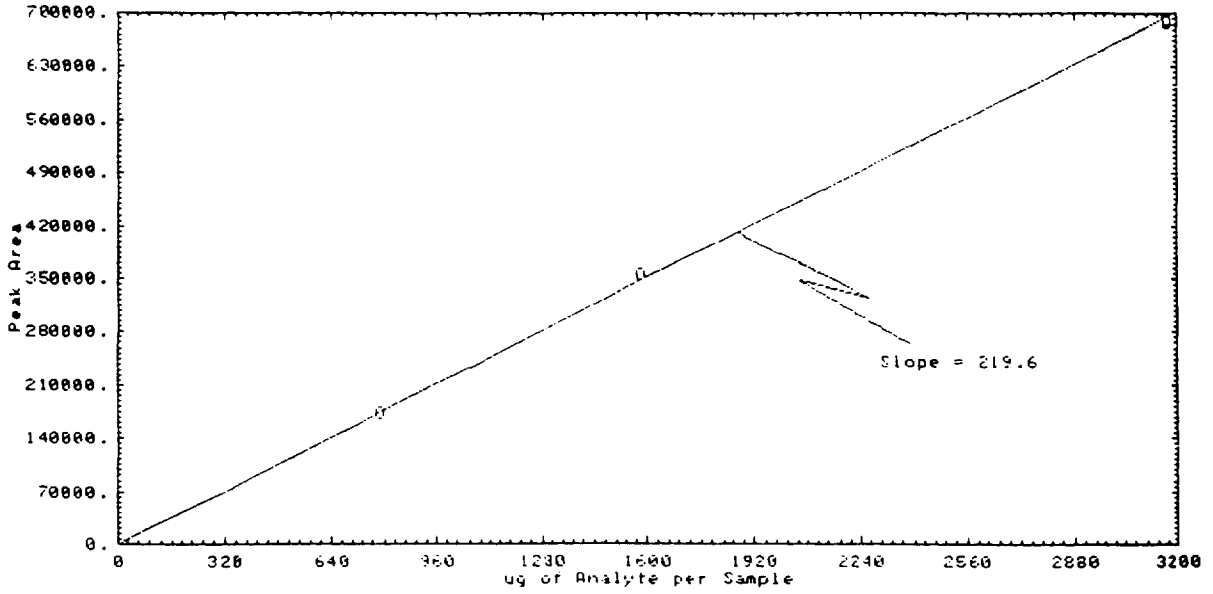

Figure 4.4.2. Instrument response to 2-butoxyethyl acetate.

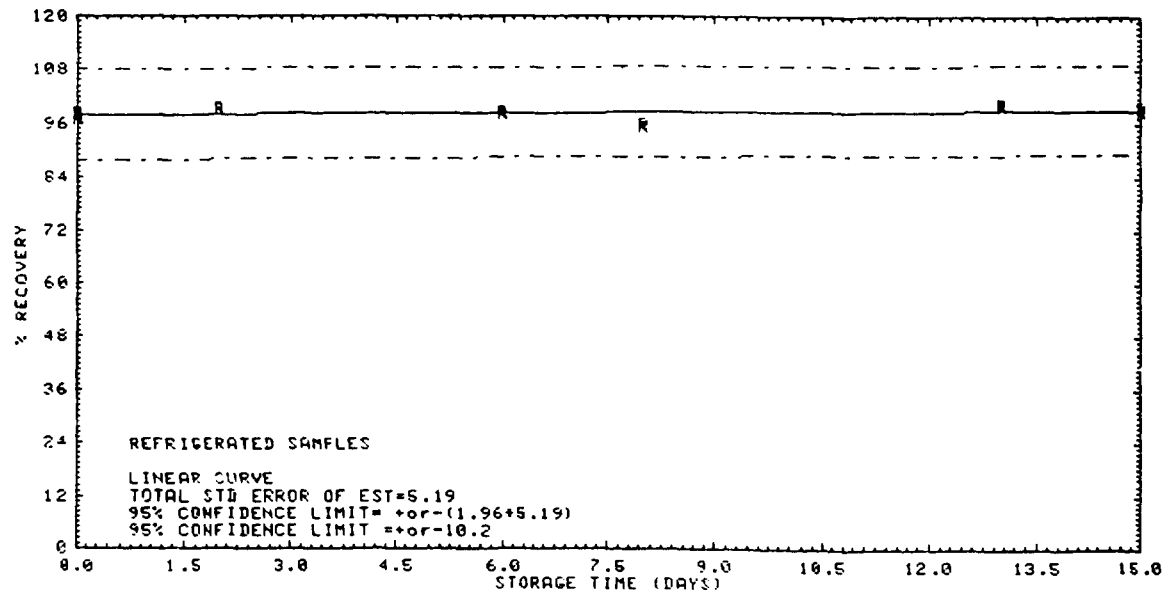

Figure 4.5.1.1. 2-Butoxyethanol refrigerated storage samples.

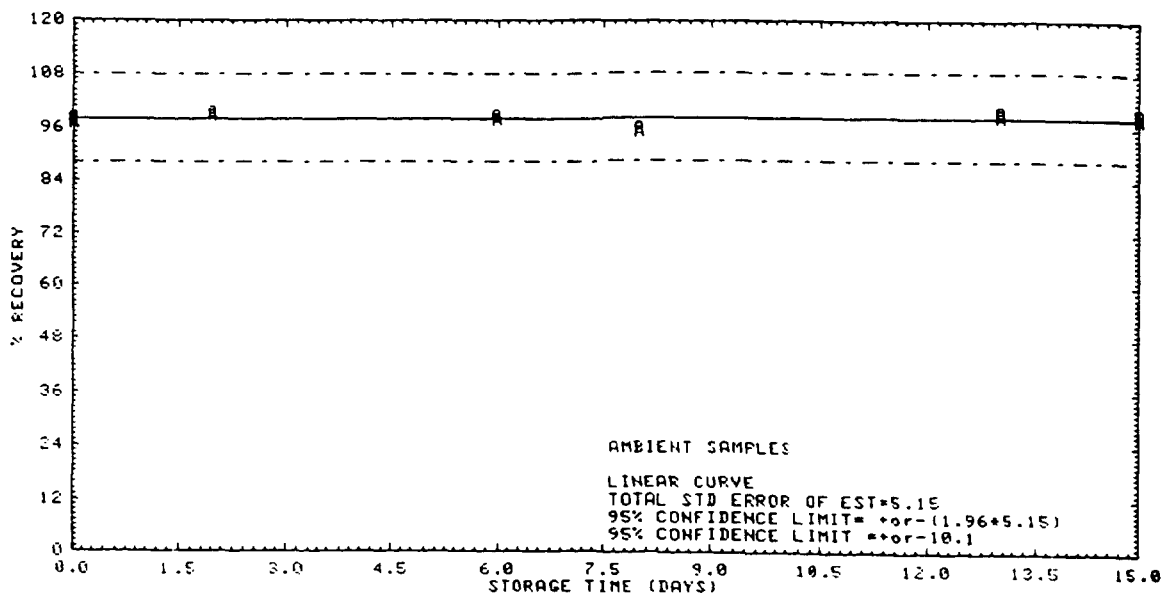

Figure 4.5.1.2. 2-Butoxyethanol ambient storage samples.

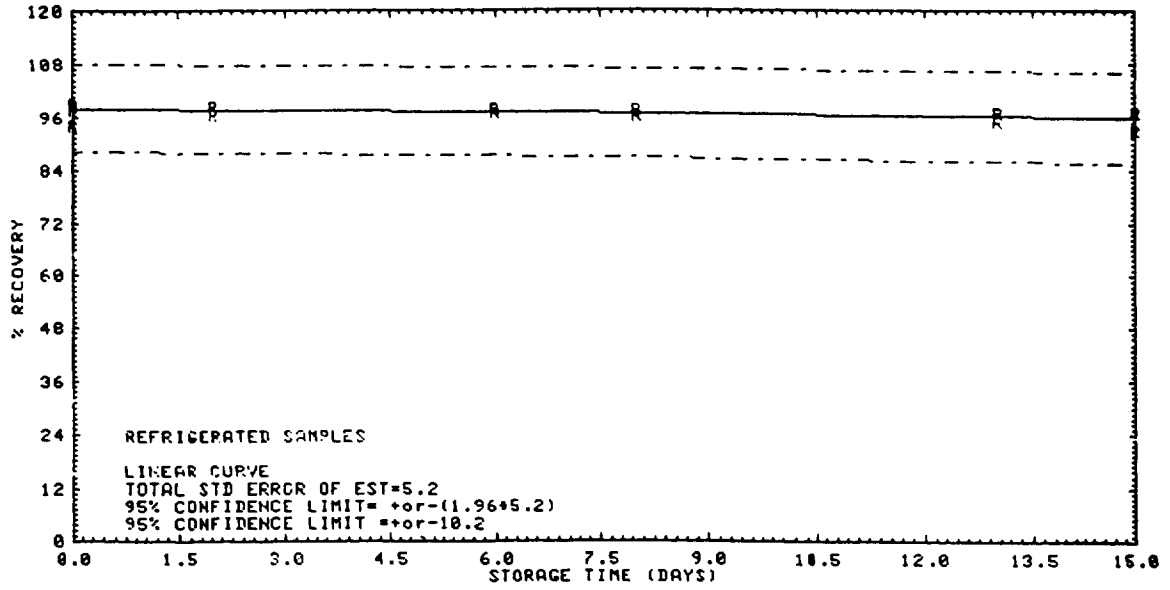

Figure 4.5.2.1. 2-Butoxyethyl acetate refrigerated storage samples.

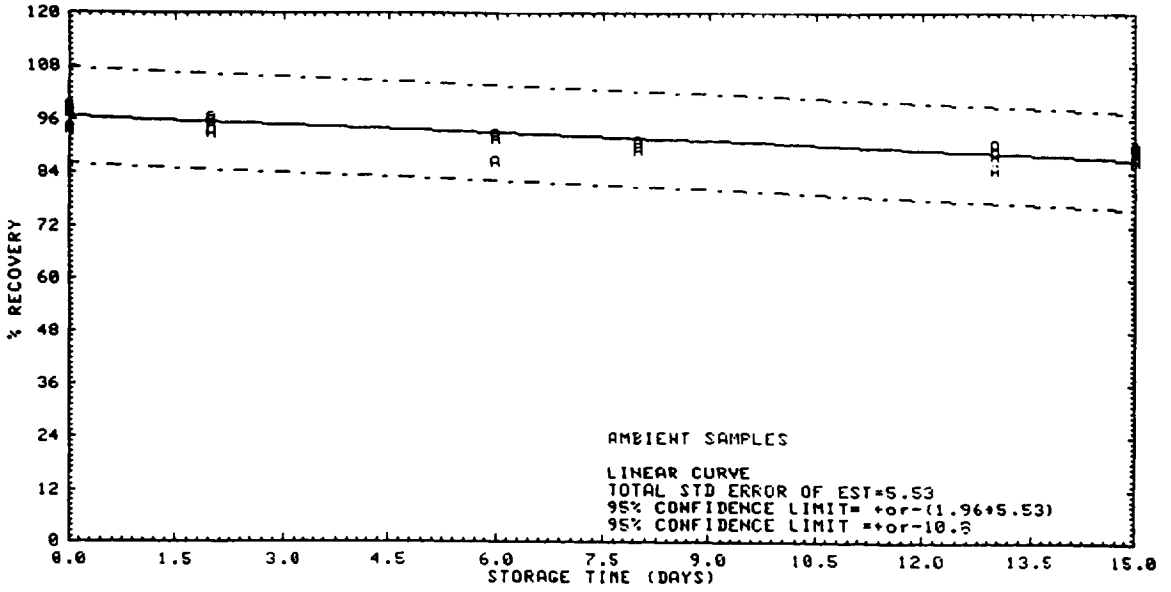

Figure 4.5.2.2. 2-Butoxyethyl acetate ambient storage samples.

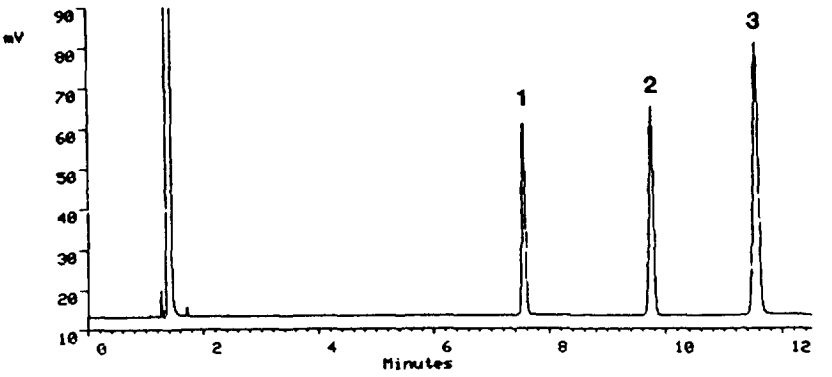

Figure 4.11. Chromatogram of a standard at the target concentrations. Key: (1) 2-butoxyethanol, (2) 2-butoxyethyl acetate, (3) 2-ethyl-1-hexanol.

5. REFERENCES

5.1. "OSHA Analytical Methods Manual," U.S. Department of Labor, Occupational Safety and Health Administration; OSHA Analytical Laboratory: Salt Lake City, UT, 1985; Method 53; American Conference of Governmental Industrial Hygienists (ACGIH): Cincinnati, OH, ISBN: 0-936712-66-X.

5.2. Elskamp, C.J. "OSHA Method 79; 2-Methoxyethanol, 2-Methoxyethyl Acetate, 2-Ethoxyethanol, and 2-Ethoxyethyl Acetate," OSHA Analytical Laboratory, unpublished, Salt Lake City, UT 84165, January, 1990.

5.3. "NIOSH Manual of Analytical Methods," 3rd ed.; U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Physical Sciences and Engineering; Cincinnati, OH, 1984, Method 1403, DHHS (NIOSH) Publ. No. 84-100.

5.4. "Air Contaminants—Permissible Exposure Limits," Code of Federal Regulations, Title 29; 1910.1000, U.S. Department of Labor, OSHA; Washington, DC, 1989, DOL (OSHA) Publ. No. OSHA 3112.

5.5. J.T. Baker Chemical Co.: Material Safety Data Sheets (MSDS) for 2-butoxyethanol and 2-butoxyethyl acetate, Jan. 1989.

5.6. ChemInfo Database on CCINFO CD-ROM disc 89-2, Canadian Centre for Occupational Health and Safety, Hamilton, Ontario.

5.7. "Hawley's Condensed Chemical Dictionary," 11th ed.; Sax, N.I.; Lewis, R.J., Eds.; Van Nostrand Reinhold, New York, 1987.

5.8. Brown, E.S. et al. In "Kirk-Othmer Encyclopedia of Chemical Technology," 3rd ed.; Grayson, M., Ed.; John Wiley & Sons, New York, 1980, Vol. 11, pp 933-956.

APPENDIX B

MATERIAL SAFETY DATA SHEET

The following items of information that are applicable to a product or material shall be provided in the appropriate block of the material safety data sheet (MSDS).

Insert the product designation in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. The MSDS should be printed to read upright with the sheet turned sideways. The product designation is the name or code that appears on the label, or the name by which the product is sold, or the name 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.

B.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.

B.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 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 could be included both for its toxicity and its reactivity. Note that the 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.

Chemical substances should be listed 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.

Toxic hazard data shall be stated 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.

B.3 SECTION III. PHYSICAL DATA

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mm Hg); vapor density of gas or vapor (air = 1); solubility in water, in parts per 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 design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of spilled substances or substances stored in improperly marked containers.

B.4 SECTION IV. FIRE AND EXPLOSION DATA

Section IV should contain complete fire and explosion data for the product, including 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."

B.5 SECTION V. HEALTH HAZARD INFORMATION

The "Health Hazard Data" should be 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. Comments should 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.
>
> "Emergency and First Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information that would be of assistance to an attending physician, including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed workers.

B.6 SECTION VI. REACTIVITY DATA

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

B.7 SECTION VII. SPILL OR LEAK PROCEDURES

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect workers assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described 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. Specific procedures shall be identified.

B.8 SECTION VIII. SPECIAL PROTECTION INFORMATION

Section VIII requires specific information. Statements such as "yes," "no," or "if necessary" are not informative. Ventilation requirements should be specific as to type and preferred

methods. Respirators shall be specified as to type and NIOSH or MSHA approval class (i.e., "supplied air," "organic vapor canister," etc.). Protective equipment must be specified as to type and materials of construction.

B.9 SECTION IX. SPECIAL PRECAUTIONS

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. 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.

B.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 correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to workers exposed to the hazardous substance. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new workers. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It 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
INCOMPATIBILITY
HAZARDOUS DECOMPOSITION PRODUCTS
CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION
VII SPILL OR LEAK PROCEDURES
STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED NEUTRALIZING CHEMICALS
WASTE DISPOSAL METHOD
VIII SPECIAL PROTECTION INFORMATION
VENTILATION REQUIREMENTS
SPECIFIC PERSONAL PROTECTIVE EQUIPMENT RESPIRATORY (SPECIFY IN DETAIL)
EYE
GLOVES
OTHER CLOTHING AND EQUIPMENT

MATERIAL SAFETY DATA SHEET (Continued)

Section IX

IX SPECIAL PRECAUTIONS
PRECAUTIONARY STATEMENTS
OTHER HANDLING AND STORAGE REQUIREMENTS

PREPARED BY _____

ADDRESS _____

DATE _____

APPENDIX C

BACKGROUND OF METHODS USED FOR ANALYSIS OF BAA IN URINE

Johanson et al. [1986] modified the method of Smallwood et al. [1984] to determine BAA in urine. An internal standard for pentoxyacetic acid was added to acidified urine. After extraction with methylene chloride, an alkaline solution of tetrabutylammonium hydrogen sulfate was added. Pentafluorobenzyl bromide (PFBB) was also added and the mixture shaken vigorously for 1 hr. Gas chromatography with a flame ionization detector (FID) was performed on a fused silica capillary column (BP-10, 12 m × 0.22 mm id) using a 1:100 split ratio. The limits of detection for BAA in urine and recovery data were not presented. Reproducibility was reported as 7.6%.

Johanson et al. [1988] modified the method used previously for BAA in urine by performing the phase transfer catalysis derivatization at pH 6 to avoid hydrolysis of potential conjugates and by using an electron capture detector to increase sensitivity. Urine (200 µl), tetrabutylammonium hydrogen sulfate, sodium phosphate buffer, pentoxyacetic acid (pH 6) (internal standard), methylene chloride, and PFBB were added to a screw-capped culture tube. The culture tube was vigorously shaken and then rotated for 1 hr at room temperature. The methylene chloride layer was evaporated to dryness and the residue taken up in hexane. A gas chromatograph equipped with an Ni^{63} electron capture detector and an autosampler was used for separation and quantitation of BAA. A fused silica capillary column (Oribond SE-30, 25 m × 0.32 mm id) was used in the split/splitless mode. The analytical range of the method was 5 to 500 µmol/liter (0.66 to 66 mg/liter). Although limits of detection were not given, they can be assumed to be lower than the standard (0.6 mg/liter). Reproducibility was stated as 14% (RSD) based on the analysis of 60 duplicate urine samples.

Groeseneken et al. [1989] further evaluated the existing methods for alkoxyacetic acids and concluded that the phase transfer catalysis procedures had the required specificity without the production of artifacts, but they lacked sufficient sensitivity to detect these metabolites at low occupational exposure concentrations. On the other hand, the methods utilizing diazomethane derivatization had the required sensitivity but lacked the specificity. Therefore, Groeseneken et al. [1989] developed an improved method that combined the best attributes of the two basic existing methods. Because background interference in urine samples can be troublesome when using the electron capture detector, the method published by Johanson et al. [1988] was not cited even though it has the required sensitivity and specificity for BAA.

The procedure developed by Groeseneken et al. [1989] was described as follows. Urine was adjusted to pH 7; 1 ml was 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 performed by adding distilled water and extracting the pentafluorobenzyl 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 11.66 min (BAA) 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 performed 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, recovery of BAA from urine averaged 95.1%. The yield for the derivatization reaction averaged 101.3% for BAA. Standard curves were set up in 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, was 0.03 mg/liter. Precision of the method, calculated from triplicate injections of 40 urine samples, averaged 3.5%, ranging from 1.1% at 25 mg/liter to 20% at 0.1 mg/liter.

The method of Groeseneken et al. [1989] is the preferred method for analysis of the alkoxyacetic acid metabolites in urine.

APPENDIX D

GUIDELINES FOR BIOLOGICAL MONITORING

Compliance with the NIOSH REL alone may not ensure that workers are protected from overexposure to EGBE and EGBEA. In addition to inhalation, dermal absorption is a significant route of entry for these chemicals. As a result, biological monitoring of workers should be done routinely on the basis of work practices.

D.1 MONITORING FOR BAA IN URINE

To conduct biological monitoring, urine samples should be evaluated for BAA using the method of Groeseneken et al. [1989] or an equivalent method. Expression of results as milligrams of metabolite per gram of creatinine (mg/m creatinine) is suggested. Factors that may affect the urinary concentration of BAA include ethanol consumption (which lowers urinary metabolite concentrations), dermal contact, heavy workloads, and nonoccupational exposures.

Urine samples should be collected at the end of the workshift following at least 2 days of typical exposure. Such specimens reflect absorption (dermal and inhalation) during the day and possibly some residual BAA from the previous day's exposure. In case of an accident or spill, urine samples should be collected 3 hr later, when peak BAA excretion occurs.

Measurable concentrations of BAA in the urine indicate uptake of EGBE or EGBEA by inhalation, skin exposure, or both. Urinary BAA reflects nonoccupational as well as occupational exposure and may not correlate with the NIOSH REL. If concentrations of BAA exceed the estimated guidelines below, excessive exposure to EGBE or EGBEA may have occurred even if airborne concentrations were not necessarily above the NIOSH REL. The source of exposure should be determined by thorough industrial hygiene evaluation, with emphasis on possible dermal absorption. The guidelines in the following subsection are suggested until better documented ones are developed.

D.2 DETERMINATION OF URINARY BAA CONCENTRATION CORRESPONDING WITH THE REL FOR EGBE

Four sources (presented in Sections 4.3 and 5.2) were investigated for quantitative data relating EGBE exposure to urinary excretion of BAA: Johanson et al. [1986], Van Vlem [1988], pp. 1-54, Van Vlem [1988], pp. 55-72, and Carpenter et al. [1956]. Because

Carpenter et al. used paper chromatography (which is not as quantitatively accurate as modern chromatographic techniques) and because these investigators did not give data for the peak urinary (end of shift) concentration of BAA, concentrations were calculated from the other three sources, as follows.

D.2.1 Johanson et al. [1986].

The estimated BAA in urine was determined after a 2-hr exposure to 20 ppm EGBE, with a 50-W workload (see Table D-1). BAA excretion rates for the seven subjects were taken from Johanson et al. [1986] (Figure 5). The y-axis values were measured in mm, converted into μmol/min, and then converted into mg BAA excreted per 2 hr, for each subject. Johanson et al. [1986] do not give the creatinine values for these subjects, so a physiologically "normal" value of 1.5 g creatinine/day was assumed [Davidson and Henry 1974].

Therefore, a 2-hr exposure to 20 ppm EGBE with a 50-W workload, is expected to yield urinary BAA concentrations of 64, 84, 114, and 90 mg BAA/g creatinine at 2, 4, 6, and 8 hr, respectively. The urinary BAA from an 8-hr exposure to 20 ppm EGBE with a 50-W workload can be estimated by "superpositioning" [Gibaldi and Perrier 1982] the urinary BAA profiles of four 2-hr exposures. For the 8-hr "end of shift" timepoint, the result is equal to the sum of the concentrations from the four 2-hr exposures given above; therefore, the expected urinary BAA concentration is 64 + 84 + 114 + 90 = 352 mg BAA/g creatinine. This can be extrapolated to a 5-ppm EGBE exposure by multiplying by 5/20 for a yield of 88 mg BAA/g creatinine.

D.2.2 Van Vlem [1988], pp. 1–54.

An estimate of BAA excretion from 4-hr EGBE exposures was determined from data by Van Vlem [1988], Appendix 3, Figure 2.10 (page 43). The exposures were 50 min/hr

Table D-1.—Excretion of BAA during various time intervals*,† (mg BAA/g creatinine)

Subject	Time interval (hr)			
	0 to 2	2 to 4	4 to 6	6 to 8
1	5.5956	5.9958	20.4336	25.1388
2	8.4693	16.1843	56.6037	30.9275
3	32.5721	20.9698	61.7085	73.3407
4	45.2215	49.2998	95.0266	112.9393
5	61.7085	52.8257	141.3661	115.9031
6	138.9457	187.9729	152.7901	123.1247
7	155.4516	252.1130	272.4866	146.3340
Average	63.9949	83.6230	114.3450	89.6726

*Adapted from Johanson et al. [1986].
†Assuming 1.5 g creatinine excreted per day. EGBE exposure = 2 hr, 20 ppm, 50-W workload.

for 4 hr, by facemask, to either 25.2 (experiment I) or 12.6 (experiments II and III) ppm EGBE. Because the subjects were exposed for only 50 minutes per hour, these are equivalent to 4-hr exposures to 21.0 (experiment I) or 10.5 (experiments II and III) ppm EGBE. Only three subjects were used; each subject was exposed once in each of the three experiments. Experiments I and II were performed with the subjects in a "resting" condition, while experiment III was done under a 30-W workload. Because of the very limited number of subjects, a separate estimate of BAA excretion was made for each of the three experiments, and the three estimates were averaged to give one overall estimate of BAA excretion.

The y-axis values in Figure 2.10 were measured (in mm) for the 4- and 8-hr time points and converted to μg BAA/min. Assuming a normal physiological level of creatinine excretion (1.5 g/day), BAA concentrations in urine at 4 and 8 hr after the beginning of an 8-hr EGBE exposure were calculated as shown in Table D-2.

The urinary BAA concentrations predicted (by "superpositioning" two 4-hr exposures) for an 8-hr end-of-shift urine sample are 87, 51, and 61 mg BAA/g creatinine for experiments I, II, and III, respectively. For a work setting, the values in experiments I and II should be approximately doubled to reflect the increased pulmonary uptake expected under nonresting conditions. Proportionally adjusting these values to a 5-ppm EGBE exposure results in predicted urinary BAA values of 41, 49, and 29 mg BAA/g creatinine for experiments I, II, and III, respectively. The arithmetic average of these three estimates is 39.6 mg BAA/g creatinine, or (rounding off) 40 mg BAA/g creatinine. The average estimate—40 mg BAA/g creatinine—is the best overall estimate of BAA excretion that can be prepared from this data set.

D.2.3 Van Vlem [1988], pp. 55–72.

These data were taken from Van Vlem [1988], Appendix 3, pp. 55–72. Van Vlem reports the average exposure to EGBE for the five women to be 3.1 mg/m^3 (0.65 ppm), resulting in a BAA value of 8.1 mg/liter at the end of the workday:

8.1 mg/liter × 1.2 liter urine/day × 1 day/1.5 g creatinine = 6.48 mg BAA/g creatinine

Adjusting this to a 5-ppm exposure yields:

6.48 × (5/0.65) = 49.8 mg BAA/g creatinine, or (rounded) 50 mg BAA/g creatinine

Table D–2.—BAA concentrations in urine after exposure to EGBE

Expt. No.	EGBE conc. (mg/m^3)	EGBE conc. (ppm)	Exercise (W)	mg BAA/g cr. 4-hr	mg BAA/g cr. 8-hr
I	120	21.0	0	48.12	38.88
II	60	10.5	0	34.38	16.50
III	60	10.5	30	38.40	22.92

D.3 OVERALL ESTIMATE OF BAA

The BAA estimates from Johanson et al. [1986] and Van Vlem [1988] can be averaged to provide a single "best" estimate as follows:

(88 + 40 + 50)/3 = 59.3, or (rounded) 60 mg BAA/g creatinine

D.4 LIMITATIONS OF ESTIMATING BAA

All of these studies have some limitations.

Johanson et al. [1986] is an excellent laboratory study; however, the seven subjects were male. The 50-W exercise level used in this study may exceed the actual workplace energy expenditure of many workers in "light" industries, leading to an overestimate of actual EGBE uptake (under working conditions). Furthermore, the experimental protocol utilized 2-hr exposures; this is a rather short exposure from which to extrapolate uptake during an 8-hr workday.

The Van Vlem [1988] laboratory studies used only three (male) subjects; this is far too few to compensate for individual variations in uptake and metabolism. Because the same three subjects were used for all three experiments, it is possible that the results of these experiments may be systematically biased (either high or low) by the presence of even one unusual EGBE metabolizer. In addition, the experiments were conducted using inhalation by face mask; this neglects any possible contribution from dermal absorption (caused by possible dermal deposition of EGBE vapor on the subject's skin). Because the subjects were exercising, and most likely sweating, the deposition of the highly water-soluble EGBE on the wet skin may conceivably be significant.

Urine samples from the Veulemans et al. study [1987] were analyzed for BAA by Van Vlem [1988]. They represent samples from five female workers under actual working conditions. The exposures were for five working days, so that the time of exposure was more than adequate. However, the average EGBE exposure concentration was only 0.65 ppm, and the exposure was to a mixture of solvents. Therefore, a substantial extrapolation is involved in using these data to project the results to a 5-ppm exposure to EGBE alone, and the possibility that the other solvents involved may have altered the metabolism of EGBE (most likely reducing BAA excretion) cannot be excluded. In addition, a dermal component of the EGBE uptake (under actual working conditions) cannot be ruled out.

In all, the published data on which this BAA estimation is based are not as complete and consistent as might be desired. It is clear that further studies of EGBE uptake (either laboratory or field studies) would be advantageous, and that the existing data do not allow an absolutely rigorous determination of a BAA concentration for corresponding to 5 ppm EGBE. However, publication of the estimated BAA concentration simply as a guideline may be of some use in situations where a mixed exposure (inhalation plus dermal) may occur. Under such conditions, a workplace standard based entirely on ambient air concentration may grossly underestimate the total uptake of EGBE (by neglecting the dermal

component), whereas biological monitoring for BAA will reflect both the pulmonary and the dermal exposure routes.

D.5 JUSTIFICATION FOR RECOMMENDING BIOLOGICAL MONITORING

The following factors justify NIOSH recommendations for biological monitoring:

- Biological monitoring for EGBE and EGBEA exposure is recommended even though no validated guidelines can be provided concerning the relationship between airborne exposure to these ethylene glycol ethers and their urinary metabolite, BAA. This metabolite is both an index of exposure or uptake of EGBE by the worker and an index of potential adverse health effects from this ethylene glycol ether.

- Dermal absorption may be a major route of exposure to EGBE or EGBEA. The potential also exists for absorption of their vapors through wet skin.

- The influence of workload is significant for inhalation exposure. Doubling the workload results in twice the uptake of EGBE and EGBEA.

APPENDIX E

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. For these reasons, the following guidelines are to be considered as informed suggestions rather than established NIOSH policy recommendations. They are intended primarily to assist the physician in developing medical evaluation criteria for respirator use.

E.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].

E.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]. While 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

*Adapted from *NIOSH Respirator Decision Logic* [NIOSH 1987b].

respirator's added resistances and dead space is usually a small decrease in ventilation [Craig 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 while vigorous exercise with a respirator does alter pleural pressures, the risk of barotrauma would seem to be substantially less than that of 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. While 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.

E.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.

E.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].

E.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].

E.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 psycho-physiologic 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.

E.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.

E.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

While 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. While 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 (PAPRs) or continuous flow, air-line respirators, might irritate the eyes of a contact lens wearer.

E.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. While 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.

- While 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 E-1.

Table E-1.—Suggested frequency of medical fitness determinations*

Type of working conditions	Worker age (years)		
	<35	35–45	>45
Most work conditions requiring respirators	Every 5 years	Every 2 years	1–2 years
Strenuous working conditions with a SCBA†	Every 3 years	Every 18 months	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.

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, firefighters 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-year intervals for firefighters below age 40 who use SCBAs and at 2-year intervals for those aged 40 to 50. He further suggested that firemen over age 50 not be allowed to wear SCBAs.

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-year 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]. While 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 most situations, a worker who can physically do an assigned job without a respirator can perform the same job without increased risk 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 one second (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.

E.3 CONCLUSIONS

Individual judgment is needed to determine the factors affecting an individual's fitness to wear a respirator. While 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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