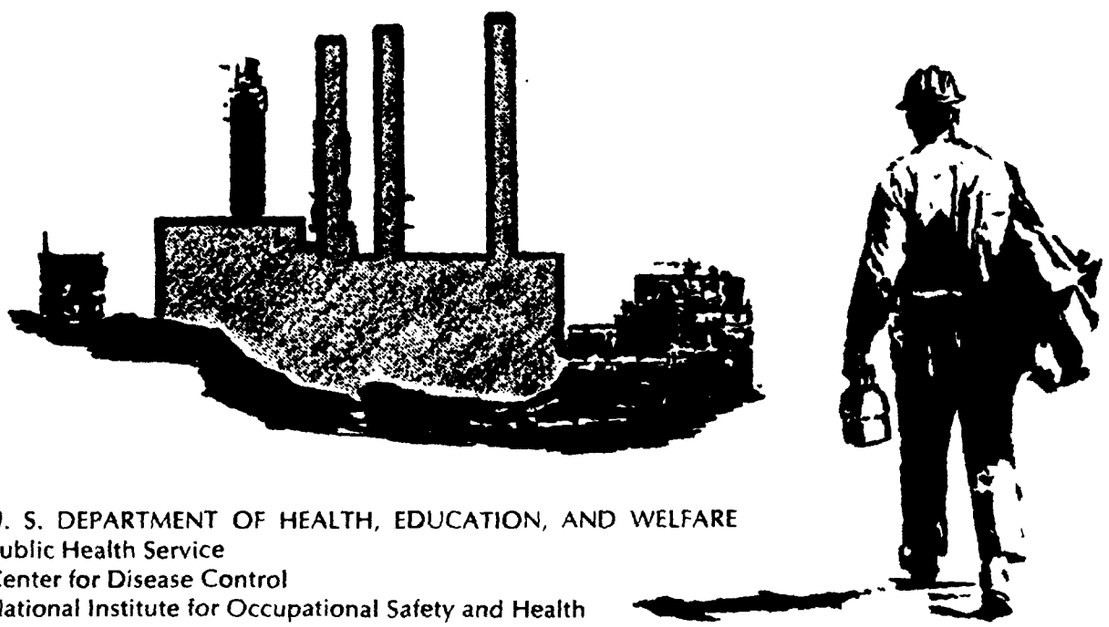
NIOSH

# CRITERIA FOR A RECOMMENDED STANDARD....

# OCCUPATIONAL EXPOSURE TO

# GLYCIDYL ETHERS



U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

# criteria for a recommended standard....

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# PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and provide for the safety of workers occupationally exposed to an ever-increasing number of potential hazards. The National Institute for Occupational Safety and Health (NIOSH) evaluates all available research data and criteria and recommends standards for occupational exposure. The Secretary of Labor will weigh these recommendations along with other considerations, such as feasibility and means of implementation, in promulgating regulatory standards.

NIOSH will periodically review the recommended standards to ensure continuing protection of workers and will make successive reports as new research and epidemiologic studies are completed and as sampling and analytical methods are developed.

The contributions to this document on glycidyl ethers by NIOSH staff, other Federal agencies or departments, the review consultants, the reviewers selected by the Society for Occupational and Environmental Health, the American Medical Association, and Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, are gratefully acknowledged.

The views and conclusions expressed in this document, together with the recommendations for a standard, are those of NIOSH. They are not necessarily those of the consultants, the reviewers selected by professional societies, or other Federal agencies. However, all comments, whether or not incorporated, were considered carefully and were sent with the criteria document to the Occupational Safety and Health Administration for consideration in setting the standard. The review consultants and the Federal agencies which received the document for review appear on pages v and vi.

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The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for the development of the criteria and recommended standard for glycidyl ethers. Catherine Woodbury, Ph.D., of this Division served as criteria manager. SRI International developed the basic information for consideration by NIOSH staff and consultants under contract CDC-99-74-31.

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Consumer Product Safety Commission
  Bureau of Biomedical Science

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# I. RECOMMENDATIONS FOR A GLYCIDYL ETHERS STANDARD

NIOSH recommends that employee exposure to glycidyl ethers in the workplace be controlled by adherence to the following sections. The recommended standard is designed to protect the health and provide for the safety of employees for up to a 10-hour workshift, 40-hour workweek, over a working lifetime. Compliance with all sections of the recommended standard should substantially reduce any risk of mutagenic or tumorigenic effects of glycidyl ethers and prevent other adverse effects of exposure in the workplace. Employers should regard the recommended workplace environmental limit as the upper boundary for exposure and make every effort to keep the exposure as low as is technically feasible. The criteria and standard will be subject to review and revision as necessary.

Glycidyl ethers are characterized by the presence of a three-carbon chain with an epoxide group and an ether linkage. This recommended standard applies to monoglycidyl ethers and diglycidyl ethers that contain an alkyl group, an aromatic group, or a moiety of the structure -(RO)n-R'. It does not include any halogenated compounds or polymerized forms.

Most of the glycidyl ethers are liquids but some are solids. The most common use of these compounds is as reactive diluents in epoxy resins. Toxicologic data concerning these compounds are scarce, but those available show that glycidyl ethers are primary skin and eye irritants and that they are potential skin sensitizing agents. Some data suggest that di(2,3-epoxypropyl) ether should be regarded as a potential occupational

carcinogen and that n-butyl glycidyl ether is a mammalian mutagen. Some glycidyl ethers have also produced cytotoxic effects in animals.

The differences in toxicity among members of the class of glycidyl ethers and the absence of data on some of them prevent the setting of a single environmental limit for all glycidyl ethers. Dermal contact is the major route of exposure to glycidyl ethers; in addition to producing irritation and sensitization, high doses of the compounds may be absorbed through the skin and cause systemic effects. Glycidyl ethers have relatively low vapor pressures, but inhalation is, nevertheless, a possible secondary route of exposure to these compounds. Exposures to airborne glycidyl ethers have caused eye irritation and, at high concentrations, systemic effects and death in animals.

"Occupational exposure" to glycidyl ethers is defined as work in any area where these substances are manufactured, stored, used, or handled.

Section 1 - Environmental (Workplace Air)

(a) Concentration

Occupational exposure to glycidyl ethers shall be controlled so that concentrations do not exceed the following ceiling concentration limits, listed in milligrams per cubic meter of air (mg/cu m) and converted to parts per million (ppm), as determined during a 15-minute sampling period:

| | |
|---|---|
| Allyl glycidyl ether (AGE) | 45 mg/cu m (9.6 ppm) |
| Isopropyl glycidyl ether (IGE) | 240 mg/cu m (50 ppm) |
| Phenyl glycidyl ether (PGE) | 5 mg/cu m (1 ppm) |
| n-Butyl glycidyl ether (BGE) | 30 mg/cu m (4.4 ppm) |
| Di(2,3-epoxypropyl) ether (DGE) | 1 mg/cu m (0.2 ppm) |

(b) Sampling and Analysis

Procedures for the collection and analysis of workroom air samples for compliance with the standard shall be as provided in Appendices I, II, and III or by any methods shown to be at least equivalent in precision, sensitivity, and accuracy to the methods specified.

Section 2 - Medical

Medical surveillance shall be made available as outlined below to all workers with occupational exposure to glycidyl ethers.

(a) Preplacement examinations shall include at least:

(1) Comprehensive medical and work histories with special emphasis directed to past exposure to glycidyl ethers or other vinyl derivatives and history of sensitivities, allergies and reproductive events.

(2) Physical examination giving particular attention to the skin, eyes, and mucous membranes.

(3) If indicated in the judgment of the responsible physician, clinical tests, such as total and differential leukocyte counts, urinalysis, pulmonary function tests, and tests of manual dexterity and visual-motor coupling.

(4) A judgment of the worker's ability to use positive pressure respirators.

(b) Periodic examinations shall be made available as directed by the responsible physician. These examinations shall include at least:

(1) Interim medical and work histories.

(2) Physical examination as outlined in (a)(2) and (a)(3) above.

(c) During examinations, applicants or employees found to have medical conditions, such as neurodermatitis, dyshydrosis, or atopy (an inherited predisposition to allergy), that would be directly or indirectly aggravated by exposure to glycidyl ethers shall be counseled on the increased risk of impairment of their health from working with these substances. Workers shall also be notified that BGE was mutagenic in mice and bacteria and DGE caused skin papillomas in mice. Strict adherence to work practices and sanitation are advised.

(d) In the event of an illness known or suspected to be due to glycidyl ethers, a physical examination as described in paragraphs (a)(2) and (a)(3) above shall be made available.

(e) In the event of an emergency involving gross contamination with or inhalation or ingestion of glycidyl ethers, appropriate first-aid treatment shall be given, and a physician shall be contacted.

(f) Pertinent medical records shall be maintained for at least 30 years after termination of employment. Records of environmental exposure applicable to an employee shall be included in that employee's medical records. These records shall be made available to the designated medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employer, and of the employee or former employee.

Section 3 - Labeling and Posting

All labels and warning signs shall be printed both in English and in the predominant language of non-English-reading workers. Workers unable to

read the labels and signs provided shall receive information regarding hazardous areas, the hazards of working with glycidyl ethers, practices and procedures for protecting themselves, and the instructions printed on labels and signs.

(a) Containers

Shipping and storage containers of glycidyl ethers shall have a readily visible label that bears the name of the ether and information on the effects of exposure on human health. The information may be arranged as in the following example:

NAME OF ETHER

(synonym)

WARNING!

COMBUSTIBLE (or FLAMMABLE, as appropriate)

MAY CAUSE SKIN SENSITIZATION

OR OTHER ALLERGIC RESPONSE

Keep containers closed when not in use.
Prevent all contact with skin and eyes.
Do not inhale vapors or aerosols.
Use only with adequate ventilation.
Store in a cool area - Compound may react violently if heated.

First Aid: In case of contact with eyes, immediately flush eyes with plenty of water and consult a physician. In case of skin contact, wash with soap and water.

Many glycidyl ethers are combustible or flammable liquids, and this information, when pertinent, shall be included on the label directly under the word "WARNING." Labels for 2,3-(epoxypropyl) ether (DGE) shall also include the words "CANCER SUSPECT AGENT."

(b) Posting

In all areas where occupational exposure to glycidyl ethers occurs, warning signs that bear the name of the ether and information on its effects on human health shall be prominently displayed. The information on these signs may be arranged as in the following example.

NAME OF ETHER

(synonym)

WARNING!

COMBUSTIBLE (or FLAMMABLE, as appropriate)

MAY CAUSE SKIN SENSITIZATION

OR OTHER ALLERGIC RESPONSE

Many glycidyl ethers are combustible or flammable, and this information, when appropriate, shall be included on the sign directly under the word "WARNING." Signs for areas where DGE is used shall also include the words "CANCER SUSPECT AGENT."

Section 4 - Personal Protective Clothing and Equipment

Engineering controls and work practices shall be used to keep concentrations of airborne glycidyl ethers at or below the recommended

ceiling concentrations and to prevent skin and eye contact with glycidyl ethers. In addition, employers shall provide protective equipment and clothing to employees when necessary.

(a) Protective Clothing

(1) The employer shall provide appropriate clothing, including gloves, aprons, suits, boots, and faceshields (8-inch minimum), made of materials impervious to glycidyl ethers, eg, milled butyl rubber or polyvinyl alcohol, and shall ensure that such clothing is worn by every employee to prevent skin contact. The protective clothing shall also be fire-resistant. Gloves shall be of sufficient length to protect the forearms of the employees.

(2) The employer shall ensure that a change of clothing is immediately available to any employee whose clothes become grossly contaminated with glycidyl ethers.

(3) Leather articles, such as belts or shoes, that become contaminated with glycidyl ethers shall be rendered unfit for use and discarded.

(4) The employer shall provide separate storage facilities for work clothes and for street clothes and shall ensure that employees do not remove protective clothing from the workplace.

(5) The employer shall inform persons involved in laundering or handling the contaminated clothing of the hazardous properties of glycidyl ethers.

(6) Safety showers and eyewash fountains shall be provided in appropriate areas. This equipment shall be checked periodically to ensure that it is in proper working condition.

(b) Eye and Face Protection

Chemical safety goggles (splashproof) or face shields (8-inch minimum) with goggles meeting the requirements listed in 29 CFR 1910.133 and ANSI Z87.1-1968 shall be provided by the employer and shall be worn during any operation in which there is a reasonable possibility of a glycidyl ether being splashed into the eyes.

(c) Respiratory Protection

Engineering controls shall be used when needed to keep concentrations of airborne glycidyl ethers at or below the ceiling concentrations specified in Section 1(a). When a local exhaust ventilation system is used, it shall be of sparkproof design and maintained to prevent the accumulation or recirculation of glycidyl ether vapors in the workplace and to remove them effectively from the breathing zone of employees. Exhaust ventilation systems discharging into outside air must conform with applicable local, state, and Federal air pollution regulations and must not constitute a hazard to employees or to the general population. Ventilation systems shall be given regular preventive maintenance and cleaning to ensure effectiveness. This shall be verified by measurements that demonstrate system efficiency, eg, air velocity, static pressure, or air volume, taken at least every 3 months, or more frequently if required for the safe and efficient operation of a particular system. Measurements of system efficiency shall also be made as soon as possible after any change in production, process, or control that might result in an increase in the concentration of airborne glycidyl ether.

(1) Compliance with the recommended workplace environmental limit may be achieved by the use of respirators only under the following conditions:

(A) During the installation, testing, maintenance, or repair of the required engineering controls.

(B) For operations such as nonroutine maintenance and repair activities causing brief exposures at concentrations in excess of the workplace environmental limit.

(C) During emergencies.

(2) When a respirator is permitted by paragraph (c)(1) of this section, it shall be selected and used in accordance with the following requirements:

(A) The employer shall establish and enforce a respiratory protective program. The requirements for an adequate program can be found in 29 CFR 1910.134.

(B) The employer shall provide respirators in accordance with Tables I-1, I-2, I-3, and I-4 and shall ensure that employees use the respirators properly when the concentrations of airborne glycidyl ethers exceed the ceiling concentrations recommended in Section 1(a). The respirators shall be those approved by NIOSH or the Mine Safety and Health Administration (MSHA). The employer shall ensure that respirators are properly cleaned, maintained, and stored when not in use.

(C) Protective equipment suitable for emergency entry shall be located at clearly identified areas outside the work area.

TABLE I-1

RESPIRATOR* SELECTION GUIDE FOR ALLYL GLYCIDYL ETHER AND ISOPROPYL GLYCIDYL ETHER

| Concentration (mg/cu m) | | | Respirator Type Approved under Provisions of 30 CFR 11 |
|---|---|---|---|
| | AGE | IGE | |
| Less than or equal to | 470 | 4,700 | (1) Chemical cartridge respirator with full facemask and organic vapor cartridge<br>(2) Gas mask with full facepiece and chin-type organic vapor canister<br>(3) Gas mask with full facepiece and front- or back-mounted organic vapor canister<br>(4) Supplied-air respirator with full facepiece operated in the pressure-demand mode<br>(5) Supplied-air respirator with full facepiece, hood, helmet, or suit, operated in the pressure-demand or continuous-flow mode<br>(6) Powered air-purifying respirator with organic vapor canister and full facepiece, hood, or helmet<br>(7) Self-contained breathing apparatus with full facepiece, operated in the pressure-demand mode |
| Greater than or Emergency | 470 | 4,700 | (1) Self-contained breathing apparatus with full facepiece, operated in the pressure-demand or other positive pressure mode<br>(2) Combination Type C supplied-air respirator with full facepiece, operated in the pressure-demand mode and equipped with an auxiliary self-contained air supply |
| (entry into area of unknown concentration for emergency purposes such as firefighting) | | | |

*Full-body protective clothing shall also be worn whenever a respirator is required.

TABLE I-2

RESPIRATOR* SELECTION GUIDE FOR PHENYL GLYCIDYL ETHER

| Concentration (mg/cu m) | Respirator Type Approved under Provisions of 30 CFR 11 |
|---|---|
| Less than or equal to 250 | (1) Chemical cartridge respirator with full facemask and organic vapor cartridge<br>(2) Gas mask with full facepiece and chin-type organic vapor canister<br>(3) Gas mask with full facepiece and front- or back-mounted organic vapor canister<br>(4) Supplied-air respirator with full facepiece operated in demand mode<br>(5) Self-contained breathing apparatus with full facepiece operated in demand mode |
| Greater than 250 or Emergency | (1) Supplied-air respirator with full facepiece operated in pressure-demand mode<br>(2) Supplied-air respirator with full facepiece, hood, helmet, or suit operated in pressure-demand or continuous-flow mode<br>(3) Powered air-purifying respirator with organic vapor canister and full facepiece, hood, or helmet |

*Full-body protective clothing shall also be worn whenever a respirator is required.

TABLE I-3

RESPIRATOR* SELECTION GUIDE FOR n-BUTYL GLYCIDYL ETHER

| Concentration (mg/cu m) | Respirator Type Approved under Provisions of 30 CFR 11 |
|---|---|
| Less than or equal to 5,000 | Supplied-air respirator with full facepiece, hood, helmet, or suit, operated in pressure-demand or continuous-flow mode |
| Greater than 5,000 or Emergency | (1) Self-contained breathing apparatus with full facepiece operated in pressure-demand mode<br>(2) Combination Type C supplied-air respirator with full facepiece operated in pressure-demand mode and equipped with auxiliary self-contained air supply |

*Full-body protective clothing shall also be worn whenever a respirator is required.

TABLE I-4

RESPIRATOR* SELECTION GUIDE FOR DI(2,3-EPOXYPROPYL)ETHER

| Concentration (mg/cu m) | Respirator Type Approved under Provisions of 30 CFR 11 |
|---|---|
| Greater than 1.0 or Emergency | (1) Self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode<br>(2) Combination Type C supplied-air respirator with full facepiece operated in pressure-demand or other positive pressure mode and auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode |

*Full-body protective clothing shall also be worn whenever a respirator is required.

Section 5 - Informing Employees of Hazards

(a) Employees working in an area that may involve occupational exposure to glycidyl ethers shall be informed of the hazards of such employment, the appropriate emergency procedures to use, and the proper procedures for safe handling and use of glycidyl ethers.

(b) The employer shall institute a continuing education program, conducted by persons qualified by experience or training, to ensure that employees have current knowledge of job hazards, proper maintenance and cleanup methods, and proper respirator use. The instructional program shall also include a description of the general nature of the medical surveillance procedures and of the advantages to the employee of undergoing the examinations recommended. Educational programs for employees engaged in maintenance and repair shall include instruction on those work situations in which they will be occupationally exposed to glycidyl ethers.

(c) Instructional material in written or published form shall be kept on file at each establishment or department where employees are occupationally exposed to glycidyl ethers. Each employee shall be informed of the availability of the required information, which shall include, as a minimum, that prescribed in Appendix IV.

(d) Required information shall be recorded on the "Material Safety Data Sheet" shown in Appendix IV or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor, and shall be kept on file, readily accessible to employees.

Section 6 - Work Practices

(a) Storage and Handling

(1) The handling and storage of liquid glycidyl ethers shall comply with the provisions of 29 CFR 1910.106 for flammable or combustible liquids.

(2) Fire extinguishers approved for use in fighting fires

supported by Class II and Class III combustible or Class I-C flammable liquids, eg, dry chemical extinguishers, shall be available in areas where glycidyl ethers are loaded, unloaded, or stored. Fire extinguishers shall be inspected annually by qualified personnel and recharged or replaced if necessary.

(3) In case of a leak, loading or unloading operations, as appropriate, should continue as rapidly as possible to drain the tank or permit necessary repairs if it is safe to make them. If the leak is severe, causing unsafe conditions, loading or unloading operations should cease and emergency procedures should be instituted.

(4) Whenever flammable or combustible liquids are transferred from one container to another, both containers must be effectively bonded and grounded to prevent the buildup and discharge of static electricity.

(b) Cleanup and Waste Disposal

Spills of large amounts of glycidyl ethers shall be washed with water into an appropriate drainage system as soon as possible where the ethers can be safely stored until they are either recovered or discarded. Discarding of waste shall conform to applicable Environmental Protection Agency (EPA) standards and must not constitute a hazard to employees or to the population at large. When it is not possible to wash a spill with water, the area should be cordoned off until cleanup operations have been completed. If a vacuum truck is used to remove the glycidyl ether, there should be no sources of ignition in the vicinity of the spill and sufficient flashback prevention devices shall be provided.

(c) Entry into Confined Spaces

(1) Entry into confined spaces, such as tanks, pits, and process vessels, that have contained glycidyl ethers shall be controlled by a permit system. Permits shall be signed by an authorized representative of the employer to certify that preparation of the confined space, precautionary measures, and personal protective equipment are adequate and that the prescribed procedure will be followed.

(2) All lines shall be disconnected or blocked while process vessels are being cleaned. All valves or pumps leading to and from the vessel shall be locked in the off position and tagged with a sign stating that work is in progress or other similar message.

(3) A confined space that has contained glycidyl ethers shall be washed with water or some other appropriate agent and purged with air or with nitrogen followed by air before any employee enters it. Provision shall be made for adequate ventilation of the confined space to provide sufficient oxygen for employees working inside.

(4) A calibrated combustible gas meter shall be used to check for explosion hazard. The test shall be performed by a person trained in the use of the combustible gas meter. When it is possible that airborne glycidyl ether vapors could increase in concentration within the confined space, this test shall be repeated every 30 minutes.

(5) The vessel shall then be checked for concentrations of airborne glycidyl ethers, possible oxygen deficiency, and concentrations of other likely contaminants. A positive pressure respirator shall be used during this checking procedure.

(6) The interiors of tanks or vessels shall be illuminated by reflected light or explosion-proof light sources during cleaning or repairs. Only nonferrous (sparkproof) tools are permitted to be used in these operations.

(7) No employee shall enter any tank or vessel that does not have an entrance large enough to admit an employee equipped with safety harness, lifeline, and appropriate respiratory equipment. The employee shall be able to leave the tank or vessel by the same opening.

(8) Employees entering contaminated tanks or vessels shall wear full-body protective clothing until inspection and testing assure safety for personnel in the tank.

(9) When an employee is working in a confined space, another employee shall be stationed at the entrance to keep the first employee under constant observation, and one or more additional employees shall be readily available in case of an emergency. A positive pressure respirator with safety harness and lifeline shall be located outside the tank or vessel for emergency use.

(d) General Work Practices

(1) Smoking, matches, open flames, and spark-producing devices shall be prohibited in areas where glycidyl ethers are handled. Tools used in these areas shall be sparkproof.

(2) Employers shall ensure that workers do not carry smoking materials into areas where glycidyl ethers are handled. If smoking areas are provided, they should be located at a safe distance from glycidyl ether work and storage areas.

(e) Emergency Procedures

The employer shall formulate emergency evacuation, medical, and firefighting procedures and shall ensure that they are posted in all work areas where emergencies involving glycidyl ethers might occur and that employees are instructed in these procedures.

(1) Procedures shall include prèarranged plans for obtaining first-aid and emergency medical care and for transportation of injured workers.

(2) Firefighting procedures shall be established and implemented. The glycidyl ether sources shall be clearly marked, and workers and emergency personnel shall be instructed in proper shutoff procedures. The instructions shall include procedures for emergencies involving the release of vapors of glycidyl ethers. In case of fire, glycidyl ether sources shall be shut off or removed. Containers shall be removed or cooled with water. Chemical foam, water, carbon dioxide, or dry chemicals shall be used for fighting glycidyl ether fires, and proper respiratory protection and protective clothing shall be worn by employees engaged in firefighting.

(3) Approved eye, skin, and respiratory protection, as specified in Section 4, shall be used by personnel engaged in emergency operations.

(4) Nonessential employees shall be evacuated from exposure areas during emergencies. During an emergency, perimeters of hazardous areas shall be roped off, posted, and secured.

(5) Personnel who may be required to shut off sources of glycidyl ethers, clean up spills, and repair leaks shall be properly trained in the appropriate procedures.

Section 7 - Sanitation

(a) Food or beverage preparation, storage, dispensing (including vending machines), and consumption shall be prohibited in work areas where glycidyl ethers are present.

(b) Adequate facilities with soap and water for handwashing shall be made available to employees who work with glycidyl ethers.

(c) Employees shall be cautioned not to touch or rub their eyes with hands that may be contaminated with glycidyl ethers.

(d) The employer should recommend that all employees wash their hands before using toilet facilities or eating.

Section 8 - Monitoring and Recordkeeping Requirements

Each employer with a place of employment where glycidyl ethers are present shall conduct an industrial hygiene survey to determine whether exposure to glycidyl ethers may occur. Surveys shall be repeated at least semiannually and within 30 days after any process change likely to result in increased concentrations of airborne glycidyl ethers. Records of these surveys, including the basis for concluding that concentrations of airborne glycidyl ethers are at or below the ceiling concentration limits specified in Section 1(a), shall be maintained.

(a) Personal Monitoring

(1) If it is determined that exposure to airborne glycidyl ethers has occurred, a program of personal monitoring shall be instituted to identify and measure, or permit calculation of, the exposure of all employees who are occupationally exposed to glycidyl ethers. Monitoring of employee exposure to airborne glycidyl ethers shall be conducted at least semiannually. If monitoring reveals that an employee is exposed to glycidyl ethers at concentrations in excess of the recommended ceiling concentration limits specified in Section 1(a), control measures shall be initiated, the employee shall be notified of the exposure and of the control measures being implemented to correct the situation, and the exposure of that employee shall be monitored at least once every 30 days. Such monitoring shall continue until two consecutive evaluations, at least 30 days apart, indicate that the employee's exposure no longer exceeds the recommended ceiling concentration limits. Semiannual monitoring may then be resumed.

(2) In all personal monitoring, samples of air representative of the breathing zones of the employees shall be collected.

(3) For each determination, a sufficient number of samples shall be taken to characterize the employee's exposure during each workshift. Variations in work or production schedules and in employee location and job function shall be considered in choosing sampling times, locations, and frequency.

(b) Recordkeeping

Records of environmental monitoring and exposure information shall be kept by the employer for at least 30 years after the employee's last

occupational exposure to glycidyl ethers. These records shall include the dates of measurements, job function and location of the employees at the worksite, sampling and analytical methods used, number, duration, and results of the samples taken, ceiling concentrations estimated from these samples, type of personal protective equipment in use at the time of sampling, and identification of exposed employees. Employees shall have access to information on their own environmental exposures. Environmental monitoring records shall be made available to designated representatives of the Secretary of Labor, the Secretary of Health, Education, and Welfare, the employer, and the employee or former employee.

# II. INTRODUCTION

This report presents the criteria and the recommended standard which were prepared to meet the need for preventing occupational disease and injury arising from exposure to glycidyl ethers in the workplace. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe exposure levels...at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

After reviewing data and consulting with others, NIOSH formalized a system for the development of criteria upon which standards can be established to protect the health and provide for the safety of employees exposed to hazardous chemical and physical agents. Criteria for a recommended standard should enable management and labor to develop better engineering controls resulting in more healthful work environments, and simply complying with the recommended standard should not be the final goal.

These criteria for a recommended standard for glycidyl ethers are part of a continuing series of criteria developed by NIOSH. The recommended standard applies to the handling, processing, manufacture, use, and storage of the glycidyl ethers. The standard was not designed for the population-at-large, and any extrapolation beyond workplace exposures is not warranted. The standard is intended to (1) protect against the

development of local irritation of the skin and eyes, (2) protect against skin sensitization and the development of systemic toxicity, (3) be measurable by techniques that are valid, reproducible, and available to industry and government agencies, and (4) be attainable with existing technology.

The primary effects of glycidyl ethers on workers reported to date are irritation and skin sensitization. There is also some evidence that cross-sensitization occurs between the glycidyl ethers and their polymerized forms (unmodified epoxy resins). Glycidyl ethers have caused cytotoxic effects and have been mutagenic in bacteria, and n-butyl glycidyl ether was mutagenic to mice in the dominant lethal test. Another glycidyl ether, di(2,3-epoxypropyl) ether, has induced skin papillomas in mice, and triethylene glycol diglycidyl ether induced lung adenomas in rats given high doses by intraperitoneal injection.

The chief use of glycidyl ethers is as reactive diluents in epoxy resin systems. However, because information on the composition of certain epoxy resins is proprietary, it is often difficult to obtain information about the glycidyl ether or ethers that are present in a particular epoxy resin. Furthermore, exposure to the epoxide moeity in both glycidyl ethers and epoxy resins can occur until the resin is completely cured. Thus, workers must be considered to be at risk of exposure to glycidyl ethers from the time the ethers are synthesized until the curing process of the epoxy resin is completed. In addition, since irritation, skin sensitization, and cross-sensitization can occur, it is necessary to take steps to ensure that workers have minimal contact with glycidyl ethers or their vapors.

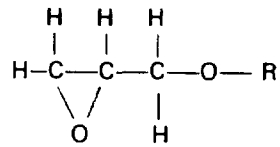
There is a great need for further research on the metabolism and toxicity of individual glycidyl ethers. Lack of data makes it impossible to determine truly safe exposure concentrations for a number of the ethers used in industry today. Studies of eye and skin irritation and of the effects of inhalation of glycidyl ether vapors by both humans and experimental animals are needed. Epidemiologic studies are necessary to assess the possible effects of long-term exposure of populations of workers on their health and longevity. There is an urgent need for studies on the carcinogenic potential of the glycidyl ethers, especially since some glycidyl ethers are cytotoxic, mutagenic, or tumorigenic.

There are no validated methods for the sampling and analysis of any of the diglycidyl ethers. It is important that such methods be devised and tested, since di(2,3-epoxypropyl) ether is potentially carcinogenic. The validated methods that do exist for some of the glycidyl ethers have not been validated at the limits recommended in this standard. They may be adequate, with certain adjustments, for lower limits and for all glycidyl ethers, but this needs to be demonstrated.

# III. BIOLOGIC EFFECTS OF EXPOSURE

Although many glycidyl ethers could theoretically be synthesized, relatively few are used in industry today. The current toxicologic data on most of these ethers are incomplete, and it is therefore necessary to draw inferences based on their physical, chemical, and toxicologic characteristics to assess their potential health hazards.

All glycidyl ethers are characterized by the presence of the 2,3-epoxypropyl group and an ether linkage to another organic group. They have the generalized formula:



The monoglycidyl ethers discussed in this document can be represented by the formula B-O-R, and the diglycidyl ethers by B-(O-R)n-O-B, where B is the 2,3-epoxypropyl group, O is oxygen, R can range from a simple alkyl to a complex hydrocarbon group, and n = 0 to 3. No polymerized forms, such as occur in cured epoxy resins, are included. Glycidyl ethers on which toxicologic data have been found are listed in Table XIV-1, with names conforming to the nomenclature of the International Union of Pure and Applied Chemistry (IUPAC), other synonyms, and structural formulas. Physical and chemical properties of some glycidyl ethers are presented in Table XIV-2 [1-5].

The three-membered ring that oxygen forms by bridging between two adjacent carbon atoms makes up the epoxide or oxirane ring. Because this ring is highly strained, epoxide-containing compounds will react with

almost all nucleophilic (electron-donating) substances [6,7]. Ring opening will occur when the compounds are treated with halogen acids, sulfonic acids, bisulfite, thiosulfate, carboxylic acids and anhydrides, hydrogen cyanide, water, alcohols, amines, aldehydes, and the like [7]. These reactions are described in more detail in Appendix V.

Glycidyl ethers have become important because of their high reactivity. In organic synthesis, epoxides are used as chemical reagents in the manufacture of a wide variety of materials [7]. The glycidyl ethers most commonly used today include allyl glycidyl ether (AGE), n-butyl glycidyl ether (BGE), o-cresyl glycidyl ether (CGE), isopropyl glycidyl ether (IGE), phenyl glycidyl ether (PGE), resorcinol diglycidyl ether, 1,4-butanediol diglycidyl ether, alkyl or aliphatic glycidyl ethers and diphenylol propane diglycidyl ether. The last compound is the oligomer with the lowest molecular weight of the diglycidyl ether of bisphenol A, probably the most common component of uncured epoxy resins. Resorcinol diglycidyl ether is a solid; the other glycidyl ethers listed are liquids, but most have low vapor pressures at ambient temperatures. However, most reactions with glycidyl ethers occur at higher than ambient temperatures, so that the vapor pressures become appreciable.

Because of its toxicity, di(2,3-epoxypropyl) ether (also called diglycidyl ether or DGE) does not appear to be generally used outside of experimental laboratories. It is included in this document, however, because it is the simplest of the diglycidyl ethers and is therefore representative of that group of compounds.

Triethylene glycol diglycidyl ether has been used as an antineoplastic agent [8-16]. Some data concerning this glycidyl ether have

been included in this chapter to aid in relating the structures and toxicities of the various glycidyl ethers.

Extent of Exposure

The major use of the glycidyl ethers is as reactive diluents in epoxy resin systems. After all the components of an epoxy resin system have been mixed, the epoxide groups react to form cross-linkages within the resin. In a completely cured epoxy resin, glycidyl ethers no longer exist [17(p 79)]. However, because epoxy resins have such a wide range of applications, workers often must handle glycidyl ethers and the uncured resins containing them in processes like tooling and molding, manufacturing and using adhesives, roof and floor construction, and applying protective coatings [17(pp 25,153),18]. Uncured resins used in protective coatings are often applied by spraying, so that the applicators could be exposed to large quantities of vapors and mists containing glycidyl ethers. Work practices appropriate for handling glycidyl ethers should be adhered to in processes involving an uncured epoxy resin system.

Glycidyl ethers such as PGE and BGE are synthesized by adding the appropriate alcohol to epichlorohydrin in the presence of a catalyst. The intermediate chlorohydrin is not isolated and undergoes dehydrochlorination to yield a glycidyl ether [17(p 152)]. Commercial manufacture of glycidyl ethers takes place within an enclosed system, but workers may be exposed to glycidyl ethers during drumming operations at the end of the process [17(p 154)]. Very small quantities of glycidyl ethers are used for other purposes, most of which are proprietary in nature [17(pp 25,153)]; in these instances, identification of exposed workers and estimation of their extent of exposure become difficult.

NIOSH estimates that 118,000 workers in the United States are exposed to glycidyl ethers and that an additional 1,000,000 workers are exposed to epoxy resins. Occupations involving potential exposure to glycidyl ethers are listed in Table XIV-3 [17(pp 11,25,153),19-22].

Effects on Humans

The only studies found describing biologic effects on humans of the glycidyl ethers used commercially in the United States concern dermatitis, sensitization, irritation, and allergic reactions following skin contact. No studies of the effects of inhalation of any of the glycidyl ethers by humans have been found.

In 1956, Hine et al [23] reviewed the medical records of workers exposed to glycidyl ethers and of all workers requiring first-aid treatment at one plant between 1947 and 1956. Exposure to PGE involved approximately 20 workers for about 2 months each year. No worker had more than 600 hours of cumulative exposure. Exposure to AGE was at about half this rate; exposure to DGE and IGE had been limited to a few man-months, and exposure to BGE had involved about eight men for 3 months. Ten cases of occupational dermatitis resulting from exposure to AGE and 13 resulting from exposure to PGE were reported in this group of workers. No cases of dermatitis from IGE, BGE, or DGE were reported.

The symptoms and signs of dermatitis resulting from exposure to AGE were tenderness, reddening, itching, swelling, blister formation, and whitish macules [23]. In one instance, there was eye irritation from AGE vapor. The signs of dermatitis resulting from exposure to PGE were more severe, consisting of second-degree burns, blister formation, brownish

lesions, diffuse erythematous rash, erythematous vesicular rash, dry and defatted areas, watery discharge from the affected area, macular rash and papules, swelling of connective tissues, and edema.

The 10 patients with dermatitis from exposure to AGE were treated by the first-aid nurses a total of 26 times and were referred to physicians a total of 7 times [23]. The duration of treatment ranged from 1 to 8 days. The 13 episodes of dermatitis from exposure to PGE required 118 first-aid visits and were referred to physicians a total of 36 times. The duration of treatment for these complaints ranged from 1 to 56 days. Three cases of dermatitis did not respond readily to treatment, and these workers were referred to dermatologists. In most cases, the absence of immediate pain or burning resulted in a delay in initial treatment, and, in one case, the worker's failure to remove socks contaminated with PGE for several days increased the severity of the burn [23]. Four of the 23 workers with occupational dermatitis developed sensitivity reactions to AGE or PGE.

Both AGE and PGE caused irritation and sensitization, but the data presented by Hine et al [23] indicated that the effects of PGE were more persistent and less responsive to treatment. The authors stated that repeated contact with any of the compounds would probably give rise to dermatitis, although no human effects have been reported from exposure to DGE, IGE, or BGE. The severity of injury from PGE was increased when the compound was not immediately removed from contact with the skin. The authors also pointed out that the vapor of AGE was irritating to the eyes. The information presented indicates that these glycidyl ethers are potentially irritating to the eyes and skin after minimal contact and that they are probably irritating to the respiratory tract as well.

Hine and colleagues [23] noticed that they suffered from irritation of the eyes, nose, and respiratory tract when exposed to the glycidyl ethers during experiments with animals. These exposures occurred at room temperature. The investigators used AGE, BGE, IGE, PGE, and DGE in their studies, and they did not indicate which glycidyl ethers were the most irritating.

In 1965, Zschunke and Behrbohm [24] observed 15 cases of occupational dermatitis in workers exposed to PGE, which was being added to "chloroparaffins" and polyvinyl chloride as a stabilizer, in two cable-manufacturing plants. In one plant, 12 of 18 workers developed eczema. In another plant, only the three persons referred to a physician because of suspected occupational eczema were examined. In these patients, the eczema had developed on areas of the hands, the lower arms, and the right side of the abdomen, which had come into contact with cable-coating material containing PGE. Workers with abdominal skin irritation had carried large pieces of sheathing material pressed tightly against their torsos while they were feeding the cable-sheathing machine. The reddened areas contained papules and papulo-vesicles, and the patients complained of severe itching. Ten of these 15 cases of occupational dermatitis were severe enough to cause the workers to miss 11-68 days of work (mean 30.5 days). Eight of the 15 patients reacted positively to 24-hour patch tests with PGE in concentrations of 1.0-0.001% in 70% ethanol or peanut oil. The authors conducted further tests with both industrial and high-purity grades of PGE. The results of these tests were described as identical, leading the authors to exclude the possibility that impurities in the industrial-grade PGE might have been the cause of the dermatitis. The authors

believed that the concentration of PGE used might have been too low to demonstrate sensitivity in the seven workers whose patch tests were negative, since the concentration at which they were occupationally exposed was about 3%.

Patch tests with 0.01% PGE were also performed on 58 persons considered not to have been exposed previously to the glycidyl ether, and no positive reactions were observed [24]. In seven other patients with eczema who had contact with epoxy resins but no known exposure to PGE, the tests were positive. These data indicate either that the epoxy resins to which the patients were exposed contained PGE as a reactive diluent or that cross-sensitization to PGE from the reactive diluent used in the resins had occurred.

Kligman [25], in 1966, tested the sensitization potential of a number of compounds, including BGE. BGE, 1 ml of a 10% suspension in mineral oil or petrolatum, was applied to the forearms or lower legs of 25 healthy adults on a cloth patch, 1.5 inches square, that was covered with plastic tape for 48 hours. A 24-hour rest period was allowed between each of five exposures. After the final induction exposure, the subjects were challenged with 0.4 ml of 10% BGE in petrolatum on a 1-inch-square patch on the lower back or forearm for 48 hours. The author classified BGE as a strong sensitizer because 19 of 24 subjects became sensitized to it (a strong sensitizer was defined as one that sensitized 14-20 of 25 subjects) [25].

Lea et al [26] have also examined the irritating and sensitizing properties of BGE. Pure BGE was applied to the backs of five persons on cotton patches that were covered with cellophane and held in place with

adhesive tape for 48 hours, unless discomfort caused earlier removal. They developed skin irritation characterized by erythema, edema, multiple vesiculation, and superficial ulceration. When lower concentrations of the ether were tested, 17 of 25 persons (68%) reacted to a 10% suspension of BGE in petrolatum, 8 of 25 (32%) reacted to a 5% suspension, 1 of 25 (4%) reacted to a 2.5% suspension, and none of 25 (0%) reacted to a 1.25% suspension. The reactions to the various dilutions of BGE ranged from mild erythema to the severe reaction described above and demonstrated that the irritation potential was dose dependent. Two weeks after these irritancy studies were completed, sensitization tests were performed with a 1.25% suspension, the concentration previously determined to be nonirritating. The results of the patch tests were checked at 24 hours, 48 hours, and 5 days. Five of 25, or 20%, had become sensitized to BGE. The induction methods reported by Lea et al [26] were less stringent than those reported previously by Kligman [25], and the challenge concentration was lower. This probably accounts for the differences in sensitization rates reported in the two papers. This study [26] provides further evidence that the sensitizing effects as well as the irritative effects of BGE, and possibly of all glycidyl ethers, are dose dependent.

In 1964, Fregert and Rorsman [27] tested the allergenic properties of AGE, BGE, and PGE on people who were known to have contact allergies to epoxy resins of the diglycidyl ethers of bisphenol A. The test compounds were diluted to 0.25% in acetone before being used in the patch tests. The type of patch and the length of time it was left in place were not specified. The authors also performed a study to determine the concentration of PGE that could be used in a patch test without producing

primary irritation in individuals not allergic to epoxy resins, so that sensitization or allergic response could be distinguished from irritation.

Fourteen of 20 persons reacted to PGE, 3 of 20 to BGE, and 2 of 20 to AGE [27]. Four persons who reacted positively to PGE were also tested with CGE to determine whether these two glycidyl ethers, which were very similar in structure, had similar effects. All four reacted positively to CGE. Ten persons not allergic to epoxy resins were patch-tested with 1.0% PGE in acetone (a concentration at which no primary irritation occurred). Two became sensitized. The authors classified PGE as a very strong sensitizing agent. This study shows that persons exposed to epoxy resins, presumably only in the uncured state, may develop sensitivities to glycidyl ethers, and that cross-sensitization between the glycidyl ethers may occur.

Lundin and Fregert [28], in 1977, reported that 34 workers who had developed allergic contact dermatitis were patch-tested with different oligomers of the diglycidyl ether of bisphenol A. No experimental details were given. All of them developed positive reactions to the smallest oligomer (diphenylol propane diglycidyl ether), with a molecular weight of 340, but none reacted to the oligomer with a molecular weight of 624. Lundin and Fregert [28] suggested that the oligomer with a molecular weight of 340 was a stronger allergen and that the workers had been exposed to it more extensively, since it makes up a large proportion of many low-molecular-weight resins. Workers who had become sensitized to low-molecular-weight epoxy resins also had positive reactions to a resin with an average molecular weight of 1,850 [28]. Lundin and Fregert believed that these were reactions to the small amounts of the oligomer with a molecular weight of 340 that were present in the high-molecular-weight

resin. They noted that the amount of the small oligomer in this resin was usually not sufficient to induce sensitization but might be sufficient to produce a reaction in a person who had previously become sensitized.

In 1977, Malten [29] reported that diphenylol propane diglycidyl ether had been used in a standard European patch-test series since 1974. Persons suffering from eczema were patch-tested with this compound, and about 2% had positive skin reactions. Malten said that most of these people were women, but it was not clear whether this referred to the persons with eczema or only to those with positive reactions in the skin tests. In general, the causes of their sensitivity could not be identified.

In a 1976 report from Procter and Gamble Limited [30], data were presented for human sensitization to two alkyl glycidyl ethers. Procter and Gamble Epoxide No. 7 (R group predominantly C8 and C10 alkyl groups) caused sensitization at concentrations of 10% in mineral oil in "several" of 12 persons during a pilot study. Epoxide No. 8 (R group predominantly C12 and C14 alkyl groups) was tested on 57 persons. Each subject received nine induction applications of the glycidyl ether as a 10% solution in diethyl phthalate. A challenge application of the same substance 14 days later produced a questionable response in one individual. No other sensitization was reported, and another challenge on this individual and nine other subjects 6 weeks later produced no evidence of sensitization. Details of the experimental procedures were not reported in this communication. These results indicated that the C8-C10 alkyl glycidyl ether was a human skin sensitizer but the C12-C14 alkyl glycidyl ether was not, under these experimental conditions; however, the report noted that

the latter compound was considered to be a potential skin sensitizer because of positive results obtained in animal studies by Thorgeirsson et al [31].

No reports describing systemic effects in humans occupationally exposed to glycidyl ethers have been found. However, toxic side effects have been described in patients who received triethylene glycol diglycidyl ether as an antitumor agent. This substance has been used in cancer therapy in Europe and Australia since the 1960's. When triethylene glycol diglycidyl ether was administered by intravenous (iv) injection, intraarterial infusion, or bladder infusion in repeated doses totaling 75-800 mg/kg, leukopenia and bone marrow depression have been the most consistent effects noted [11-13,15,16]. In one study [16], a dose-related incidence of leukopenia was observed, with the condition occurring in 11 of 13 patients given weekly iv injections of 100 mg/kg, in 4 of 6 treated with 50 mg/kg, and in none of 6 at 10 mg/kg. Hypotension and loss of consciousness [13], drowsiness and lethargy [16], and nausea and vomiting [13,16] have also been reported. Intraarterial administration has produced edema [12,32] and hair loss [12,13,15,16] in the region of the injection, and dysuria has been reported following bladder infusion [11].

The results of the human studies indicate that the glycidyl ethers are sensitizers and irritants and that these effects are dose dependent. The relative sensitization potentials appear to be PGE and CGE > BGE > AGE. There is insufficient information to include DGE, IGE, or diphenylol propane diglycidyl ether (the diglycidyl ether of bisphenol A) in a series based on relative potencies. Systemic toxicity was also observed after high, repeated doses by intrarterial or iv infusion of triethylene glycol

diglycidyl ether. The systemic effects included nausea and vomiting, cardiovascular and bone marrow depression, hair loss, and irritation and edema. These results suggest that all of the lower-molecular-weight glycidyl ethers are irritants and sensitizers and that they may attack rapidly dividing tissues.

Epidemiologic Studies

No epidemiologic studies of workers occupationally exposed to glycidyl ethers have been found in the literature.

Animal Toxicity

Toxicologic data on only a few glycidyl ethers have been found, and much of this work has been done by the same few investigators. Studies of carcinogenicity, mutagenicity, and effects on reproduction are especially scarce.

(a) General Toxicity

Range-finding studies have provided data on the toxicities of several glycidyl ethers in various animal species. These are summarized in Table XIV-4. Hine et al [23] evaluated the effects of AGE, BGE, IGE, PGE, DGE, and, in a separate study [33], resorcinol diglycidyl ether. Smyth et al [34] and Czajkowska and Stetkiewicz [35] have also reported acute toxicity data on PGE, and Soellner and Irrgang [36] compared the toxicities of PGE and CGE. BGE and butanediol diglycidyl ether were evaluated in a study of uncured epoxy resins by Cornish and Block [32]. Weil et al [37] also tested BGE, and a study by Procter and Gamble Limited [30] compared the toxicities of BGE and of two alkyl glycidyl ethers containing alkyl radicals in the ranges C8-C10 and C12-C14. Hine et al [23,33] used Long-

Evans rats (body weight 89-150 g), Webster mice (16-22 g), and albino rabbits (2.0-3.2 kg); Smyth et al [34] and Weil et al [37] used Carworth-Wistar rats (90-120 g) and albino rabbits; Cornish and Block [32] used Sprague-Dawley rats (150-250 g) and albino rabbits; and Czajkowska and Stetkiewicz [35] used Wistar rats (280-350 g).

Toxicity was evaluated in single-dose oral studies by administering the material by gastric intubation. In dermal studies, test material was kept in contact with the shaved skin under a plastic sleeve for 24 hours [32,34] or 7 hours [23]. Soellner and Irrgang [36] administered a single subcutaneous (sc) injection of the test substances to mice. Acute inhalation hazard was evaluated by determining the longest single exposure at concentrations near saturation that permitted all animals to survive for 14 days [32,34], or by using nominal concentrations and calculating the resulting LC50's for 4-hour or 8-hour exposures [23]. Mortality during a 14-day observation period was the basis for all calculations except those of Hine et al [33] on resorcinol diglycidyl ether, which were based on mortality within 10 days of exposure.

DGE and AGE were the most toxic of the glycidyl ethers tested when administered in a single oral dose (Table XIV-4). LD50 values for other glycidyl ethers with molecular weights of less than 250 were similar; they were generally in the range of 2-4 g/kg in rats, indicating that these compounds are only slightly hazardous by this route [38]. The two alkyl glycidyl ethers (C8-C10 and C12-C14) and diphenylol propane diglycidyl ether, which have molecular weights of more than 300, were much less toxic than the other compounds.

Hine et al [23,33] also administered two of the glycidyl ethers intraperitoneally (ip). BGE administered ip to groups of five rats (121-161 g) and five mice (21-29 g) gave LD50's of 1.14 and 0.70 g/kg, respectively. These LD50 values showed a relatively small decrease (2.4 and 2.0 times, respectively) by this route, which, according to the authors, suggested ready absorption from the gastrointestinal tract [23]. However, ip administration of resorcinol diglycidyl ether gave LD50's of 0.178 g/kg in rats and 0.243 g/kg in mice, a decrease of approximately 14.5-fold in rats and 4-fold in mice, indicating that this aromatic glycidyl ether was less readily absorbed when administered orally than when injected ip [33]. Unfortunately, Hine et al [33] did not present data on the LD50 of resorcinol diglycidyl ether by percutaneous absorption. The LD50's obtained by painting glycidyl ethers on the skin of rabbits were generally similar to the oral LD50's, suggesting that these materials are readily absorbed through the skin.

In acute inhalation exposures (Table XIV-4), DGE was by far the most lethal to mice, with an LC50 of 30 ppm (160 mg/cu m), but it was nonlethal to rats at the highest concentration tested, 200 ppm (1,060 mg/cu m) [23]. BGE was more lethal to rats than to mice, while AGE and IGE showed no marked species differences; LC50's for PGE were not obtained. Hine et al [23] reported that the LC50 for PGE was greater than 100 ppm (600 mg/cu m). However, their calculations were based on a vapor pressure of 0.1 mmHg for PGE; other investigators have reported that this is an erroneous figure, the actual vapor pressure being estimated to be 0.01 mmHg at 25 C [39,40]. The latter figure yields a theoretical saturated air concentration of 13 ppm (80 mg/cu m) at 25 C. Hence, throughout this document, the

concentration of PGE vapor obtained by Hine et al is corrected to "about 10 ppm" (60 mg/cu m).

Smyth et al [34] determined that the maximum period for which rats could tolerate exposure to "concentrated" PGE vapor with no mortality was 8 hours; Cornish and Block [32] reported values for butanediol diglycidyl ether and BGE of 8 and 2 hours, respectively, and Weil et al [37] also reported 2 hours for BGE. It should be noted that the theoretical saturated air concentration for BGE at 25 C is about 4,000 ppm (21,300 mg/cu m) while that for PGE is only 13 ppm (80 mg/cu m).

(b) Dermal Effects

The irritant effects of several of the glycidyl ethers have been studied in single- and repeated-application experiments [23,30,32-35,37,41,42]. In the single-application studies, 0.5 ml of the undiluted compounds was applied to the clipped skin of albino rabbits on two abraded and two intact sites, according to the method described by Draize [43]. The test compounds were left in contact with the skin for 24 hours. In repeated-application studies, the undiluted test compounds were applied to the clipped skin of rabbits for 1 [23] or 7 hours [33]. Applications were repeated 5 days/week until maximum eschar formation or signs of systemic toxicity were noted.

Results of these skin application studies are summarized in Table XIV-5. All the glycidyl ethers tested produced moderate or severe skin irritation under these conditions. DGE was the most irritating of the compounds, and it also produced severe irritation in both rabbits and rats when the duration of skin contact was reduced to 7 hours [23,41]. It was followed in irritant potential by resorcinol diglycidyl ether [33], AGE and

IGE [23], butanediol diglycidyl ether [32], and the C12-C14 and C8-C10 alkyl glycidyl ethers [30]. BGE [23,30,32,37,42] and PGE [23,30,34], produced widely disparate degrees of skin irritation, ranging from very mild to severe, in tests by different investigators using similar methodology.

In a 1977 study designed to determine the effects of repeated exposure to airborne PGE at concentrations close to the 1976 TLV of 10 ppm (60 mg/cu m), Terrill and Lee [39] found hair loss and associated skin damage in exposed rats. Groups of 32 rats of each sex and 6 male beagles were exposed to PGE at 0 (controls), 1, 5, and 12 ppm (6, 30, and 70 mg/cu m) for 6 hours/day, 5 days/week, for 90 days. Chamber concentrations were monitored by ultraviolet analysis of impinger samples taken hourly and were determined as TWA concentrations. Animals were weighed twice weekly, and blood and urine samples were taken for analysis from 20 rats from each group and from all dogs on days 30, 60, and 90 of exposure and 30, 60, and 90 days after exposure ended. Twelve rats from each exposure group were killed at days 30, 60, and 90 of exposure and 28 days after exposure ended, and three dogs from each group were killed at the end of exposure and 90 days later, for examination of all major organs.

The only effect seen in any of the test animals was hair loss in the rats exposed at 5 and 12 ppm (30 and 70 mg/cu m), affecting 10% of the males and 25% of the females by the 90th day of exposure [39]. Microscopic examination of the skin showed inflammatory cellular infiltration of the dermis, damaged hair follicles, and hyperkeratosis. The authors concluded that these conditions were attributable to chemical irritation of the skin and not to systemic toxicity. They concurred with the observations of Hine

et al [23] that dermatitis is the principal hazard associated with exposure to PGE and suggested that a TLV of 1 ppm (6 mg/cu m) might be necessary to protect workers against skin irritation.

Several glycidyl ethers have been evaluated for their allergenic activity in skin sensitization tests. Thorgeirsson et al [31,44] and Lundin and Fregert [28] investigated the allergenicity of several glycidyl ethers using the guinea pig maximization test described by Magnusson and Kligman [45]. Groups of 10-20 guinea pigs were exposed to the glycidyl ethers in a two-stage induction process. In the first stage, test materials were administered by intracutaneous injection in a shaved area on the animal's back. Each guinea pig received three pairs of injections: (1) 0.1 ml of the test substance in propylene glycol at a dilution previously found not to cause severe irritation or serious systemic toxicity; (2) 0.1 ml of the glycidyl ether solution mixed with 0.1 ml of Freund's complete adjuvant; (3) 0.1 ml of Freund's adjuvant blended with 0.1 ml of water. Control animals were inoculated only with Freund's adjuvant, an emulsion of paraffin oil and water containing heat-killed tubercule bacteria [46], which has increased the sensitivity of guinea pigs to allergens so that it approximates that of humans [45]. In the second stage of induction, conducted 1 week later, a 2 x 4-cm piece of filter paper saturated with the 10% glycidyl ether in propylene glycol was placed on the skin of the animals, covering the original injection sites, and occluded for 48 hours. Two weeks later, the animals were challenged by applying 1 drop of the test substances, at a dilution previously found to be nonirritating, to the shaved skin of the flank, with occlusion for 24 hours [31]. Some compounds were also tested for their ability to induce

cross-sensitization by challenging with glycidyl ethers other than the one used in the induction procedure. Twenty-four hours after removal of the patches, the challenge sites were shaved and evaluated for redness and swelling.

All animals exposed to the alkyl glycidyl ether became sensitized to the substance; 75% of the test animals were cross-sensitized to an epoxy resin of bisphenol A, and 33% were sensitized to BGE and CGE [31]. Diphenylol propane diglycidyl ether (the diglycidyl ether of bisphenol A with a molecular weight of 340) produced sensitization in 80-100% of the test animals, but exposure to the oligomer of this glycidyl ether with a molecular weight of 624 produced only 56-60% positive reactions, and oligomers with molecular weights of 908 and 1,192 produced no sensitization. Of the animals sensitized to the oligomer with a molecular weight of 624, 30% reacted to that having a molecular weight of 340, but no reciprocal cross-sensitivity was observed. One animal sensitized with the oligomer having a molecular weight of 908 cross-reacted to that having a molecular weight of 624. Neopentyl glycol diglycidyl ether produced sensitization in 87% of the test animals, CGE in 75%, and butanediol diglycidyl ether in 60% [28]. Only 50% of the animals exposed to BGE had a positive response to the challenge dose of BGE, but all reacted positively to the C12-C14 alkyl glycidyl ether and 67% to CGE; none reacted to an epoxy resin of bisphenol A [31].

Thorgeirsson et al [44] also found that, although a single intradermal injection of the diglycidyl ether of bisphenol A was sufficient to sensitize 30% of the guinea pigs tested, no sensitization was produced by topical application alone. However, when the skin was pretreated with

sodium lauryl sulfate to produce irritation, 47% of the animals were sensitized, indicating that skin irritation enhanced the development of sensitization. None of the oligomers of bisphenol A studied were primary irritants; patch tests with 25% solutions of each of them caused no irritation. These data suggest that workers who come in ccntact with these oligomers are much more likely to become sensitized if their skins are irritated.

Weil et al [37] reported that BGE had sensitized 16 of 17 guinea pigs tested with the material 3 weeks after being given a series of 8 intracutaneous injections; PGE sensitized 1 of 18 animals in a similar test. Zschunke and Behrbohm [24] reported probable sensitization to PGE in guinea pigs induced by repeated topical applications, but they did not obtain positive reactions to PGE at low challenge concentrations.

Sensitization studies in guinea pigs have shown that all the glycidyl ethers tested that had molecular weights of 624 or less caused some degree of allergic response. The sensitizing capacity of oligomers of the diglycidyl ether of bisphenol A decreased with increasing molecular weight [44]; however, the oligomer of bisphenol A with a molecular weight of 340 (diphenylol propane diglycidyl ether) and the C12-C14 alkyl glycidyl ether were more allergenic than the low-molecular-weight glycidyl ethers tested. Thorgeirsson et al [31] postulated that one factor making the alkyl glycidyl ether a more active sensitizer than BGE was its longer aliphatic chains, which caused it to be more lipid soluble; thus, it could penetrate the skin more readily.

Although the C12-C14 alkyl glycidyl ether and diphenylol propane diglycidyl ether were the most active sensitizers, they are relatively low

in acute toxicity [30,37] and have low irritation potential [30,44]. The very limited animal toxicity data available are not sufficient for an attempted correlation of sensitization and irritation potentials. The most severe irritant, DGE, has not been examined for sensitization potential.

(c) Eye Effects

The abilities of glycidyl ethers to irritate the eyes have been evaluated in direct-application studies on rabbits [23,30,32-35,37,41,42]. The undiluted glycidyl ethers were introduced into the conjunctival sac of one eye of each animal, while the other eye served as a control. Eye irritation was scored at intervals after application by the method described by Draize [43] or by Smyth et al [34].

Results of these studies are presented in Table XIV-5. From these findings, the eye irritant potentials of the glycidyl ethers tested can be ranked in descending order as follows: DGE, AGE, butanediol diglycidyl ether, resorcinol diglycidyl ether, IGE, and the C8-C10 and C12-C14 alkyl glycidyl ethers. Irritation produced by PGE in different tests was reported to range from mild to severe, and that for BGE ranged from mild to moderate. None of the glycidyl ethers used in these tests caused permanent damage to the eye.

In 1962, Mettier et al [47] studied the effects of a 4-hour exposure to DGE at concentrations of 20-27 ppm (106-144 mg/cu m), average 24 ppm (128 mg/cu m), on intact corneal epithelium, on deepithelialized cornea, and on the regeneration of corneal tissue of 3-month-old male white rabbits. Airborne DGE vapor was produced by volatilizing the pure material at a constant rate. The rate of regeneration of corneal epithelium was measured by the time required for regeneration of an area (7-10 mm in

diameter) of cornea denuded of epithelium by trephination. In both untrephined and trephined rabbits exposed to DGE, there was an almost total loss of adhesion between the corneal epithelium and the stroma [47]. This effect was very severe, but it did not seem to increase the regeneration time of the epithelium. The exposure did produce a dense, milky opacification of the corneal stroma, resulting in permanent corneal scarring and new vessel formation. The iritis and keratitis that resulted appeared to be related to exposure, but the trauma of removal of the epithelium may also have been a factor.

Hine et al [23] also noted eye irritation from some glycidyl ethers during exposures to the airborne vapors. Corneal opacity was seen in some rats after a single 8-hour exposure to AGE and IGE at unspecified concentrations, but not in rats exposed for 8 hours to BGE, PGE, or DGE. In rats exposed to AGE for 7 hours/day, 5 days/week, corneal opacity developed in all 10 animals exposed at 900 ppm (4,200 mg/cu m) for 5 weeks, in 6 of 10 exposed at 600 ppm (2,800 mg/cu m) for 5 weeks, and in 1 of 10 exposed at 400 ppm (1,870 mg/cu m) for 10 weeks. No eye damage was reported in rats exposed to AGE at 260 ppm (1,210 mg/cu m) for 10 weeks. Slight eye irritation was also observed in rats exposed to IGE at 400 ppm for 10 weeks, but only "minimal signs" of eye irritation were observed in rats exposed to PGE at a concentration of about 10 ppm (60 mg/cu m). In another study [41], rabbits exposed to DGE for 24 hours at 3, 6, 12, or 24 ppm (16-128 mg/cu m) developed erythema and edema of the conjunctiva at all concentrations. In those exposed at 24 ppm (128 mg/cu m), corneal opacity appeared by the 3rd day.

Corneal opacity has also occurred after cutaneous applications of DGE to the shaved backs of rats at a dose of 125 mg/kg/day, 5 days/week, for 4 weeks [41]. Six such applications at 250 and 500 mg/kg/day also produced corneal opacity. Animals in this study were not caged individually, and the application sites were not covered, permitting the eyes of the animals possibly to touch the application areas on other animals. Thus, the eye effects may have resulted from direct ocular contact with DGE.

All the glycidyl ethers tested produced some degree of primary eye irritation when applied directly to the eyes. DGE, AGE, and IGE have been reported to affect the eyes of animals exposed to their airborne vapors [23,41].

(d) Systemic Effects

The toxic effects resulting from acute exposure to DGE, AGE, BGE, IGE, PGE [23], and resorcinol diglycidyl ether [33] were described by Hine et al. In the former study [23], all the compounds produced labored breathing and CNS depression when administered orally. This was preceded by incoordination, reduced motor activity, and, with BGE, by agitation and excitement. The animals were usually comatose at the time of death. Animals that survived exposure to PGE showed reversal of depression, with increased CNS activity. Watering of the eyes was noted in animals given AGE. With dermal application, signs of toxic activity were described as minimal. Depression was noted only with DGE and PGE. Death usually occurred within 17 hours, but was delayed for up to 5 days in some cases. The most frequent effect produced by inhalation of the glycidyl ethers was irritation of the lungs. Microscopic examination of stained sections showed pneumonitis. Discoloration of the liver and kidneys was frequently

noted in exposed animals, but microscopic examination of sections of these organs did not show consistent tissue changes. Focal inflammatory cells and moderate congestion were seen in the livers of some rats after administration of AGE, BGE, and IGE. Gross examination also showed hyperemia of the adrenal gland and adhesions of the stomach to adjacent tissues after oral administration.

Orally administered resorcinol diglycidyl ether also produced few evident effects [33]. The authors reported moderate CNS depression, slightly labored breathing, and, in surviving animals, loss of weight and diarrhea. Findings from gross examination of organs were described as nonspecific, with local irritation being the principal effect. There were no notable specific differences among rats, mice, and rabbits.

In a study designed to compare effects of different routes of administration of PGE, Czajkowska and Stetkiewicz [35] described the toxic effects occurring in rats as a result of single oral and dermal exposures. The organs of animals that died as a result of exposure or that were killed 6-72 hours or 14 days after exposure were examined for gross changes. Tissue samples for microscopic examination were taken from the cerebrum, cerebellum, lungs, heart, spleen, liver, kidneys, stomach, intestines, bladder, and skin.

In rats given PGE orally, deaths occurred within 6-24 hours, while those exposed dermally died after 12-48 hours [35]. Narcosis was observed in both groups. With both routes of exposure, gross and microscopic examination showed hyperemia of internal organs, especially the liver and kidneys, hemorrhages in the submeningeal and subpleural regions, and darkening of the epithelium in the kidney tubules and in liver tissue.

Rats receiving PGE orally also showed necrotic foci in the mucous membranes of the stomach. The most apparent changes from exposure by this route were in the liver. Rats dying 6-8 hours after oral administration had acute degenerative changes, including necrosis in the subcapsular region of the liver where it contacted the stomach wall; after 20-72 hours, the necrosis in this area of the liver was extensive. After 14 days, adhesion of the liver to the stomach wall was macroscopically evident; microscopically, there were necrotic foci in the subcapsular region separated from the remaining parenchyma by a fibrous band of tissue composed largely of uninuclear cells and offshoot noduli, which indicated that regeneration was occurring. After dermal application, the major changes were in the skin, which showed hyperemia and necrosis involving the subcutaneous layers. In two rats that died after 18 and 20 hours, extravasation within the peritoneal cavity indicated sites of damage to the internal organs. One of these animals had necrosis of the subcapsular region of the liver, and the other had a hyperemic and hemorrhagic loop of the small intestine. After 14 days, no effects were observed in the internal organs of the surviving rats, and the skin showed evidence of regeneration and scar formation.

The authors [35] concluded that PGE had a strong toxic effect at the site of administration, resulting in necrosis of the mucous membranes or skin, and was able to penetrate such barriers and damage underlying or contiguous tissue. They noted that systemic effects with both routes of administration included circulatory disorders resulting in hyperemia, increased permeability of the capillaries, and damage to parenchymatous organs.

These authors [35] also calculated the rate of skin absorption of PGE, using a total of eight rabbits and five rats. The material was placed in contact with the skin for 1-4 hours by one of two methods: (1) Petri dishes filled with cotton saturated with PGE were applied to the abdominal skin of rabbits, and the difference in weight of the petri dish at the beginning and end of exposure was used to calculate the absorption rate; (2) gauze saturated with 900-1,200 mg of PGE was applied to the skin of rats and rabbits, and the amount absorbed was calculated as the difference between the amount applied and the amount determined titrametrically at the end of the experiment. In both cases, evaporation was prevented by covering the area with foil and an elastic bandage. The calculated absorption rates were 4.2 mg/sq cm/hour for rabbits and 13.6 mg/sq cm/hour for rats. Using the dermal LD50 determined in this study (2.16 g/kg), the authors calculated that a rat weighing 250 g with an exposed surface of 16 sq cm would absorb a lethal dose within about 2 hours. They postulated that, assuming 100% absorption from the lungs, a rat with a pulmonary ventilation rate of 73 ml/minute exposed to airborne PGE vapors at 0.6 mg/liter (600 mg/cu m; 100 ppm) for 8 hours would absorb 0.084 g/kg, about 1/30 of the LD50. However, it is very rare for all of an inhaled substance to be absorbed from the lungs.

Because of its low toxicity and low vapor pressure, the authors [35] concluded that PGE presents little risk from acute inhalation exposure under industrial conditions, although they cautioned that this does not apply where aerosols of PGE are released into the air. They deemed irritative effects and dermal absorption to be the major risks to workers occupationally exposed to PGE.

Effects of repeated exposures to the glycidyl ethers were also evaluated in the studies by Hine et al [23,33]. For the long-term inhalation studies [23], groups of 10 rats were exposed to vapors of AGE or IGE at 400 ppm (1,870 and 1,900 mg/cu m, respectively) for 7 hours/day, 5 days/week, for 10 weeks or to PGE on the same schedule at a concentration approaching saturation, approximately 10 ppm (60 mg/cu m). In another experiment, groups of 10 rats received, on the same schedule, exposures to AGE at 260, 600, and 900 ppm (1,210, 2,800, and 4,200 mg/cu m) [23]. Severe toxic effects made it necessary to terminate the study after 25 exposures to AGE at 600 and 900 ppm, but the group exposed at 260 ppm (1,210 mg/cu m) received 50 exposures. The rats were observed throughout the exposure period and were weighed weekly. Control groups were exposed to uncontaminated air. All survivors were killed at the end of the experiment, and blood samples were collected for hemoglobin determinations. At necropsy, lung, liver, and kidney weights were recorded, and sections of these organs and of the brain, thyroid, thymus, heart, stomach, intestine, pancreas, adrenals, testes, and bladder from alternate animals were prepared for microscopic examination.

Only AGE was lethal in this inhalation test; at 600 and 900 ppm (2,800 and 4,200 mg/cu m), 7 or 8 of 10 animals in each group died between the 7th and 21st exposures and, at 400 ppm (1,870 mg/cu m), one rat died after the 18th exposure. [23]. AGE caused decreased weight gain ($P<0.01$) at all concentrations. At 260 ppm (1,210 mg/cu m), the only other changes observed were slight eye irritation and respiratory distress persisting throughout the exposure period. The only statistically significant change in organ/body weight ratio was that for the kidneys of the animals exposed

to AGE at 400 ppm ($P<0.01$). Because only a few animals survived exposure to AGE at 600 and 900 ppm, statistical comparisons could not be made. Animals exposed to IGE showed slight eye irritation and respiratory distress [23]. They also had a significant decrease in mean weekly weight gains ($P<0.01$). Concentrations of hemoglobin in the blood increased in rats exposed to all compounds except AGE, but there was no evidence that red blood cell production in the bone marrow or extramedullary hemopoietic centers had been affected.

Necropsy of rats exposed to AGE at 400 ppm (1,870 mg/cu m) showed a greater decrease in peritoneal fat than was found in rats exposed to IGE [23]. Necropsy of one rat that died after the 18th exposure revealed severe emphysema, a mottled liver, and enlarged and congested adrenal glands; emphysema, bronchiectasis, and bronchopneumonia were each seen in single rats that survived the entire exposure period. Rats exposed to AGE at 600 and 900 ppm (2,800 and 4,200 mg/cu m) had more severe abnormal changes in the lungs, including bronchopneumonic consolidation, severe emphysema, bronchiectasis, and inflammation. Necrotic spleens were found in two of the rats exposed to AGE at 900 ppm.

Weight gain in rats exposed to PGE was similar to that in controls [23]. The tissues of these rats did not differ in appearance from those of control animals, except that two rats showed peribronchial and perivascular pulmonary infiltration by inflammatory cells and "cloudy swelling" (early stage of necrosis) in their livers.

The chronic toxicity of resorcinol diglycidyl ether was also evaluated by repeated inhalation studies in rats [33]. Ten male Long-Evans rats, 80-104 g, were exposed 7 hours/day, 5 days/week, for 10 weeks to air

described as saturated with resorcinol diglycidyl ether. The authors did not report the concentration of airborne resorcinol diglycidyl ether, but since it is a solid at room temperature, the concentration at saturation in air would probably be low. Ten control rats were exposed to uncontaminated air. The only toxic effect observed in exposed rats was slight encrustation of the eyelids of some animals. No gross or microscopic lesions were found, and exposed animals did not differ significantly from controls in weight gain or organ weight/body weight ratios.

Soellner and Irrgang [36] reported that CGE and PGE had antispasmodic and muscle relaxant effects in animals. These glycidyl ethers were 3-40 times more effective than their corresponding glycerol ethers in relieving spasms induced in guinea pig small intestine with barium chloride, acetylcholine, or histamine. Muscle relaxant effects were investigated in revolving drum tests with mice. By sc injection, the minimum effective doses that caused mice to lose their ability to remain in the drum were 430 mg/kg for PGE and 390 mg/kg for CGE, indicating only slight muscle relaxant effects.

Kodama et al [48] and Hine et al [41] investigated effects on the hemopoietic system in animals exposed to glycidyl ethers. In the first study [48], groups of five male Long-Evans rats weighing 151 ±32 g received intramuscular (im) injections of BGE, PGE, or AGE at 400 mg/kg/day or DGE at 25 mg/kg/day. Rats that served as negative controls received injections of propylene glycol at 230 mg/kg/day, and positive control animals received a single im injection of a known alkylating agent, either busulfan at 10 mg/kg or mechlorethamine hydrochloride at 0.5 or 5 mg/kg. Blood samples were analyzed, and sections of bone marrow, lungs, liver, kidneys,

adrenals, thymus, spleen, and testes were examined microscopically as well.

Since both BGE and PGE had minimal toxic effects, and the leukocyte counts in the rats rose rather than fell after three injections [48], no further work was done with these compounds. Rats that received four injections of AGE had swelling at the injection site and lost weight [48]. Two rats died, and post-mortem examination showed pulmonary congestion in one and a small spleen and no visible thymus in the other. The three surviving rats had involuted thymuses at necropsy. Microscopic examination showed atrophy or loss of lymphoid tissue, focal necrosis of the pancreas and testes, hemorrhage into the thymus, hemorrhage into the periphery of the liver, and pneumonia. The leukocyte count was significantly reduced in all animals. Bone marrow contained a normal number of nucleated cells, but the myeloid-to-erythroid ratio was low. The rats that received six injections of DGE gained weight normally, and none died. Edema at the injection site was the only grossly observable effect. The leukocyte count was significantly decreased. Bone marrow was not examined in these animals.

Negative controls gained weight normally and showed no signs of intoxication, but their mean leukocyte count rose almost 40% [48]. The positive control animals that received busulfan continued to gain weight, and none died. The mean leukocyte count, the number of nucleated marrow cells, and the ratio of myeloid to erythroid cells were decreased. Animals that received mechlorethamine lost weight, and three died. Nucleated marrow cells and the myeloid-to-erythroid ratio decreased.

The absence of hemopoietic effects with BGE and PGE was considered by the authors [48] to indicate that monofunctional alkylating agents are

considerably less active than polyfunctional alkylating agents. The activity of AGE was attributed to the reactive sites on the double-bonded carbon rather than to the epoxide moiety.

In a more extensive study of the effects of DGE on the hemopoietic system, Hine et al [41] administered the compound by several routes to three species of animals, using both single and repeated exposures. General chronic toxicity of the compound was also evaluated in rats exposed to the vapor at low concentrations. Male Long-Evans rats (115-145 g) received single and repeated cutaneous applications to their shaved backs and repeated vapor exposures. Male New Zealand rabbits (1.9-4.2 kg) were given single applications on their shaved backs, single and repeated iv injections, and single vapor exposures. A total of 14 mongrel dogs were administered the material by im or iv injections. Hematologic examinations were the same as those used by Kodama et al [48].

Single cutaneous applications of DGE at 0.5 and 1 g/kg to groups of five rats each and of 1.13 g/kg to four rabbits produced a reduction in the leukocyte count and weight loss in all three groups [41]. The rabbits showed a decrease in hemoglobin concentration, and one died on day 11. Repeated cutaneous applications of 125 mg/kg, 5 days/week, for 4 weeks killed two of five rats. Six applications of 250 or 500 mg/kg in 11 days killed four rats and produced weight loss, enlarged myeloid cells, reductions in number of leukocytes and increases in percentages of polymorphonuclear cells, hemorrhage of the adrenal medulla, increased myeloid-to-erythroid ratios among the nucleated cells of the bone marrow, corneal opacity, and swollen forepaws. Necrosis was seen in microscopic examination of sections of the skin, proximal convoluted tubules, lymphoid

tissue, and testes of these rats. Focal necrosis of the pancreas and lymphoid atrophy of the thymus were found in rats exposed at 500 mg/kg.

A second 4-week series of cutaneous applications to rats was conducted with DGE, 10% in acetone [41]. This series resulted in focal inflammation of the epithelium in animals given 15, 30, and 60 mg/kg. In animals given 30 and 60 mg/kg, weight gain was retarded, and there was a decrease in the percentage of polymorphonuclear cells but no decrease in total leukocyte counts. According to the authors, 15 mg/kg appeared to be the no-effect level for repeated cutaneous applications.

Groups of three rabbits were exposed by inhalation for a single 24-hour period to DGE at 3, 6, 12, or 24 ppm (16, 32, 64, or 128 mg/cu m) [41]. Body weights, leukocyte counts, and percentages of polymorphonuclear cells were checked weekly for 3 weeks after exposure. Corneal opacity appeared by the 3rd day in rabbits exposed at 24 ppm. Two of these rabbits died on the 5th day, the third died on the 7th day, and all three lost 30-35% of body weight before they died. There were increases in total leukocytes and percentage of polymorphonuclear cells prior to death; thrombocytosis was noted on the 3rd day. Necropsies on the two rabbits that died first showed purulent lungs with pericardial adhesions in one and peribronchiolitis in the other; both had atrophied testes. Microscopic examination revealed bronchopneumonia, serous hepatitis, focal atelectasis, peribronchiolitis, and focal hemorrhages in lungs and kidneys in one animal or the other. Some basophilia at 6 ppm and possibly increased thrombocyte counts at 12 ppm were seen. Conjunctival erythema and edema with respiratory distress and nasal discharge were seen in all groups.

Rats exposed to DGE 3 or 4 times at 20 ppm (106 mg/cu m) for 4 hours lost weight, and 3 of 30 rats died [41]. Lung edema and congestion were seen in two that died and in one of the survivors. Blood changes seen in the rats included intense cytoplasmic basophilia, grossly distorted lymphocytic nuclei with indistinct cellular membranes, and lowered leukocyte and marrow cell counts.

In chronic inhalation experiments, groups of 30 male rats each were exposed to DGE at nominal concentrations of 3 and 0.3 ppm (16 and 1.6 mg/cu m), 4 hours/day, 5 days/week, for 19 exposures in 29 days and 60 exposures in 90 days, respectively [41]. The authors reported that the actual concentrations in the higher-exposure experiments ranged from 1.3 to 2.5 ppm (7-13 mg/cu m); for exposure at 0.3 ppm, the true value was estimated on the basis of "occasional" analysis to vary within ±0.2 ppm (±1 mg/cu m).

Five rats died during exposure at 3 ppm (16 mg/cu m) [41]. One had bronchopneumonia and necrosis of the pancreas and spleen and another had pneumonia. After the final exposure, 15 rats were killed and examined; autopsy showed one rat with necrosis of the testicular tubules and one with inflammation of the larynx. Seven of the 15 experimental animals and 4 of 10 unexposed controls had peribronchiolitis. The exposed animals differed significantly from controls ($P<0.05$) in the following criteria: decreased body weight and organ weight/body weight ratios of thymus and spleen; decreased leukocytes, polymorphonuclear cells, and marrow nucleated cells; increased erythrocytes and myeloid-to-erythroid ratio; and increased mortality. The other 10 rats were killed 1 year after exposure; their weight gain and blood and bone marrow findings were within the expected normal range. One had acute inflammation of the large bronchi and

"atypical epithelium of neoplastic appearance"; three had peribroncholitis; and one had fatty dystrophy of the liver.

None of the rats exposed to DGE at 0.3 ppm died (1.6 mg/cu m) [41]. One case of pneumonia was the only abnormality in 10 rats killed for autopsy after 20 exposures. After 60 exposures, 5 of 10 rats examined had "poorly defined" focal degeneration of the germinal epithelium and 1 had acute periobronchiolitis. Exposed animals had reduced weight gain and lower leukocyte counts than controls, but the differences were not significant. The blood of two animals showed eosinophilia in over half the polymorphonuclear cells. The remaining 10 experimental and 10 control rats were killed 1 year after exposure ended. Two control rats and one experimental rat had bronchopneumonia, and one reticulum-cell sarcoma was reported in an experimental rat. All blood values were normal.

Hine et al [41] concluded that exposure to DGE at 3 ppm (16 mg/cu m) depressed the hemopoietic system in rats, but that exposure at 0.3 ppm (1.6 mg/cu m) did not. They noted that testicular necrosis occurred at both exposure levels. It is difficult to evaluate the significance of the damage to the testes seen at 0.3 ppm from the description provided by the authors, but it is noteworthy that this effect was seen in 5 of 10 animals after 60 exposures at this low concentration. The authors considered that the bronchopneumonia might be related to the regimen forced upon the rats, but they concluded that the "possible neoplasms" were not attributable to exposure to DGE.

Hine et al [41] also administered DGE by iv injection to dogs and rabbits. Two of three dogs receiving weekly injections of 25 mg/kg died of pnemonia; one had loss of bone marrow with fat replacement after three

injections, and the other had massive infarction in the lungs, slight glycogen degeneration of the renal tubules, and hyaline degeneration of the testicular tubules after three injections. All three dogs at this dose showed significant decreases in leukocytes ($P<0.01$). Three dogs given injections of 12.5 mg/kg showed no gross signs of systemic toxicity, but irritation at the injection site occurred in two. Leukocyte counts decreased in all three but returned to normal after 1-5 weeks. These dogs were killed for autopsy after one to three series of three injections. Their bone marrows were normal, and the only abnormalities noted were hemorrhage into the spleen in one and "possible testicular atrophy" in another.

Rabbits given four weekly iv injections of DGE at 25 mg/kg had slight decreases in leukocyte counts [41]. Higher iv doses, 50-200 mg/kg, caused decreases in leukocyte counts, severe lung congestion, kidney ischemia, ascites, and death.

The most consistent systemic effects reported in animals exposed to glycidyl ethers have been in rapidly dividing tissues, ie, the bone marrow [23,41,48] and the germinal epithelium of the testes [33,41,48,49]. At higher doses, glycidyl ethers have produced more severe tissue damage; irritation, congestion, and necrotic changes were observed in many organ systems, generally appearing first at or near the site of administration [23,35,41,48].

(e) Carcinogenesis, Mutagenesis, Teratogenesis, and Effects on Reproduction

Investigations of carcinogenic activity have been found only for DGE, resorcinol diglycidyl ether, hydroquinone diglycidyl ether, diphenylol

propane diglycidyl ether, and triethylene glycol diglycidyl ether. Many glycidyl ethers have been assessed for their ability to induce mutations and chromosomal aberrations, but studies of teratogenic and reproductive effects are scarce.

In 1957, McCammon et al [50] tested a number of compounds thought to be present in the air pollutants that result from the oxidation of aliphatic hydrocarbons in gasoline and diesel fuels. Twenty compounds were evaluated for their tumorigenic potentials in C57Bl mice by painting on the interscapular skin three times/week. In addition, Long-Evans rats received three of the compounds by sc injection. The authors reported that resorcinol diglycidyl ether was tumorigenic in both mice and rats. DGE was said to be tumorigenic only in mice, but the authors did not indicate whether it was tested in rats. These compounds also produced sebaceous gland suppression, intense hyperkeratosis, parakeratosis, and epithelial hyperplasia in mice. Because this report was an abstract, details of the study were not given. One of the authors (HL Falk, personal communication, May 1978) has indicated that the data from this study have been lost, but that the tumors produced were benign papillomas.

In a 1963 report on the tumorigenic potential of selected epoxides, Kotin and Falk [51] provided additional information on the tumorigenicity of glycidyl ethers in mice [50]. Twenty C57BL mice were used in each treatment group. In the animals exposed to DGE at a total dose of 0.75 millimole in acetone, the first tumor appeared after 5 months; 4 of the 10 animals (40%) surviving at this time developed skin tumors. One mouse (8%) in the group exposed to DGE at 0.25 millimole and 1 of 14 surviving mice (7%) exposed to resorcinol diglycidyl ether at 0.75 millimole developed

skin tumors. Resorcinol diglycidyl ether at 0.25 millimole and hydroquinone diglycidyl ether at 1 millimole caused no skin tumors in any of the mice. No malignant lymphomas or pulmonary adenomas were produced by any of these diepoxides. In a written communication (January 1978), Falk noted that the skin tumors produced by the glycidyl ethers in this study were all benign papillomas and that controls receiving only acetone did not develop any papillomas.

In 1963, Weil et al [37] tested the effects of diphenylol propane diglycidyl ether on mice in a lifetime carcinogenicity study. The compound was tested in trials on two groups of mice by painting the undiluted compound on the shaved backs of 90-day-old C3H mice three times/week. Up to 40 mice were used in each trial, but the exact number was not specified. The mice were painted for up to 23 months. Positive controls were treated similarly with a 0.2% solution of methyl cholanthrene in acetone. At the end of 12 months, 26 mice from one trial and 36 from the other were still alive. At the end of 17 months, 14 and 26 remained alive, and at the end of 24 months, 1 and 0 were alive. No carcinomas were found in these mice; the only tumor, a papilloma, appeared in one group after 16 months of exposure. The positive control substance produced an unspecified number of tumors in mice, with a mean latent period of 3-5 months.

Shimkin et al [52], in 1966, reported the results of a study designed to show the carcinogenic potential of several alkylating agents, including triethylene glycol diglycidyl ether. Mice of the A strain received 12 ip injections, 3 times/week for 4 weeks, at 5 different total doses ranging from 56 to 7,208 mg/kg. Each group contained 15 mice of each sex. During the experimental period, untreated controls were maintained and killed at

monthly intervals to determine the incidence of spontaneous pulmonary tumors. An additional control group received only the vehicle (water) by ip injection. The duration of the experiment was 39 weeks.

A slight increase in lung tumors over the expected spontaneous incidence was observed (37% or a mean of 0.48 tumors/mouse for males, 27% or 0.29 tumors/mouse for females) [52]. At the highest dose (7,208 mg/kg), the tumor incidence was 70%, with 1.2 tumors/mouse. At total doses estimated by the authors to be below 3,777 mg/kg, the tumor incidence decreased to expected spontaneous levels. The spontaneous incidence was estimated from a mathematical relationship between the logarithm of the number of lung tumors and the logarithm of the dose that best represented the point at which one lung tumor/mouse would be predicted. The authors concluded that triethylene glycol diglycidyl ether was only weakly carcinogenic at the highest doses used. However, this study lasted for only about 9 months, whereas assays of carcinogenic potential with this strain commonly are conducted for 18-20 months. The authors also reported that testicular atrophy with decreased spermatogenic activity was seen in mice 39 weeks after treatment with this compound at high doses.

Cytotoxic effects on mammalian bone marrow cells have been observed with AGE and DGE [41,48]. Studies with other cell types have also shown cytotoxic effects of glycidyl ethers. Loveless [6] found that treating root-tip meristems of the broad bean, Vicia faba, with DGE or resorcinol diglycidyl ether produced radiomimetic effects. He defined a radiomimetic agent as one that acted upon the resting cell to produce chromosomal aberrations apparent in subsequent cell divisions. Other studies have also

demonstrated chromosomal aberrations produced by DGE in the broad bean [53,54] and other plant species [55].

Certain glycidyl ethers have damaged mammalian tumor cells. Triethylene glycol diglycidyl ether has been used therapeutically as an antitumor agent [11-13,15,16]. Hendry et al [56] have shown tumor inhibition and radiomimetic effects of diethylene glycol diglycidyl ether and butanediol diglycidyl ether in an in vivo study. Rats were implanted with Walker tumors, and the compounds to be tested were injected ip during a 10- to 12-day period after tumor implantation. According to the authors, there was a correlation between tumor inhibitory activity of the glycidyl ethers and the ability to induce chromosomal changes of the radiomimetic type in the implanted tumors. Diethylene glycol diglycidyl ether at a total ip dose of 1.5 mg/g inhibited tumor growth by 84% compared with that in controls. At a daily dose of 0.4 mg/g, some inhibition of mitosis was seen in the tumor as well as in the bone marrow. "Exploded" metaphases were seen in the tumor and chromosome fragmentation and pyknotic nuclei were seen in the bone marrow at this dose. At 0.2 mg/g/day, there was almost complete inhibition of mitosis with a few chromosome fragments, but only partial inhibition of mitosis with some pyknotic nuclei was seen in the bone marrow. A dose of 0.1 mg/g/day caused a few pyknotic nuclei in the bone marrow. Tumors in rats exposed to diethylene glycol diglycidyl ether at doses of 0.4 and 0.1 mg/g/day showed an increased number of anaphases (over control values) after 24 hours, indicating that the compound caused specific chromosomal damage in tumor tissue in rats with the Walker tumor.

Butanediol diglycidyl ether at a total dose of 1.2 mg/g caused a 74% inhibition in tumor growth compared with controls [56]. Doses of 0.2 mg/g/day caused "exploded" metaphases in the tumor and true chromosome bridges and chromosome fragmentation in the bone marrow. At a dose of 0.1 mg/g/day, no cytotoxic effects were observed in the tumor. However, chromosome bridges and fragmentation were found in the bone marrow. After 24 hours, an excess number of anaphases with chromosome damage in tumor tissue was noted at both daily dose levels.

In a study from EI du Pont de Nemours and Company [49], Terrill reported no increase in chromosomal aberrations in the bone marrow cells of rats exposed to PGE at concentrations up to 11.2 ppm (68.8 mg/cu m) 6 hours/day for 19 consecutive days.

Wade et al [57] examined the mutagenicity of AGE, BGE, DGE, diphenylol propane diglycidyl ether, and the diglycidyl ether of substituted glycerin with Salmonella typhimurium. They used the histidine-dependent mutant strains TA98, which is reverted to histidine independence by frameshift mutation, and TA100, which is reverted by base-pair substitution. The compounds were tested with and without the addition of liver microsomal extract from rats pretreated with phenobarbital. A substance was considered mutagenic in this test if it produced histidine-independent revertants at two or more times the spontaneous rate.

When 10 mg of the glycidyl ether was applied to the center of agar plates containing bacteria of the TA100 strain, AGE and BGE caused mutations at over 10 times the spontaneous rate, and the diglycidyl ether of substituted glycerin increased the mutation rate about 4 times [57].

Diphenylol propane diglycidyl ether showed no mutagenic activity at this dose. None of these four glycidyl ethers produced an increase in mutations when 50 μg was spotted on the agar plates. DGE was toxic to bacteria even at this low dose, reducing the number of revertant colonies/plate to below spontaneous levels. When DGE was incorporated directly into the medium in quantities of 50-500 μg/plate, it produced a dose-dependent mutagenic effect in strain TA100, with the highest dose inducing mutations at about 10 times the spontaneous rate. Addition of the liver microsomal extract generally produced a decrease in the mutagenic activity of DGE, to about 5 times the spontaneous rate at the highest dose. Liver microsomes had little effect on the mutagenic activity of the other glycidyl ethers tested. Results of these tests are summarized in Table XIV-6.

The glycidyl ethers did not show mutagenic activity in strain TA98, indicating that they act by causing base-pair substitutions [57]. Since diphenylol propane diglycidyl ether and two higher-molecular-weight oligomers of this compound (the diglycidyl ether of bisphenol A) were nonmutagenic, the authors suggested that the size of these molecules may have inhibited uptake by the bacteria or caused decreased rates of reaction with genetic material because of steric hindrance. This view is supported by the fact that glycidyl ether of the next-highest molecular weight, the diglycidyl ether of substituted glycerin (molecular weight 300), induced fewer revertant colonies than AGE or BGE (molecular weights 114 and 130).

In a 1977 report prepared for Dow Chemical USA by Pullin and Legator [58], the mutagenic potential of BGE, CGE, the C12-C14 alkyl glycidyl ether, neopentyl glycol diglycidyl ether, diphenylol propane diglycidyl

ether, and dicyclopentadiene glycidyl ether were examined. The mutagenicity testing program evaluated the compounds in six microbial and mammalian test systems:

(1) The microbial mutagenic assay (Ames test) determined activity in reverting histidine-requiring mutant strains of S. typhimurium to histidine independence. The compounds were tested at 0.5-2.0 μmoles/plate, both with and without a microsomal extract from the livers of rats pretreated with phenobarbital or Aroclor.

(2) In the body-fluid analysis, the urine of mice treated with the glycidyl ethers was tested for mutagenic activity against S. typhimurium both with and without the addition of beta-glucuronidase. The mice received the glycidyl ethers orally in doses of 125-1,000 mg/kg/day for 4 days before urine was collected for testing.

(3) The host-mediated assay is designed to determine the effects of in vivo metabolism of a compound on its mutagenicity. Mutant strains of S. typhimurium were injected into the peritoneal cavity of mice that had been given glycidyl ethers in oral doses of 125-1,000 mg/kg/day for 5 days. Six hours after inoculation, exudate was withdrawn from the peritoneal cavity and plated in serial dilutions to determine the frequency of mutations to histidine independence.

(4) In the micronucleus test, the bone marrow from mice that had received glycidyl ethers orally for 5 days was examined microscopically for the presence of micronuclei.

(5) To study the induction of DNA repair, glycidyl ethers were incubated at 37 C with human mononucleated white blood cells (G-0 phase) and tritiated thymidine. Cells were analyzed for incorporation of tritiated thymidine by liquid scintillation counting and autoradiography.

(6) The dominant lethal assay tested mutagenic effects of glycidyl ethers on the reproductive cells of mice. Male B6D2F1 hybrid mice, 8-10 weeks old, were bred to three virgin females each week for 2 weeks to provide baseline information on the fertility of each male, litter size, and spontaneous fetal deaths. The male mice were then treated topically with undiluted glycidyl ethers on their shaved and chemically depilated backs three times/week for a minimum of 8 weeks. Groups of 10 male mice of proven fertility received BGE, CGE, or neopentyl glycol diglycidyl ether at 1.5 g/kg, the alkyl glycidyl ether or dicyclopentadiene glycidyl ether at 2.0 g/kg, or diphenylol propane diglycidyl ether at 3 g/kg. Two other groups were treated with saline, as a negative control, or with triethylene-melamine, as a positive control. The exposed mice were caged individually with three 8- to 10-week-old virgin females each week for 2 weeks. All females were killed for examination of their uteri 13-14 days after presumptive mating. The percentage of pregnancies, total number of implants, and number of fetal deaths were used as criteria of dominant lethality.

Results of these tests are summarized in Table XIV-6. All of the glycidyl ethers tested showed some activity in the Ames test with S. typhimurium strain TA1535, which is reverted by base-pair substitution, but not with strain TA98 [58]. One glycidyl ether was minimally active in the body-fluid analysis, and three showed some activity in the host-mediated assay, which the authors attributed to decreased growth of microorganisms in the host animals. Three diglycidyl ethers produced an increase in unscheduled DNA synthesis in human white blood cells, but none produced excess micronuclei in the bone marrow cells of mice.

Only BGE was significantly mutagenic to mice in the dominant lethal test, causing a significant increase in the number of fetal deaths (P=0.04) [58]. The number of pregnancies was significantly less than in the control group (P=0.05), but pretreatment data also showed significantly fewer pregnancies in the test group than in the controls. In the Ames test, BGE produced mutations at 4-13 times spontaneous rates, and its mutagenic activity was markedly decreased by the addition of microsomes. BGE also caused a significant increase ($P<0.05$) in unscheduled DNA synthesis in white cells. The authors classed this compound as mutagenic and suggested that the lack of activity of BGE in the body-fluid analysis, host-mediated assay, and micronucleus test might have resulted from the low doses used in these tests. Since BGE was detoxified by mammalian microsomes in the microbial assay but was apparently not deactivated by metabolism in the dominant lethal test, they concluded that the metabolic properties of the liver homogenate did not "truly reflect the complex and dynamic metabolic processes of an intact animal." The authors emphasized that BGE posed a hazard through percutaneous absorption, a common route of exposure for the worker. However, the dosage of BGE used in the dominant lethal test was very high.

CGE and neopentyl glycol diglycidyl ether were classified as weakly mutagenic on the basis of these test results [58]. CGE was the most mutagenic of the compounds in the Ames test, producing mutations at up to 58 times the spontaneous rates, but it was deactivated to control levels in the presence of microsomes. Neopentyl glycol diglycidyl ether caused mutations in S. typhimurium at up to 7 times the spontaneous rate, and addition of microsomes had no consistent effect on its activity. In the

body-fluid analysis, both compounds had minimal mutagenic effects only in the presence of betaglucuronidase. Both caused significant unscheduled DNA synthesis in human white blood cells ($P<0.05$).

Dicyclopentidiene glycidyl ether and diphenylol propane diglycidyl ether were mutagenic in bacteria but not in animal systems [58]. In the absence of mammalian microsomes, they produced mutations in S. typhimurium at about 2-4 times the spontaneous rate; effects of adding microsomes were inconsistent, but diphenylol propane diglycidyl ether at 2.0 μmoles/plate was activated by liver microsomes from Aroclor-pretreated rats. Diphenylol propane diglycidyl ether also increased mutation frequencies in the host-mediated assay. The authors described these two glycidyl ethers as minimally mutagenic in humans.

The C12-C14 alkyl glycidyl ether was minimally active in the microbial assay only in the presence of microsomes from Aroclor-pretreated rats [58]. It also showed minimal activity in the host-mediated assay. The authors classified this glycidyl ether as nonmutagenic.

Results of these screening tests [58] suggest that all these glycidyl ethers have some mutagenic potential. Only BGE was reported to be a mammalian mutagen on the basis of the results of the mouse dominant lethal test. However, only a single negative control group of 10 rats was used in this test, and several of the test groups differed significantly from controls in pretreatment data for the criteria used as indicators of dominant lethality. Despite these shortcomings in experimental design, there were significant differences ($p = .04$) between the control groups and the BGE-treated group in the proportion of deaths/pregnancy.

In a 1974 study from EI du Pont de Nemours and Company [49], Barsky reported mutagenicity tests of PGE in S. typhimurium. PGE was tested at concentrations of 25-300 μg/plate without rat liver homogenate and 500-10,000 μg/plate in the presence of the homogenate. PGE was mutagenic in strains TA1535 and TA100 both with and without metabolic activation, but it showed some increase in activity in the presence of the liver homogenate (Table XIV-6). At the highest concentration used in the activated assay, PGE produced mutations in strain TA100 at nearly 70 times the spontaneous rate. No mutagenic activity was observed in strains sensitive to frameshift mutation.

In the same laboratory report [49], Terrill described a two-generation reproduction and mutagenesis study in rats exposed to PGE vapor. Three groups of eight male ChR-CD rats (360 g) were exposed to PGE at 1.75, 5.84, or 11.20 ppm (10, 33, or 71 mg/cu m) 6 hours/day for 19 consecutive days. A fourth group of rats served as controls. The male rats were mated for 6 consecutive weeks to three females/week. One of each group of three females was killed on the 18th day of pregnancy and examined for implantations, resorptions, and any abnormalities of the ovaries, uterus, or fetuses. The two remaining females were allowed to raise their pups, which were then paired for mating, and the offspring of these rats were also examined for abnormalities. Exposed males were killed for autopsy after the mating trials, and the testes and epididymides were examined microscopically. Eight first-generation offspring of each sex were also killed for autopsy.

No significant increases in fetal deaths or preimplantation loss were seen in females bred to mice exposed to PGE, indicating that PGE did not

produce dominant lethal mutations [49]. The only abnormality noted in the autopsies was focal degeneration of the seminiferous tubules in 1 of 8 rats exposed at 1.75 ppm (10 mg/cu m), 1 of 8 at 5.84 ppm (33 mg/cu m), and 3 of 8 at 11.20 ppm (71 mg/cu m). Personnel evaluating these slides felt that the evidence of degeneration was inconclusive and might have resulted from improper sectioning. Statistical analysis of the incidence of testicular atrophy using the Fisher exact test showed no significant treatment-related effect in any exposed group. The author concluded that the testicular effects were not treatment-related. However, since testicular degeneration has also been reported in animals exposed to DGE at low concentrations or to AGE, DGE, or triethylene glycol diglycidyl ether at high doses [41,48,52], the effects seen in this study [49] may be related to exposure to PGE.

The teratogenic potential of PGE was also evaluated by Terrill in this study [49]. Four groups of 25 female ChR-CD rats (200 g) were exposed to PGE vapor at 1.7, 5.7, or 11.5 ppm (10, 35, or 71 mg/cu m) for 12 days, beginning on the 4th day of gestation. No abnormal signs were observed in the exposed females. They were killed on the 20th day of gestation, and the corpora lutea and fetuses were enumerated. All the fetuses were examined for visible defects. Two-thirds of the fetuses were fixed and cleared and their skeletons stained in situ to show any variations and anomalies of ossification. The other fetuses were fixed and sectioned for examination. There were no significant differences between the control group and experimental groups in maternal body weight, mortality, early delivery, gross pathology, implantation efficiency, fetal survival, size, sex, ossification variations, or malformations. The author [49] concluded

that, under the test conditions, PGE was not teratogenic.

Of the few glycidyl ethers that have been investigated for their carcinogenicity, only two were demonstrated to produce an increased incidence of tumors in animals. Triethylene glycol diglycidyl ether injected ip at very high doses produced an excess of lung tumors in mice [52]. DGE at a concentration of 0.75 millimole produced papillomas in 4 of 10 mice when painted on the skin 3 times/week in a lifetime study [50]. In similar skin painting tests, resorcinol diglycidyl ether [50] and diphenylol propane diglycidyl ether [37] each produced only one papilloma in 14 and 40 mice, respectively, and hydroquinone diglycidyl ether [50] produced no tumors.

All glycidyl ethers that have been tested have shown mutagenic activity in bacteria [49,57,58]. Data from these studies permit the compounds to be ranked in descending order approximately as follows on the basis of their activity in the Ames assay: CGE and DGE > BGE > PGE > neopentyl glycol diglycidyl ether > dicyclopentadiene glycidyl ether > the diglycidyl ether of substituted glycerin > diphenylol propane diglycidyl ether > the C12-C14 alkyl glycidyl ether. The four most active compounds showed reduced mutagenic activity in the presence of a mammalian liver homogenate, a 10-fold reduction in the case of CGE; the two least mutagenic compounds showed a slight increase in activity when the liver homogenate was added, and the activity of the other glycidyl ethers was generally unaffected.

Only one glycidyl ether, BGE, was mutagenic in mammals in the dominant lethal test [58]. BGE also induced unscheduled DNA synthesis in human white blood cells, as did CGE and neopentyl glycol diglycidyl ether.

(f) Metabolism

Little is known about specific pathways for catabolism of glycidyl ethers. Since glycidyl ethers contain the epoxide ring, it seems reasonable to assume that they have common pathways with other epoxide compounds. Glycidyl ethers are highly reactive in biologic systems. One demonstration of such activity is a short biologic half-life. Duncan and Snow [59] injected rats iv with 300 mg/kg of triethylene glycol diglycidyl ether. After 1 minute, less than 10% of the dose could be found in the blood, and its metabolic half-life was calculated to be about 12 minutes. Only 0.4% of the administered dose was excreted unchanged.

Three types of metabolic reactions have been proposed for epoxide compounds [60]. These are shown in Figure III-1.

Two of these conversions are enzymatic. Oesch et al [60-63] have isolated an enzyme that they called epoxide hydrase from the livers of various species of animals, including rats, guinea pigs, monkeys, and humans. The enzyme reduced epoxides to their corresponding diols. BGE and PGE were among the glycidyl ethers acted upon by epoxide hydrase. Soellner and Irrgang [36] presented evidence that CGE was metabolized to its corresponding diol, which was apparently more neurotoxic than the parent compound.

The second enzymatic reaction is a conjugation of epoxides with glutathione. Glutathione-S-epoxide conjugase has been isolated from the livers of rats and ferrets [64] and of several wild birds [65]. Boyland and Williams [64] reported activity with PGE, substituted PGE's, resorcinol diglycidyl ether, 1-napthyl glycidyl ether, and 4,4'-bisglycidyl bisphenyl ether. Wit and Snel [65] reported conjugation of glutathione with PGE.

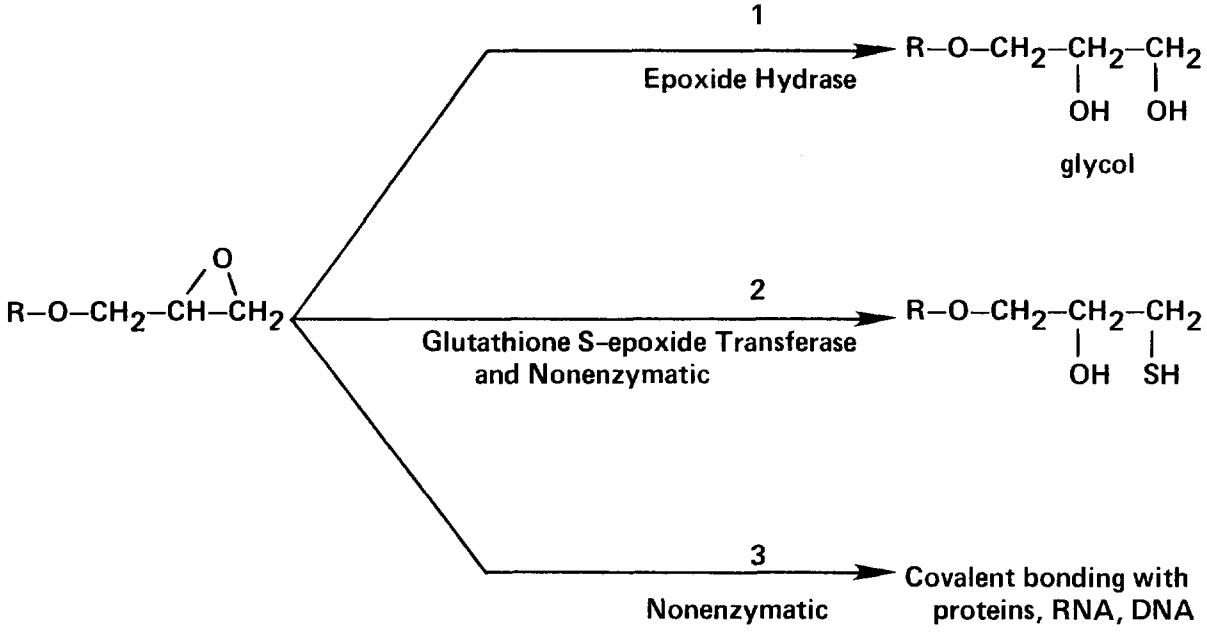



FIGURE III-1

PROPOSED METABOLIC PATHWAYS FOR GLYCIDYL ETHERS

Adapted from reference 60

Mukhtar and Bresnick [66] demonstrated that pretreatment of rats with 3-methylcholanthrene and phenobarbital enhanced glutathione-S-epoxide conjugase activity by 40%-60%.

The nonenzymatic reactions of epoxides are covalent bonding to proteins [60]. Loveless [6] has proposed a mechanism that would explain the high degree of biologic activity demonstrated by epoxides. He suggested that the "strained" character of the epoxide ring caused it to undergo an SN1 type of reaction in which the ring opened under the polarizing influence of a reactant, forming a carbonium ion which then reacted with water, proteins, or such nucleophilic compounds as RNA, DNA, histones, or proteins. The bulk of the available evidence on humans occupationally exposed to glycidyl ethers indicates that these substances reacted with skin proteins, giving rise to a contact skin sensitivity [24-28,30]. In animal experiments, only when large amounts contaminated the skin or were absorbed into the body was there evidence that glycidyl ethers reacted with nuclear elements to induce hemopoietic effects, mutations, or neoplasms [11-13,15,37,54,58,67].

## Correlation of Exposure and Effect

Adverse effects reported in humans exposed to glycidyl ethers have generally been limited to irritation and sensitization. PGE [23] and BGE [26] have produced severe skin irritation in humans, causing vesiculation, blistering, burns, and ulceration. The response to BGE was dose-dependent, with no irritation observed at 1.25%. AGE has produced skin irritation and eye irritation in humans [23].

Sensitization tests in humans with glycidyl ethers have been positive for all compounds tested, including PGE [24], BGE [25,26], and the C8-C10 alkyl glycidyl ether [30]. Cross-sensitization to CGE has occurred in humans sensitive to PGE, and sensitivity to AGE, BGE, and PGE has been demonstrated in humans occupationally exposed to epoxy resins of bisphenol A [27].

In patients treated with the antitumorigenic drug triethylene glycol diglycidyl ether, CNS effects, leukopenia, bone marrow depression, and regional edema and hair loss have been reported as side effects of therapy [12,13,16]. These systemic effects occurred following iv or intraarterial injection of repeated doses, and no comparable effects have been reported after occupational exposure to other glycidyl ethers.

Several glycidyl ethers have produced irritation and sensitization in animals. All the glycidyl ethers tested (DGE, AGE, IGE, PGE, BGE, resorcinol diglycidyl ether, butanediol diglycidyl ether, and diphenylol propane diglycidyl ether) were skin irritants in tests on guinea pigs, ranging from mild to very severe [28,31,44]. In addition, all of those tested for skin sensitization (BGE, PGE, CGE, the C12-C14 alkyl glycidyl ether, diphenylol propane diglycidyl ether, neopentyl glycol diglycidyl ether, and butanediol diglycidyl ether) gave positive results [24,28,30,31,37,44]. Eye irritation in animals resulted from exposure to airborne AGE, IGE, and DGE [23,41,47] and from direct instillation of these compounds or of PGE, resorcinol diglycidyl ether, butanediol diglycidyl ether, or the C8-C10 and C12-C14 alkyl glycidyl ethers [23,30,32-35,37].

In animals, glycidyl ethers have produced CNS effects, including muscular incoordination, reduced motor activity, agitation and excitement,

deep depression, narcotic sleep, and coma [23,33,35]. The route of administration plays an important role in the onset, duration, and severity of CNS effects. Each of the following, DGE, AGE, BGE, IGE, PGE, and resorcinol diglycidyl ether, produced CNS depression when administered orally [23,33,35], whereas only DGE and PGE [23,35] produced depression with dermal administration; after inhalation exposures, CNS depression was reported to have occurred immediately before death, appearing earlier only with BGE and AGE [23]. The progression of signs was usually from muscular incoordination and reduced motor activity to moderate depression (and, with BGE, agitation and excitement) to deep depression and coma before death. Animals that survived exposure to PGE showed a reversal of the progression [23]. CGE at very high doses has had antispasmodic and muscle relaxant effects in animals [36].

Many of the glycidyl ethers produced widespread systemic effects, such as necrosis, edema, inflammation, hyperemia, hemorrhaging, and tissue degeneration. The most frequent effect produced by inhalation of DGE, AGE, BGE, IGE, or PGE was lung irritation, specifically pneumonitis [23]. Rats exposed to AGE at 400 ppm (2,000 mg/cu m) for 7 hours/day, 5 days/week, for 10 weeks had abnormal changes in the lungs, such as severe emphysema, bronchiectasis, and bronchopneumonia; those exposed to PGE at about 10 ppm (50 mg/cu m) on the same schedule had peribronchial and perivascular pulmonary inflammatory cell infiltration [23]. Resorcinol diglycidyl ether did not produce any lung anomalies in rats exposed to an airstream saturated with it for 7 hours/day, 5 days/week, for 10 weeks; the concentration of airborne resorcinol diglycidyl ether was not reported, but it would have been very low, since this glycidyl ether is a solid at room

temperatures [33]. No gross changes were noted in the lungs of rabbits exposed to DGE at 3, 6, or 12 ppm (16, 32, or 64 mg/cu m) for 24 hours. At 24 ppm (128 mg/cu m) for 24 hours, DGE caused purulence in the lungs, with pericardial adhesions, peribronchiolitis, bronchopneumonia, focal atelectasis, and focal hemorrhages in rabbits. DGE also caused pneumonia and massive infarction in the lungs of one of three dogs injected iv at a dose of 25 mg/kg [41]. Intramuscular injections of 400 mg/kg of AGE produced pulmonary congestion in one rat after the second daily injection; microscopic examination confirmed pneumonia [48].

The effects of glycidyl ethers in organ systems were primarily irritation and necrosis. Local and widespread inflammation, congestion, and necrosis resulted after exposure of rats to DGE, AGE, IGE, PGE, and BGE by the oral, inhalation, or dermal routes [23,35,41,48]. The organs and tissues affected were the adrenal gland, liver, lungs, stomach, kidneys, brain, skin, peritoneum, small intestine, thymus, spleen, lymph nodes, testes, and pancreas.

Circulatory system disorders were also evident in animals exposed to PGE and included hyperemia and increased permeability of the capillaries [35]. AGE given by im injection to rats produced significantly reduced leukocyte counts and a decreased myeloid-to-erythroid ratio, although the number of nucleated cells in the bone marrow and the percentage of polymorphonuclear cells was normal [48]. Animals given im injections of IGE, PGE, and BGE did not show evidence of hemopoietic changes [23,48].

In rabbits, DGE produced decreases in leukocyte counts and percentages of polymorphonuclear cells at iv doses of 50, 100, or 200 mg/kg [41]. By inhalation, DGE at 24 ppm (128 mg/cu m) caused an increase in

leukocytes and polymorphonuclear cells prior to death; thrombocytosis was also noted. At DGE concentrations of 12 ppm (64 mg/cu m), thrombocyte counts were increased, and at 6 ppm (32 mg/cu m), some basophilia was seen. In rats, three or four exposures to DGE at 20 ppm (110 mg/cu m) for 4 hours produced intense cytoplasmic basophilia, grossly distorted lymphocytic nuclei with indistinct cellular membranes, and lowered leukocyte and marrow cell counts. Long-term exposures of rats for 4 hours/day, 5 days/week to DGE at 3 ppm (16 mg/cu m) for 19 exposures in 29 days caused decreases in leukocyte counts, polymorphonuclear cells, and marrow nucleated cell counts. Blood cell morphology was normal in rats exposed at 0.3 ppm (1.6 mg/cu m) for 20 exposures, but over half the polymorphonuclear cells of two rats contained eosinophilic granules after 60 exposures.

A summary of the effects of dermal contact with glycidyl ethers on humans is presented in Table III-1. A summary of the effects of exposure to glycidyl ethers on animals is presented in Table III-2.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

No reports of the carcinogenic, mutagenic, teratogenic, or reproductive effects of the glycidyl ethers on humans were found in the literature. However, such effects have been investigated in animals for some of the glycidyl ethers.

The carcinogenic potentials of DGE, resorcinol diglycidyl ether, diphenylol propane diglycidyl ether, and hydroquinone diglycidyl ether have been studied in skin painting tests on animals [37,50,51]. No malignant tumors have been observed with any of these compounds. DGE at a total dose of 0.75 millimole produced skin papillomas in 4 of 10 surviving mice

painted with the compound 3 times/week, with the first tumor appearing after 5 months; DGE at 0.25 millimole produced a papilloma in one test animal [51]. Resorcinol diglycidyl ether was said to be carcinogenic in both mice and rats, but no supporting data were provided [50]. A later paper by the same investigators showed that resorcinol diglycidyl ether had induced a benign tumor in 1 of 14 test animals at a dose of 0.75 millimole and produced no tumors at 0.25 millimole [51]. Undiluted diphenylol propane diglycidyl ether painted on the skin three times/week produced 1 papilloma in 40 surviving mice after 16 months [37]. Hydroquinone diglycidyl ether at a dose of 1 millimole caused no skin tumors in mice [51].

Triethylene glycol diglycidyl ether, which has been used as an antitumor agent, has been found to be carcinogenic in mice at very high ip doses [52]. A total dose of 7,208 mg/kg over a 4-week period produced a 70% incidence of lung tumors. The authors calculated that the lowest dose that would raise the incidence of tumors above spontaneous levels was greater than 3.7 g/kg.

Several glycidyl ethers have produced effects described as radiomimetic or cytotoxic. As in the case of triethylene glycol diglyicdyl ether, diethylene glycol diglycidyl ether and butanediol diglycidyl ether have had antitumorigenic effects [56]. Diethylene glycol diglycidyl ether injected ip at a total dose of 1.5 mg/g caused an 84% inhibition of implanted Walker tumors in rats. This compound produced chromosomal aberrations and inhibition of mitosis in the tumor cells and bone marrow at doses of 0.1-0.4 mg/g/day. Butanediol diglycidyl ether at a total dose of 1.2 mg/g caused a 74% inhibition in tumor growth. At 0.2 mg/g, this

compound caused chromosomal aberrations in tumor and bone marrow cells, and at 0.1 mg/g, the only cytotoxic effects seen were chromosome bridges and fragmentation in the bone marrow.

Exposure to AGE and DGE caused decreased leukocyte counts attributed to cytotoxic effects on the bone marrow in rats, rabbits, and dogs [41,48]. In the same study [48], BGE and PGE did not produce a decrease in leukocytes when administered to rats by ip injection. Rats exposed to PGE by inhalation at up to 11.2 ppm (68.8 mg/cu m), 6 hours/day for 19 days, had no increase in chromosomal aberrations in the bone marrow [49]. None of six glycidyl ethers tested, including BGE and CGE, produced micronuclei in the bone marrow cells of mice [58]. DGE and resorcinol diglycidyl ether have produced radiomimetic effects in plant cells [6,53-55].

Several glycidyl ethers have been tested for mutagenic activity (see Table XIV-6). AGE, BGE, CGE, DGE, PGE, neopentyl glycol diglycidyl ether, dicyclopentadiene diglycidyl ether, and the diglycidyl ether of substituted glycerine all produced a mutagenic response in Salmonella typhimurium in the Ames assay [49,57,58]. Diphenylol propane diglycidyl ether gave weakly positive results in this test in one study [58] and negative results in another [57]. The C12-C14 alkyl glycidyl ether showed weak mutagenic activity only when activated by the addition of a rat-liver microsomal extract [58]. Metabolism by mammalian microsomes decreased the activity of BGE, CGE, DGE, and PGE and had little or no effect on the mutagenicity of the other compounds tested [49,57,58]. None of the compounds tested showed definite mutagenic activity in the host-mediated assay test [58].

Urinary metabolites of CGE and neopentyl glycol diglycidyl ether caused a weak mutagenic response in Salmonella in the mouse body-fluid analysis, but other glycidyl ethers were not active in this test [58]. These two compounds and BGE also induced unscheduled DNA synthesis in human mononucleated white blood cells [58]. Only BGE has shown mutagenic activity in mice in the dominant lethal test [58]. When this compound was painted on the skin of male mice at 1.5 g/kg, it produced a significant increase in the number of fetal deaths in females to which they were subsequently bred.

Only PGE has been studied for its teratogenic effects, and it produced no teratogenesis in the offspring of female mice exposed at 11.5 (68.8 mg/cu m) ppm during days 4-15 of gestation [49].

Testicular degeneration has been noted in several animal species after exposure to AGE, DGE, PGE, and triethylene glycol diglycidyl ether [41,48,49,52]. Necrosis of the testes was reported in rats that received six dermal applications of DGE at 250 or 500 mg/kg [41] or four im injections of AGE at 400 mg/kg [48]. Testicular atrophy with decreased spermatogenic activity was seen in mice receiving high ip doses of triethylene glycol diglycidyl ether [52]. Atrophied testes were found in two rabbits that died after a single 24-hour exposure to DGE at 24 ppm (128 mg/cu m) and possibly in a dog that received six 12.5 mg/kg iv doses of this compound [41]. In chronic inhalation experiments, 1 of 15 rats exposed to DGE at 3 ppm (16 mg/cu m) had necrosis of testicular tubules after 19 exposures; 5 of 10 rats exposed at 0.3 (1.6 mg/cu m) had "poorly defined" focal degeneration in the testes after 60 exposures [41]. In rats exposed to PGE at 1.75-11.2 ppm (10-71 mg/cu m) for 19 days, focal

degeneration of the seminiferous tubules was observed in 5 of 24, but the investigator considered that this damage was of questionable significance and was probably not treatment related [49]. Only in the PGE study was any attempt made to correlate testicular damage with effects on reproduction, and this study showed no significant mutagenic or reproductive effects [49].

Lack of data on most of the glycidyl ethers makes it difficult to correlate variations in the results of tests of their mutagenicity and carcinogenicity with differences in the structure of particular compounds within the class. Thus, only tentative conclusions can be drawn about the potential of glycidyl ethers to cause cancer or mutations.

Because of the presence of epoxide groups, the glycidyl ethers would be expected to be biologically active; epoxides have been shown to be mutagenic and carcinogenic [37,56], and epoxide intermediates have been identified or postulated as the mutagenic or carcinogenic metabolites of other compounds [68]. However, the limited data available on metabolism of glycidyl ethers indicates that they are rapidly metabolized to less cytotoxic substances [36,59,60]. They conjugate readily with proteins, and are thus active skin sensitizers, but the available evidence indicates that effects that might result from conjugation with nuclear macromolecules occurred only at very high dose levels, when detoxification mechanisms may have been overwhelmed.

Because diglycidyl ethers include twice as many of the hypothetically active epoxide moieties, they might be expected to have greater carcinogenic or mutagenic potential than monoglycidyl ethers. All 10 compounds that have been tested showed mutagenic activity in bacterial

tests [49,57,58]. The most active mutagens, however, were monoglycidyl ethers. The quantitative difference in activity and the varying effects produced by the addition of mammalian liver microsomes suggest differences in metabolic pathways for the glycidyl ethers. Their mutagenic activity was also variously affected by test systems involving in vivo mammalian metabolism. BGE, a monoglycidyl ether, was the only glycidyl ether shown to be a mammalian mutagen in the mouse dominant lethal test, and it was not the most active compound in bacterial tests; BGE was also partially deactivated by mammalian microsomes in vitro and showed no mutagenic activity in the body-fluid test, host-mediated assay, or micronucleus test [58]. Since the only data found on tumorigenicity testing concerned diglycidyl ethers, no direct evidence is available on their activity relative to that of monoglycidyl ethers. However, Weil et al [37] found that 5 of 17 diepoxide compounds tested were tumorigenic to mice, while none of 11 monoepoxides were. They concluded that the "currently prevalent" generalization that diepoxides are carcinogenic was not supported. Because no generalizations about the carcinogenic hazards of working with epoxy compounds could be made from the existing data, they emphasized that each compound must be individually tested for its carcinogenic potential.

Shimkin et al [52] have pointed out certain structural factors that may affect the carcinogenic potential of alkylating agents such as the glycidyl ethers. They suggest that those that are stable enough to survive the transfer to a susceptible organ and that structurally resemble a naturally occurring substrate tend to be the most active.

Such diversity in results after testing various monoglycidyl and diglycidyl ethers only serves to emphasize the necessity to avoid making generalizations regarding the potential of an individual glycidyl ether to be mutagenic or carcinogenic. However, these findings, together with studies indicating that DGE, and possibly resorcinol diglycidyl ether and neopentyl glycol diglycidyl ether, can produce skin tumors [50,51], indicate that gross skin contact with glycidyl ethers may represent an important hazard to worker health. Because of their low vapor pressures, most of these compounds are unlikely to be present in workplace air at concentrations sufficient to permit their reaching the nuclei of somatic or reproductive cells and causing neoplastic or mutagenic effects. However, because of their demonstrated mutagenicity, the glycidyl ethers should, in the absence of adequate carcinogenicity test data on individual compounds, be regarded as potentially serious hazards.

TABLE III-1

EFFECTS OF SKIN CONTACT WITH GLYCIDYL ETHERS ON HUMANS

| Compound | Exposure Concentration | Exposure Duration | Effects | Reference |
|---|---|---|---|---|
| AGE | - | 300 hr | Dermatitis in 10/20 | 23 |
| BGE | - | 3 mo | Dermatitis in 0/8 | 23 |
| " | 100% | 48 hr | Severe irritation in 5/5 | 26 |
| " | 10% | - | Positive patch-tests with 10% BGE in 19/24 | 25 |
| " | 10% | 48 hr | Irritation in 17/25; positive patch tests with 1.25% BGE in 5/25 | 26 |
| " | 5% | " | Irritation in 8/25 | 26 |
| " | 2.5% | " | Irritation in 1/25 | 26 |
| " | 1.25% | " | Irritation in 0/25 | 26 |
| DGE | - | a few mo | No dermatitis reported | 23 |
| IGE | - | " | " | 23 |
| PGE | - | 600 hr | Dermatitis in 13/20 | 23 |
| " | 3% | - | Dermatitis in 12/18; positive patch-tests with 0.001-1% PGE in 8/15 with dermatitis | 24 |

TABLE III-2

EFFECTS OF EXPOSURE TO GLYCIDYL ETHERS ON ANIMALS

| Compound | Effect | Species | Dose or Exposure Concentration | Duration | Route of Exposure | Reference |
|---|---|---|---|---|---|---|
| AGE | Death | Rats | 2,800 mg/cu m | 5 wk | inhalation | 23 |
| " | " | Mice | 1,260 mg/cu m | 4 hr | " | 23 |
| " | Decreased weight gain | Rats | 1,210 mg/cu m | 10 wk | " | 23 |
| " | Lung damage | " | 1,870 mg/cu m | 10 wk | " | 23 |
| " | Testicular degeneration | " | 400 mg/kg/d | 3-4 d | im | 48 |
| " | Decreased leukocytes | " | " | " | " | 48 |
| " | Skin irritation | Rabbits | Undiluted | - | dermal | 23 |
| " | Eye irritation | " | " | - | ocular | 23 |
| " | " | Rats | 1,200 mg/cu m | 10 wk | inhalation | 23 |
| BGE | Death | " | 5,500 mg/cu m | 8 hr | " | 23 |
| " | Dominant lethal | Mice | 1,500 mg/kg/d | 24 d | dermal | 58 |
| " | Increased leukocytes | Rats | 400 mg/kg/d | 3 d | im | 48 |
| " | Sensitization | Guinea pigs | 10% | 8 d | dermal | 31 |
| " | Skin irritation | Rabbits | Undiluted | - | dermal | 23,30, 32,42 |
| " | Eye irritation | " | " | - | ocular | 23,32 |
| CGE | Death | Mice | 980 mg/kg | 1 dose | sc | 36 |
| " | Muscle relaxation | Rats | 390 mg/kg | " | " | 36 |
| " | Sensitization | Guinea pigs | 5-25% | - | dermal | 28 |

TABLE III-2 (CONTINUED)

EFFECTS OF EXPOSURE TO GLYCIDYL ETHERS ON ANIMALS

| Compound | Effect | Species | Dose or Exposure Concentration | Duration | Route of Exposure | Reference |
|---|---|---|---|---|---|---|
| DGE | Death | Mice | 160 mg/cu m | 4 hr | inhalation | 23 |
| " | " | Rabbits | 128 mg/cu m | 24 hr | " | 41 |
| " | " | Rats | 106 mg/cu m | 3-4 d | " | 41 |
| " | " | " | 200 mg/kg/d | 6 d | dermal | 41 |
| " | Organ damage | Rabbits | 128 mg/cu m | 24 hr | inhalation | 41 |
| " | Lung damage | Rats | 106 mg/cu m | 3-4 d | " | 41 |
| " | Testicular degeneration | Rabbits | 128 mg/cu m | 24 hr | " | 41 |
| " | " | Rats | 1.6 mg/cu m | 60 d | " | 41 |
| " | Weight loss | Rabbits | 128 mg/cu m | 24 hr | " | 41 |
| " | " | Rats | 106 mg/cu m | 3-4 d | " | 41 |
| " | " | " | 250 mg/kg/d | 6 d | dermal | 41 |
| " | Decreased weight gain | " | 32 mg/kg/d | 6 d | " | 41 |
| " | Decreased leukocytes | " | 16 mg/cu m | 19 d | inhalation | 41 |
| " | " | " | 500 mg/kg | 1 dose | dermal | 41 |
| " | " | " | 200 mg/kg d | 6 d | " | 41 |
| " | Skin tumors | Mice | 0.25 mM | 8 wk | " | 41 |
| " | Skin irritation | Rabbits | Undiluted | - | " | 41 |
| " | Eye irritation | " | " | - | ocular | 23 |
| " | " | Rats | 250 mg/kg/d | 6 d | dermal | 41 |

TABLE III-2 (CONTINUED)

EFFECTS OF EXPOSURE TO GLYCIDYL ETHERS ON ANIMALS

| Compound | Effect | Species | Dose or Exposure Concentration | Duration | Route of Exposure | Reference |
|---|---|---|---|---|---|---|
| IGE | Death | Mice | 7,130 mg/cu m | 4 hr | inhalation | 23 |
| " | " | Rats | 5,230 mg/cu m | 8 hr | " | 23 |
| " | Decreased weight gain | " | 1,900 mg/cu m | 10 wk | " | 23 |
| " | Respiratory distress | " | " | " | " | 23 |
| " | Skin irritation | Rabbits | Undiluted | - | dermal | 23 |
| " | Eye irritation | " | " | - | ocular | 23 |
| " | " | Rats | 1,900 mg/cu m | 10 wk | inhalation | 23 |
| PGE | Death | Rabbits | 3,000 mg/kg | 1 dose | dermal | 23 |
| " | Organ necrosis | Rats | 2,200 mg/kg | " | " | 35 |
| " | Muscle relaxation | " | 430 mg/kg | " | sc | 36 |
| " | Lung irritation | " | 60 mg/cu m | 10 wk | inhalation | 23,39 |
| " | Testicular degeneration | " | 10 mg/cu m | 19 d | " | 49 |
| " | Increased leukocytes | " | 400 mg/kg/d | 3 d | im | 24 |
| " | Sensitization | Guinea pigs | Undiluted | 7 d | dermal | 24 |
| " | Skin irritation | Rats | 70 mg/cu m | 3 mo | inhalation | 39 |
| " | " | Rabbits | Undiluted | - | dermal | 23,34, 35 |
| " | Eye irritation | " | " | - | ocular | 23,34, 35 |
| " | " | Rats | 60 mg/cu m | 10 wk | inhalation | 23 |
| Alkyl glycidyl ether (C12-C14) | Sensitization | Guinea pigs | 5-25% | - | dermal | 28 |

TABLE III-2 (CONTINUED)

EFFECTS OF EXPOSURE TO GLYCIDYL ETHERS ON ANIMALS

| Compound | Effect | Species | Dose or Exposure Concentration | Duration | Route of Exposure | Reference |
|---|---|---|---|---|---|---|
| Butanediol diglycidyl ether | Death | Rats | 1,130 mg/kg | 1 dose | dermal | 32 |
| " | Bone marrow cytotoxicity | " | 100 mg/kg | " | ip | 56 |
| " | Tumor cell inhibition | " | 1,200 mg/kg (total dose) | - | | 56 |
| " | Sensitization | Guinea pigs | 10% | - | dermal | 28 |
| " | Skin irritation | Rabbits | Undiluted | - | " | 32 |
| " | Eye irritation | " | " | - | ocular | 32 |
| Diethylene glycol diglycidyl ether | Bone marrow cytotoxicity | Rats | 100 mg/kg | 1 dose | ip | 56 |
| " | Tumor cell inhibition | " | 1,500 mg/kg (total dose) | - | | 56 |
| Diphenylol propane diglycidyl ether | Death | Rabbits | 22,000 mg/kg | 1 dose | dermal | 37 |
| " | Sensitization | Guinea pigs | 5% | - | " | 7 |
| " | Skin irritation | Rabbits | Undiluted | - | " | 37 |
| " | Eye irritation | " | " | - | ocular | 37 |
| Resorcinol diglycidyl ether | Death | " | - | 7 d | dermal | 33 |
| " | Skin tumors | Mice | 0.75 mM | 8 wk | " | 51 |
| " | Skin irritation | Rabbits | Undiluted | - | " | 33 |
| Triethylene glycol diglycidyl ether | Lung tumors | Mice | 7,200 mg/kg (total dose) | - | ip | 52 |
| " | Testicular degeneration | " | - | - | " | 52 |

# IV. ENVIRONMENTAL DATA

## Engineering Controls

Most glycidyl ethers are liquids with low vapor pressures, ranging from 0.01 mmHg at 25 C for PGE to 3.2 mmHg for BGE, 4.7 mmHg for AGE, and 9.4 mmHg for IGE at 25 C. The vapor pressures for BGE, AGE, and IGE are great enough to permit vapor concentrations of up to 4,000, 6,000, and 12,000 ppm, respectively. Glycidyl ether vapors are generated in certain processes, such as resin curing, and the inhalation of these vapors may be a health hazard. Engineering controls must therefore be installed wherever possible to maintain the concentration of glycidyl ethers at or below the recommended environmental limits. Closed-system operations should be used whenever feasible to control exposure to vapors produced during the manufacture or use of glycidyl ethers. Closed-system operations are effective only when the integrity of the system is maintained, so the equipment should be inspected frequently for leaks, and any that are found should be promptly repaired.

A sparkproof ventilation system may be required where a closed system proves to be impractical and is desirable as a standby if the closed system should fail. Industrial Ventilation--A Manual of Recommended Practice [69], published by the American Conference of Governmental Industrial Hygienists, and Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z9.2-1971 [70], published by the American National Standards Institute, provide useful guidelines for the design and installation of adequate ventilation systems. The air intake for ventilation systems should be sited so that exhaust air is not recirculated

in the work area. Ventilation systems will require regular inspection and maintenance to facilitate effective operation, and a regular schedule for inspections and repair should be established. These routine checks should include face velocity measurements of the collecting hood, inspection of the air mover, ducts, and collector, and measurements of airborne concentrations of glycidyl ethers in the workroom. Any process changes that may affect the ventilation system or the operations being ventilated must be assessed promptly to ensure that engineering controls will continue to provide adequate protection for employees.

If it is determined that glycidyl ether vapors are generated in a particular process in amounts sufficient to create a possible fire or explosion hazard, several precautions should be taken. If a fan is located in ductwork and the air concentration of glycidyl ether vapors may exceed 25% of the lower flammable limit, the rotating element should be constructed of nonsparking material and the casting should also be constructed of a nonsparking material. Devices to prevent flashback should be installed along the entire length of the ventilation system.

The addition of glycidyl ethers and other components to epoxy resin systems immediately before the resins are to be used should be done in a ventilated hood. Unnecessary worker exposure to and contamination of the physical plant by glycidyl ethers can be minimized by using separate areas of the plant for mixing, molding, and curing the resins [71,72].

## Sampling and Analysis

Only a few reports describing procedures for the sampling and analysis of glycidyl ethers have been found. The sampling and analytical

methods recommended in Appendices I, II, and III have not been validated for detecting glycidyl ethers at concentrations as low as the recommended limits. Further testing of these methods is an important need.

The Intersociety Committee of the American Public Health Association, Inc., has reported an analytical method for organic solvent vapors in air [73]. The method was tested for AGE, BGE, and IGE; these compounds were reported to have greater than 80% desorption efficiency by this method. Air samples were collected with a charcoal tube and an air-sampling pump. The tube was glass, 7 cm long, with a 6-mm outer diameter and a 4-mm inner diameter, and contained two sections of 20/40-mesh activated charcoal separated by a 2-mm portion of urethane foam. After a known volume of air was drawn through the tubes at a specific flowrate (50-200 cc of air/minute), the collected organic vapors were desorbed separately from each section of charcoal in the tube with carbon disulfide and analyzed by gas chromatography with flame ionization detection. The area of the peaks was compared with a standard curve to determine the concentration of the samples.

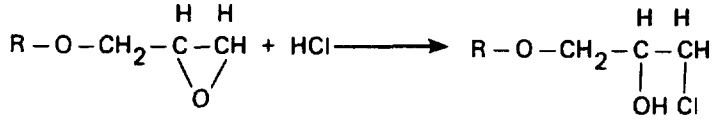
High humidity and high temperatures were reported to interfere with the adsorption capacity of the activated charcoal [73]. The precision of the method was limited by the reproducibility of the pressure drop across the tubes, and the amount of sample collected was limited by the adsorption efficiency of the charcoal. Advantages of the method are that the sampling device is small, portable, and requires no liquids, and there are few interferences; these can usually be eliminated by altering the gas chromatographic operating conditions.

Little information has been found on portable direct-reading instruments that can be used to perform immediate evaluations of concentrations of glycidyl ethers in the workplace. The Wilks Miran 1A is a portable instrument that uses infrared absorbance to detect many air contaminants. The reported minimum detectable concentrations for AGE and BGE were 0.07 ppm (0.33 mg/cu m) and 0.05 ppm (0.27 mg/cu m), respectively [74]. It is possible that this instrument might be useful for detecting other glycidyl ethers, but no data concerning the performance of the instrument with them are currently available.

In 1977, Terrill and Lee [39] described a paired sampling and analysis regimen for PGE and phenol. The sampling device was a midget impinger containing 15 ml of a 0.1 N sodium hydroxide solution in equal parts of ethyl alcohol and water. A 10-liter air sample was collected at a sampling rate of 1 liter/minute, and ultraviolet analysis was performed on it. A 5-ppm v/v solution of PGE had an absorbance of 0.4 (1-cm cell) at a maximum of 270 nm. Phenol had a lambda maximum at 288 nm and could be detected when the phenol concentration was 5% or more of the PGE concentration. The relative proximity of the two lambda maximums is a factor that limits the minimum detectability for the system. When phenol concentrations were greater than or equal to 0.05 ppm, 0.25 ppm, and 0.6 ppm, the minimum sensitivities for PGE were 1, 5, and 12 ppm (6, 30, and 74 mg/cu m), respectively. The phenol concentrations were monitored because trace amounts of phenol (found by gas chromatographic analysis) were present in the PGE that was sampled.

Jungnickel et al [7] have reviewed several methods for the analysis of materials containing alpha-epoxide rings, a group common to all glycidyl

ethers. The tendency of the epoxide group to react readily with nucleophilic reagents is the basis for all of the methods. Hydrogen chloride (HCl) is added to a flask containing the sample material and allowed to react. This reaction can be represented schematically as follows:



Since each dissociated molecule of HCl reacts with only one epoxide group, the calculated value for HCl is a measure of the number of epoxide groups present. When monoglycidyl ethers are analyzed, the number of moles HCl is equal to the amount of glycidyl ether in the sample. When diglycidyl ethers are sampled, the number of moles of HCl is equal to twice the number of moles of the diglycidyl ether in the sample.

The seven methods described by Jungnickel et al [7] differ principally in the solvent for HCl, the temperature at which the reaction is carried out, the specific indicator, and the solvent (water or methanol) in the solution of sodium hydroxide used as a titrant. The nature of the sample is one of the factors to be considered when selecting a particular hydrochlorination method. The reagents chosen should be good solvents for the sample, especially if it is in solid form. The conditions under which the reaction is carried out are also important. The method that allows the smallest number of side reactions (such as isomerization to the

corresponding carbonyl compound) should be selected. The authors [7] reported that glycidyl ethers of very high purity were sampled quite accurately unless alcoholic magnesium chloride hydrochlorinate was used as a reagent; then the results were 1-2% low. The authors did not report results of analysis of impure glycidyl ether samples, such as might be encountered in sampling workplace air. It can be seen, however, that any impurities that would react with the hydrochlorination agent or the glycidyl ether would affect the accuracy of the method. The possibility that other substances in the workplace environment will interfere with the determination of glycidyl ethers should be considered when the analyses are performed.

These hydrochlorination methods are not suitable for the sampling and analysis of glycidyl ethers in workplace air for a number of reasons. Solvent selection is extremely important and must be based on the knowledge of other substances that may be present as sample contaminants and the hydrochlorination reactions. Most of the solvents suggested (eg, dioxane, pyridine, diethyl ether) are toxic. Finally, because a dye is used as an indicator, these methods should be routinely performed by the same technician to provide reproducible results.

NIOSH has validated methods for the sampling and analysis of BGE [75], IGE [76], and PGE [77]. A draft report on validated sampling and analytical methods for AGE [78] indicates that the methods for these four glycidyl ethers are similar. The attempts to determine methods of sampling and analysis for DGE failed because desorption efficiency was not adequate to permit acceptable recovery [79].

The method tested for DGE under the NIOSH Standards Completion Program involved the use of a charcoal tube to collect the vapors; methylene chloride was used to desorb the DGE from the charcoal [79]. The samples were then analyzed by gas chromatography. When the method was tested, 15-minute samples were collected from chambers containing concentrations of airborne DGE at 0.5, 1, and 2 times the current Federal standard (2.8 mg/cu m). The amounts recovered were 71.6, 75.6, and 68.8%, respectively, which were considered too low to be acceptable. For this reason, and because the experimental work exceeded the time allotted to the project, the method received a "failure report." A review of the data indicates that the desorption efficiency ranged from 0.783 to 0.976 when 0.02 to 0.85 mg of DGE was placed on, and desorbed from, charcoal. The experimenters inferred from preliminary data that desorption efficiency may be, to some extent, a function of storage temperature and time; the time allotted for the investigation did not allow the experimenters to ascertain and clarify the role of storage times and temperature. It is reasonable to conclude that if these variables are determined, as they have to be with any method relying on sorption on, and desorption from, charcoal, the method will be useful for sampling airborne DGE.

Because of the similarities in the chemical structures of all glycidyl ethers, the methods presented in Appendices I, II, and III may be adequate for sampling and analysis of any glycidyl ether if certain parameters, such as the desorption solvents and operating conditions for the gas chromatograph, are appropriately modified. These modifications have not yet been tested by NIOSH.

To sample for concentrations of airborne BGE, IGE, and PGE, a known volume of air is drawn through a charcoal tube that traps the organic vapors. The analytes are desorbed with carbon disulfide and analyzed by gas chromatography. Further details of this procedure are presented in Appendix I.

To sample for concentrations of airborne AGE, a known volume of air is drawn through a Tenax-GC resin tube and the organic vapors are adsorbed on the resin. The sample is then desorbed with ether, and an aliquot is analyzed in a gas chromatograph. Further details of this procedure are presented in Appendix II.

To sample for concentrations of airborne DGE, a known volume of air is drawn through a charcoal tube that traps the organic vapors. The analyte is then immediately desorbed with methylene chloride and analyzed with a gas chromatograph. Further details of this procedure are presented in Appendix III.

Certain conditions may interfere with the analysis of these five glycidyl ethers. High humidity in the sampling environment may decrease the collection efficiency of the collecting tube, and the presence in the sample of compounds that have similar retention times at the prescribed operating conditions of the gas chromatograph will interfere with the detection of the ether being analyzed. If the possibility of interference exists, separation conditions (column packing, temperature, etc) must be changed to alter the retention times of the ether and the interfering compounds in order to circumvent the problem.

The upper limits of the ranges of the methods are dependent on the adsorptive capacity of the charcoal or Tenax-GC resin tubes. The

efficiency of the collecting tubes will change drastically as the tube becomes heavily loaded with organic vapors. In practice, lower limits are often dependent on the desorption efficiency, ie, the percentage of the glycidyl ether that is desorbed and dissolved in the solvent. Desorption efficiency must be determined over the range used for each ether being analyzed.

The NIOSH recommended methods for the sampling and analysis of AGE, BGE, IGE, PGE, and DGE have several advantages over the other methods discussed in this section. The recommended sample tubes contain either activated charcoal or, for AGE, Tenax-GC, and both of these are solid sorbents. A method that requires no liquids during sampling eliminates the possibility of spills and evaporation. The chosen sorbents involve no exposure to a toxic chemical used as a sampling medium, such as the solvents required for the hydrochlorination methods [7]. The sampling device is small and portable. Furthermore, interferences are few, and those that occur can be eliminated by altering chromatographic conditions. In the hydrochlorination method [7], interferences during sampling may alter the reaction that is the basis of the analysis and invalidate the results of the titration. In ultraviolet analysis of a liquid sample [39], the limit of detectability for PGE was seriously affected by the presence of phenol.

The primary disadvantage of the recommended sampling and analytical methods is that they have not been tested at the recommended sampling rate and size. However, the methods are capable of determining concentrations of airborne glycidyl ethers at the recommended limits. The method for DGE has the distinct disadvantage of requiring desorption immediately after

sampling because desorption efficiency decreases with time. Immediate desorption creates a need for the proper packaging of the methylene chloride-desorbed analyte for shipment. The substitution of Tenax-GC for charcoal may eliminate the need for these procedures, but the recommended method has not been tested by NIOSH with Tenax-GC in the tube.

## Environmental Data

A manufacturer of BGE and PGE used the NIOSH-validated sampling and analytical methods [75,77] to monitor these compounds during two production runs [17(p 155)]. Airborne concentrations below 1 ppm were recorded for both ethers. During drumming operations at the same facility, airborne concentrations of BGE were determined to be 2-4 ppm. No other data on concentrations of airborne glycidyl ethers have been found.

# V. WORK PRACTICES

Human skin contact with glycidyl ethers has resulted in rashes, burns, and sensitization [23,25,80], and studies in animals indicate that skin irritation, sensitization, and systemic effects can result from dermal exposure to these compounds [23,31,32,34]. Glycidyl ethers have also caused hemopoietic and other systemic effects in animals exposed by inhalation [23,33,41], but, for glycidyl ethers other than DGE, these effects have occurred only at high concentrations. Eye irritation has resulted from both direct contact with liquid glycidyl ethers and exposure to airborne vapors [23,41,47]. Glycidyl ethers have proven to be cytotoxic or mutagenic or have caused radiomimetic effects in tests using several different routes of exposure, including dermal contact [56,58]. DGE and resorcinol diglycidyl ether have caused nonmalignant skin tumors in mice [51], and triethylene glycol diglycidyl ether was carcinogenic to mice at very high doses [52].

Work practices and sanitation measures applied in the manufacture, handling, and storage of glycidyl ethers must therefore be designed to minimize or prevent inhalation of glycidyl ether vapors or mists and to protect workers' skin and eyes from contact with liquid glycidyl ethers. Most glycidyl ethers are liquids. All of them have relatively low vapor pressures (Table XIV-2), but because of their toxicity, precautions to prevent inhalation of vapors or mists should nevertheless be taken. Throughout the process of manufacturing epoxy resin systems, glycidyl ethers can be present along with other components of the system, such as

amine hardeners. Good work practices designed to protect the worker from contact with glycidyl ethers should therefore be observed until the resin is fully polymerized. A fully polymerized resin has been considered to be inert [71,81,82], but wet or uncured resins, and the chemicals used to thin, strengthen, or harden them, should be considered hazardous substances [71]. Work practices appropriate for handling the other components of the epoxy resin system, such as the amine hardeners, should also be followed.

Workers should be provided with protective clothing that is impervious to glycidyl ethers and, if possible, fire-resistant. They should be protected against contact with liquids by the use of gloves, aprons, boots, faceshields (8-inch minimum), and other protective equipment or clothing. For processes in which manual dexterity requirements limit the types of gloves that can be worn, protective hand creams have been suggested as supplements to gloves that will permit the required dexterity [17(pp 5,141),83]. Extreme care should be taken to avoid contamination inside gloves. Tests done at Argonne National Laboratory in 1964 indicated that only 2 of 10 glove materials tested provide acceptable protection for work with AGE and PGE [84]. Milled butyl rubber and polyvinyl alcohol were found to be acceptable materials. Unacceptable glove materials were natural rubber (latex), neoprene-natural rubber (latex), milled neoprene, neoprene with nylon, milled Buna-N, vinyl and polyethylene (disposable), and polyvinyl chloride [84]. Gloves made of polyvinyl chloride or polyethylene-coated fabric may be used for a single workshift exposure (BW Karrh, M.D., written communication, January 1978). Only adequate test data should be used as a basis for deciding which glove materials provide proper protection against specific glycidyl ethers. At the end of the workshift,

workers should use conditioners to keep the skin on their hands and arms supple because absorption of, and sensitization to, glycidyl ethers occurs more readily through irritated or cracked skin [44,72]. Neutral or acid soaps that protect the skin from drying and cracking should be used instead of alkaline, powdered, and abrasive cleaning agents or lipid solvents [71,72].

Safety showers and eyewash fountains should be readily accessible to employees working in or near areas where splashes of glycidyl ethers are possible, and this equipment should be properly maintained. Handwashing facilities, with neutral or acid soap or an alternative cleanser, must be available to the employees, who shall be instructed to wash their hands before eating or using toilet facilities. The preparation, dispensing, consumption, or storage of food or beverages in exposure areas should be prohibited.

The effects of glycidyl ethers on workers are intensified by the penetration of the ethers into clothing and shoes, which act as reservoirs and prolong the contact [23]. For this reason, clothing contaminated with any of the ethers must be removed as soon as possible and stored in a closed container until it is either laundered or discarded. The employer should inform the persons laundering or otherwise handling the contaminated clothing of the hazardous properties of glycidyl ethers. Shoes or other leather apparel on which glycidyl ethers have been spilled should be made unfit for use and discarded [17(p 5)].

To protect workers' eyes, the employer should provide chemical safety goggles (splashproof) meeting the requirements of 29 CFR 1910.133 and ANSI Z87.1-1968 and should ensure that they are worn whenever there is a

reasonable probability that glycidyl ethers could be splashed into the eyes. Workers should be cautioned to avoid rubbing their eyes with hands that may be contaminated with glycidyl ethers. If eye contact occurs, the eyelid should be lifted, the eye should be flushed with copious amounts of water, and the worker should be referred to a physician.

When concentrations of airborne glycidyl ethers cannot be kept at or below prescribed limits by engineering controls, eg, because of spills or equipment failure or during maintenance or entry into confined spaces, special respiratory protection is required. Employers should establish and enforce a respiratory protective program meeting the requirements of 29 CFR 1910.134 and should provide proper respiratory devices as outlined in Tables I-1, I-2, I-3, and I-4.

Because the glycidyl ethers vary in their physical properties and toxic effects, no single respirator selection guide can be devised that would be applicable to all compounds. Instead, the selection of a respirator that will provide adequate protection at a given concentration of airborne glycidyl ethers must be performed on a compound-by-compound basis for each glycidyl ether. Respirator guidelines have been developed for five of the glycidyl ethers, and these are presented in Tables I-1, I-2, I-3, and I-4. These guidelines should not be followed in choosing respirators for use with other glycidyl ethers unless additional information indicates that there are very close similarities in their physical properties and toxic effects.

However, available information on the glycidyl ethers as a class permits certain general recommendations. Quarter-mask and half-mask respirators should not be used with any glycidyl ether because all of the

compounds are potentially irritating to the eyes. Full-body protective clothing should also be provided in any situation that requires the use of a respirator because of the hazard of skin absorption and skin irritation and sensitization.

Protective clothing and equipment, including respirators, should be kept clean and maintained in good condition. This equipment should be cleaned and inspected by trained personnel after each use and should be replaced when necessary. The employer must ensure that all equipment is in working order and that it is stored properly when not in use.

If evacuation of the process or work area might be required in an emergency, a program permitting rapid egress from the area should be designed, and the employer should ensure that it is implemented. All potentially exposed employees must be aware of escape procedures, of the location of and proper use of respirators designated for emergency situations, and of firefighting methods. Instructions should be given for transporting injured employees to areas where emergency medical care can be given.

There is considerable variation in the fire and explosion hazards associated with the use, handling, and storage of various glycidyl ethers. IGE is classified, under the provisions of 29 CFR 1910.106, as a Class IC flammable liquid, which is a liquid with a flashpoint at or above 73 F (22.8 C) and below 100 F (37.8 C). AGE and BGE are Class II combustible liquids, and PGE is a Class III A combustible liquid. A Class II combustible liquid has a flashpoint at or above 100 F (37.8 C) and below 140 F (60 C), and a Class III A liquid has a flashpoint at or above 140 F (60 C) and below 200 F (93.3 C) (29 CFR 1910.106). Whenever a combustible

liquid is heated to within 30 F (16.7 C) of its flashpoint, the compound should be handled as if it belonged to the next lower class (29 CFR 1910.106). No data were found on the other glycidyl ethers covered in this document that would permit their classification as either flammable or combustible.

The vapor of IGE can easily form explosive mixtures in air; consequently, all sources of ignition must be controlled where IGE is used, handled, or stored. Furthermore, because this glycidyl ether is heavier than air, distant ignition sources can present problems [85]. Although the fire and explosion hazards associated with the use of AGE, BGE, and PGE are not as severe, it is necessary to ensure that flames or other sources of ignition, such as smoking, are not permitted in areas where these glycidyl ethers are used, stored, or handled. Should a fire involving glycidyl ethers occur, a medium such as water, carbon dioxide, or dry chemicals should be used to extinguish it [3]. Fire extinguishers should be readily accessible to all employees exposed to glycidyl ethers and should be maintained in good condition.

The storage of bulk amounts of glycidyl ethers must meet the requirements for their classification (flammable or combustible as specified in 29 CFR 1910.106(f). There is evidence that PGE and BGE will undergo violent polymerization when subjected to high temperatures, whether alone or in the presence of catalysts or strong oxidizing agents such as acids, bases, and salts [17(pp 62,69)]. IGE will react in a similar fashion [85]. No data concerning violent polymerization by other glycidyl ethers have been found; nonetheless, since all glycidyl ethers have structural similarities, it seems reasonable to assume that at least some

of the rest of the glycidyl ethers might also polymerize violently under similar circumstances. Consequently, glycidyl ethers should be stored in a cool place where they will not be subjected to extreme temperatures, and they should not be stored near acids, bases, and salts.

Special precautions are necessary for entering confined spaces, such as tanks or reaction vessels and enclosed application sites, that may contain glycidyl ethers, for performing flame- or spark-generating operations such as welding and cutting, and for transferring glycidyl ethers. Before any employee enters a vessel, all pipelines leading into or out of the vessel must be blanked to prevent the entry of liquid or vapors. The vessel interior should be rinsed with water and then purged with air or with nitrogen followed by air. After the purging, and during all operations in the vessel, its atmosphere should be tested with an oxygen meter, a combustible gas meter, and other approved instruments. No employee should enter any tank or vessel that does not have an entrance large enough to admit the employee equipped with safety harness, lifeline, and appropriate respiratory equipment. The employee must be able to leave the tank or vessel by the same opening. Employees entering contaminated tanks or vessels should wear full-body protective clothing until inspection and testing assure safety for personnel in the tank. When employees are working in confined spaces, another employee should be stationed at the entrance to keep them under constant observation, and one or more additional employees shall be readily available in case of an emergency. A positive pressure respiratory protective device with safety harness and lifeline should be located outside the tank or vessel for emergency use. The use of portable lights to illuminate the interior of tanks, vessels, or

reactors when they are undergoing cleaning or repairs should be prohibited. Such interiors should be illuminated by reflected light or explosion-proof light sources. Only nonferrous (sparkproof) tools should be used for scraping away clinging residues or accumulated deposits, and rags and other materials used to wipe and absorb ethers should be placed in standard safety containers for subsequent disposal. Cutting or welding must be performed only after an authorized representative of the employer has signed a permit indicating that all actions prescribed in pertinent sections of 29 CFR 1910.252 have been taken.

Whenever flammable or combustible liquids are transferred from one container to another, both containers must be effectively bonded and grounded to prevent the buildup and discharge of static electricity.

The employer should assume responsibility for providing proper initial training and periodic retraining of employees on correct operating procedures and use of protective equipment. If all recommended work practices are observed, good engineering controls as discussed in Chapter IV are installed, and adequate educational programs are conducted, employees working with glycidyl ethers can be adequately protected from the hazards associated with them.

# VI. DEVELOPMENT OF STANDARD

## Basis for Previous Standards

In 1961, the American Conference of Governmental Industrial Hygienists (ACGIH) published tentative threshold limit values (TLV's) for a number of glycidyl ethers. The tentative TLV's were: AGE, 45 mg/cu m; BGE, 270 mg/cu m; DGE, 55 mg/cu m; IGE, 240 mg/cu m; and PGE, 310 mg/cu m [86]. The ACGIH adopted these TLV's in 1962 [87].

In 1963, the ACGIH [88] recognized that TLV's expressed as 8-hour time-weighted average (TWA) concentrations did not provide a safety margin for certain fast-acting substances comparable with that provided by a TWA limit for slow-acting substances. A "C" or "ceiling" designation was therefore affixed to AGE and DGE, indicating that the limit should not be exceeded under any circumstances. The TLV for DGE was lowered to 2.8 mg/cu m at the same time. According to the 1966 Documentation of Threshold Limit Values [89], the earlier limits had been based on a single study by Hine et al [23] and a determination of the LD50 for PGE by Smyth et al [34]; no other data were available. The former report [23] described extensive animal studies but contained limited human data. The change in the limit for DGE was based on a 1962 written communication to the ACGIH from NG White, who had concluded on the basis of industrial experience that the TLV was too high. The documentation indicated that animal studies suggested that 2.8 mg/cu m would be a no-effect level.

In 1968, the TLV for PGE was lowered from 310 mg/cu m to 60 mg/cu m [90]. In 1970, an intent to change the limit for AGE from 45 to 22 mg/cu m

and to drop the ceiling designation was published [91].

The TLV's and accompanying notations for BGE, DGE, and IGE remained unchanged through 1971, and the 1971 Documentation of Threshold Limit Values for Substances in Workroom Air [92] used the previously cited study by Smyth et al [34] as the basis for the change in the limit for PGE and the study by Hine et al [23] as the basis for the proposed change for AGE. The earlier limits were not considered sufficiently low to protect against irritation or against systemic effects such as sensitization [92].

In 1972, the limit for AGE remained a ceiling concentration of 45 mg/cu m [93]. In 1973, the ACGIH adopted the proposed TLV for AGE of 22 mg/cu m without a ceiling designation [94], and in 1974 AGE was given a "skin" designation to indicate that skin contact should be prevented if possible and that contact with the skin should be considered in the evaluation of exposure [95]. ACGIH TLV's for BGE, DGE, IGE, and PGE have remained unchanged since 1968. However, tentative short-term exposure limits (STEL's) of 360 mg/cu m for IGE and 90 mg/cu m for PGE were proposed by ACGIH in 1976 [96]; these limits were for periods of up to 15 minutes, separated by at least 1 hour and not to exceed four such exposures in an 8-hour day. Changes in ACGIH TLV's for the glycidyl ethers are summarized in Table VI-1 [86,88,90,94,95].

According to the 1976 joint report of the International Labour Office (ILO) and the World Health Organization (WHO) [97], nine other contries have set limits to regulate exposure to the glycidyl ethers. These maximum allowable concentrations (MAC's) are presented in Table VI-1.

TABLE VI-1

PERMISSIBLE ENVIRONMENTAL LIMITS FOR GLYCIDYL ETHERS (MG/CU M)

| Standard | | AGE | BGE | DGE | IGE | PGE |
|---|---|---|---|---|---|---|
| ACGIH TLV's | | | | | | |
| 1962 | | 45 | 270 | 55 | 240 | 310 |
| 1963 | | 45 C* | " | 2.8 | " | " |
| 1968 | | " | " | " | " | 60 |
| 1973 | | 22 | " | " | " | " |
| 1974 | | 22 S* | " | " | " | " |
| Current US Federal Standard | | 45 C* | 270 | 2.8 | 240 | 60 |
| Foreign MAC's** | | | | | | |
| Australia | | 22 C* | 270 | 2.8 | 240 | 60 |
| Belgium | | 22 H* | " | " | " | " |
| Federal Republic of Germany | | 45 SP* | - | 2.8 | " | 310 SP* |
| Finland | | 22 H* | 270 | 2.8 C* | " | 60 |
| Netherlands | | " | " | " | " | " |
| Rumania | Average: | 100 | 100 | - | 50 | 75 |
| | Maximum: | 200 | 200 | 2.0 | 100 | 100 |
| Sweden | | - | - | 2.8 C* | - | - |
| Switzerland | | 22 H* | 270 | " | 240 | 60 SP* |
| Yugoslavia | | 45 | " | 2.8 | " | 60 |

*C = ceiling limit never to be exceeded; S = skin contact should be prevented if possible and should be considered in evaluating exposure; H = skin irritant; SP = sensitization potential
**Maximum Allowable Concentrations

Adapted from references 86,88,90,94,95,97

Present Federal standards (29 CFR 1910.1000(a)), expressed as 8-hour TWA concentrations for the workplace environment, are BGE, 270 mg/cu m; IGE, 240 mg/cu m; and PGE, 60 mg/cu m. The present Federal standards for AGE and DGE, designated as ceilings, are 45 mg/cu m and 2.8 mg/cu m, respectively. These limits are based on the TLV's for workplace exposure adopted by the ACGIH in 1968.

Basis for the Recommended Standard

Adverse effects reported in humans occupationally exposed to glycidyl ethers have been limited to irritation of the skin and mucous membranes and sensitization, and systemic effects in animals have generally been reported only at relatively high concentrations or doses. However, the glycidyl ethers are biologically reactive compounds because of the presence of the epoxide group. They have been shown to have cytotoxic effects and to be mutagenic in bacteria and other test systems. At least one, DGE, should be regarded as a potential occupational carcinogen on the basis of animal tests. Because there is evidence that some glycidyl ethers have the potential to produce tumorigenic, mutagenic, or reproductive effects, and because few have been adequately tested for such effects, occupational exposure to glycidyl ethers is defined in this document as work in any area where these substances are manufactured, stored, used, or handled. All employees working in such areas should receive adequate medical surveillance and their environmental exposures should be evaluated. Appropriate engineering controls, monitoring and recordkeeping, sanitation procedures, work practices, protective clothing and equipment, and training

programs should be used to keep worker exposure to the glycidyl ethers as low as is technically feasible.

(a) Permissible Exposure Limits

Data currently available make it possible to set environmental limits for only five of the glycidyl ethers. The primary effect of these compounds at relatively low concentrations is irritation of the skin, eyes, and respiratory system. To minimize irritative effects by preventing exposures at high concentrations of airborne glycidyl ethers, NIOSH recommends environmental limits as ceiling concentrations based on a 15-minute sampling period.

Although no data have been found on possible additive effects, employers should consider the possibility of such effects when employees are simultaneously exposed to more than one glycidyl ether. The following formula can be used to calculate the appropriate environmental limit when such additive effects may occur:

$$CPEL_n \leqq \left\{ 1 - \left( \frac{C_1}{PEL_1} + \ldots + \frac{C_{n-1}}{PEL_{n-1}} \right) \right\} PEL_n$$

$CPEL_n$ = conditional permissible exposure limit for the nth compound
$C_1$ to $C_{n-1}$ = measured concentrations of compounds 1 to n-1
$PEL_1$ to $PEL_n$ = permissible exposure limits for compounds 1 to n

(1) Allyl Glycidyl Ether (AGE)

Eye irritation has been noted by one worker and by experimenters exposed at unknown concentrations to AGE vapor [23]. Corneal opacity has been observed in rats exposed to AGE at vapor concentrations as low as 400 ppm (1,870 mg/cu m) for 7 hours/day, 5 days/week, for 10 weeks. This exposure also produced emphysema, bronchiectasis, and

bronchopneumonia. Inflammation and congestion have been observed in various organ systems of rats after inhalation of AGE [23,48]. Inhalation exposure of rats at concentrations of 260 ppm (1,210 mg/cu m) for 7 hours/day, 5 days/week, for 10 weeks caused decreased weight gain, slight irritation of the eyes, and mild respiratory distress for the duration of exposure [23]. AGE has shown mutagenic activity in bacteria [57], but mutagenicity has not been confirmed in other tests.

The limited data available suggest that the current Federal standard provides an adequate safety margin to prevent systemic effects from inhalation of AGE. NIOSH therefore recommends that worker exposure to airborne AGE be limited to 45 mg/cu m (9.6 ppm), measured as a 15-minute ceiling concentration.

(2) Isopropyl Glycidyl Ether (IGE)

No effects have been demonstrated in workers exposed to IGE [23]. Inhalation exposure to IGE at a concentration of 400 ppm (1,900 mg/cu m), 7 hours/day, 5 days/week, for 10 weeks caused only slight eye irritation, respiratory distress, and decreased weight gain in rats [23].

Because only slight irritation was produced in these animals and because there are no reports of human effects, NIOSH recommends that the present Federal standard for IGE of 240 mg/cu m (50 ppm) be retained, but that it be changed from a TWA value to a ceiling concentration for a 15-minute sampling period to provide adequate protection against irritative effects.

(3) Phenyl Glycidyl Ether (PGE)

No reports were found of adverse effects in humans from exposure to airborne PGE. Respiratory tract irritation [23] and skin

irritation [39] have been reported in rats exposed repeatedly to airborne PGE at concentrations of 5-12 ppm (30-72 mg/cu m). Exposure to PGE at 12 and 5 ppm caused skin damage and loss of hair in rats, but no effects were observed at 1 ppm (6 mg/cu m) [39]. The only effects reported in rats exposed to PGE at about 10 ppm (60 mg/cu m) 5 days/week for 10 weeks were respiratory tract inflammation and early stages of necrosis in the liver [23]. The weight gain and tissues of these animals did not differ from those of controls. PGE has shown mutagenic activity in bacteria, but it produced no dominant lethal or teratogenic effects in mice exposed at 11.5 ppm (71 mg/cu m) for 12-19 days [49]. Inconclusive evidence of testicular degeneration was reported in some rats exposed to PGE at 1.75-11.20 ppm (11-71 mg/cu m) [49].

Because irritation has been observed in animals after exposure at concentrations as low as 5 ppm (30 mg/cu m), and in order to provide an adequate safety margin, NIOSH recommends that the environmental limit for PGE be set at 5 mg/cu m (1 ppm), designated as a ceiling concentration for a 15-minute sampling period.

(4) n-Butyl Glycidyl Ether (BGE)

No reports were found of adverse effects in humans from exposure to airborne BGE. In LC50 studies with BGE, some exposed rats developed focal inflammatory cells with moderate congestion in the liver and hyperemia of the adrenal glands at unspecified vapor concentrations [23]. The only other study found that investigated systemic effects of BGE reported minimal toxic effects and a slight increase in leukocyte counts in rats given three im injections of 400 mg/kg [48].

BGE was mutagenic in microbial and mammalian test systems [57,58]. It produced a significant increase in the number of fetal deaths in the dominant lethal test when applied to the skin of male mice in doses of 1.5 g/kg during an 8-week period [58].

No studies have investigated the effects of long-term inhalation of BGE at low concentrations in humans or animals; thus, calculation of a safe exposure concentration is not possible. However, BGE has been implicated as a mammalian mutagen, and it has caused skin and eye irritation and sensitization. NIOSH therefore recommends that the limit for worker exposure to BGE be set at the lower limit of detectability permitted by the NIOSH-recommended sampling and analytical method, 30 mg/cu m (4.4 ppm), as a ceiling concentration for a 15-minute sampling period.

(5) Di(2,3-epoxypropyl) Ether (DGE)

DGE is not widely used in industry, and no reports of effects on humans have been found. When tested in animals, it was the most irritating and the most toxic of the glycidyl ethers [23]. DGE has produced a 40% incidence of skin papillomas in those mice that survived a dose of 0.75 millimole [51]. It has also shown mutagenic activity in bacteria [57]. Corneal opacity has been reported in rabbits exposed to airborne DGE at concentrations of 20-27 ppm (106-144 mg/cu m) [47]. In single 24-hour exposures, DGE at 24 ppm (128 mg/cu m) killed three rabbits and produced changes in the lungs, liver, kidneys, and testes [41]. A similar exposure at 6 ppm (32 mg/cu m) produced basophilia in rabbits, but no effects were observed in those exposed at 3 ppm (16 mg/cu m).

Exposure to DGE at 3 ppm (16 mg/cu m) for 4 hours/day, 5 days/week, for 19 exposures during 29 days killed 5 of 30 rats and caused

bronchopneumonia, inflammation of the larynx, peribronchiolitis, and necrosis of pancreas, spleen, and testicular tubules [41]. Rats exposed at this concentration also showed significant decreases, compared with controls, in weight gain, organ weight/body weight ratio of thymus and spleen, leukocyte count, percentage of polymorphonuclear cells, and bone marrow nucleated cells, and a significant increase in the ratio of myeloid to erythroid cells. Rats exposed to DGE at 0.3 ppm (1.6 mg/cu m) had no significant changes in weight gain, bone marrow, or blood; however, "poorly defined" degeneration of the testes was reported in 5 of 10 rats killed after 60 exposures [41].

Because DGE has shown tumorigenic activity in mice and produced mutations in bacteria, it should be regarded as a potential occupational carcinogen. Exposure to DGE at 3 ppm (16 mg/cu m) has produced irritative and systemic effects in rats, including evidence of cytotoxicity, and testicular changes have been reported in rats exposed at concentrations as low as 0.3 ppm (1.6 mg/cu m). NIOSH therefore believes that the current Federal standard of 2.8 mg/cu m does not provide adequate protection and recommends that exposure to airborne DGE not exceed 1.0 mg/cu m (0.2 ppm) as a ceiling concentration determined in a 15-minute sampling period.

(6) Other Glycidyl Ethers

Limited data are available on several other glycidyl ethers. All glycidyl ethers that have been tested have been mutagenic in bacteria [49,57,58], and CGE and neopentyl glycol diglycidyl ether have also induced unscheduled DNA synthesis in human white blood cells [58]. Triethylene glycol diglycidyl ether, which is not currently used or manufactured in the United States, has produced lung tumors in mice receiving ip doses in

excess of 3.6 g/kg [52]. Resorcinol diglycidyl ether [51] and diphenylol propane diglycidyl ether [37] each produced a single skin papilloma in tests on mice. Only hydroquinone diglycidyl ether has given clearly negative results in a test of its tumorigenicity [51]. In addition, all glycidyl ethers that have been tested, including alkyl glycidyl ethers, diphenylol propane diglycidyl ether, neopentyl glycol diglycidyl ether, and butanediol diglycidyl ether, have produced sensitization [28,32,44].

The complete absence of inhalation toxicity data on these compounds makes it impossible to set limits for environmental concentrations. The vapor pressures of some of the compounds, such as diphenylol propane diglycidyl ether and resorcinol diglycidyl ether, are extremely low at ambient temperatures, so that the risk to workers from inhalation of these compounds is probably negligible. Other glycidyl ethers in this document may have appreciable vapor pressures at ambient or higher temperatures, but no data are currently available on which limits can be based.

Because the epoxide moiety is highly strained, all the glycidyl ethers are chemically reactive. In biologic reactions, the epoxide ring may cleave to form a carbonium ion, which can react with nucleophilic centers such as protein, RNA, and DNA [6]. For the diglycidyl ethers, this reaction may result in crosslinking of nucleophilic centers, which may be responsible for the high biologic activity of DGE. These considerations and the similar effects of the glycidyl ethers in producing sensitization and bacterial mutations suggest that the glycidyl ethers have the potential to produce harmful effects under occupational exposure conditions. Therefore, glycidyl ethers for which limits have not been recommended should be treated with the same caution required for the manufacture,

handling, and storage of those for which there are environmental limits.

(b) Sampling and Analysis

Little information on methods other than those recommended by NIOSH for the sampling and analysis of glycidyl ethers has been found in the literature.

To monitor the concentration of glycidyl ethers in the employee's breathing zone, one must periodically take air samples. NIOSH recommends sampling by drawing a known volume of air, which will vary according to the ether being sampled, through a tube containing charcoal or, for AGE, resin, to adsorb any organic vapors that are present. The organic material should then be desorbed with carbon disulfide (for BGE, IGE, or PGE), diethyl ether (for AGE), or methylene chloride (for DGE), and an aliquot of this extract should be analyzed by gas chromatography. Because the other glycidyl ethers are structurally similar to AGE, BGE, and IGE, the method should be adequate for them as well if certain factors, such as solvents, adsorbents, and gas chromatographic conditions, are appropriately adjusted. The NIOSH-recommended method for these three compounds is presented in Appendix I, and the proposed NIOSH method for the sampling and analysis of AGE is presented in Appendix II. A similar method for DGE is described in Appendix III. These methods have not been validated for detecting these glycidyl ethers at the recommended ceiling concentrations. However, it is probable that their sensitivities can be increased by increasing the sampling rate, as is proposed in Appendix I. The method recommended for DGE was not validated by NIOSH because the recovery of DGE was unacceptably low [79]. Preliminary data indicated that desorption efficiency may be a function of the temperature and length of storage. It is reasonable to

assume that, when the roles of these variables have been determined so that a standard procedure of maximal efficiency and reliability can be established, this method will be useful for determinations of DGE at the recommended ceiling concentration.

(c) Medical Surveillance and Recordkeeping

Glycidyl ethers are primary skin and eye irritants and may sensitize the skin [23-26,30]; NIOSH recommends, therefore, that preplacement and periodic medical examinations, with special attention to the skin and eyes, be made available to all employees occupationally exposed to glycidyl ethers. Although some glycidyl ethers had effects on the hemopoietic system [23,41,48], these have been observed only at high exposure concentrations or doses. Blood changes in workers would therefore be expected to appear only at exposure concentrations much higher than those that would produce irritation or sensitization of the skin. Because important toxic effects of the glycidyl ethers on the lungs, CNS, and kidneys have been found in animals, examination of the functions of these systems is suggested as a part of the general medical examination.

During the medical examination, workers in places of employment where DGE or BGE is used should be warned that DGE was tumorigenic in mice and that BGE was mutagenic in tests on mice [49,50,52,57,58].

Pertinent medical and other records should be maintained for all employees occupationally exposed to glycidyl ethers. These records should be kept for at least 30 years after termination of employment.

(d) Personal Protective Equipment and Clothing

Because of the irritating and sensitizing potentials of glycidyl ethers, personal protective equipment and impervious clothing should be

worn to prevent skin and eye contact with the compounds or their vapors or mists. Gloves, boots, aprons, faceshields (8-inch minimum), and goggles or safety glasses with side shields are recommended. Tests performed at the Argonne National Laboratories in 1964 showed that protective gloves made from natural rubber (latex), neoprene natural rubber (latex), milled neoprene, neoprene with nylon, milled Buna-1, vinyl and polyethylene (disposable), and polyvinyl chloride would not protect the skin dependably from contact by AGE and PGE [84]. Only milled butyl rubber and polyvinyl alcohol proved to be adequate. Gloves made of polyvinyl chloride or polyethylene-coated fabric may be used for a single workshift exposure. The employer should ensure that the gloves and protective clothing worn by the employees are impervious to glycidyl ethers and that they are maintained in good condition and replaced as necessary. An alternative and less desirable tactic is to issue new gloves each day.

The use of protective hand creams is suggested as a supplement to gloves where manual dexterity requirements limit the types of gloves that can be worn. Because absorption of and sensitization by glycidyl ethers occurs more readily through irritated and cracked skin, lipid solvents should not be used for cleaning the skin [28,45,71]. When leather clothing or equipment, such as belts or shoes, becomes obviously contaminated with a glycidyl ether, it should be made unfit for use and discarded [17(p 5)].

The employer should institute a respiratory protection program in accordance with 29 CFR 1910.134, and respirator types approved under provisions of 30 CFR 11 for the concentrations specified should be provided. Approved respiratory protective equipment, as shown in Tables I-1, I-2, I-3, and I-4, should be used during nonroutine maintenance,

emergencies, or installation of equipment, and at any other time when employees are potentially exposed to glycidyl ethers at concentrations above the recommended ceiling concentrations. Because of the potential of these compounds for irritating and sensitizing the skin and eyes, full-body protective clothing should be worn in any situation in which a respirator is required. Workers should be properly trained in the use and care of all respirators assigned to them.

(e) Informing Employees of Hazards

The employer should initiate a continuing education program to ensure that employees have current knowledge of job hazards and of proper work practices and emergency procedures. Employees should also be informed before job placement that irritation and sensitization may result from exposure to glycidyl ethers and that DGE has caused skin tumors in mice and BGE has been found to be a mammalian mutagen.

(f) Work Practices

Glycidyl ethers are primary irritants and sensitizers, and several of them have been mutagenic or tumorigenic. Safe handling of these compounds depends, therefore, upon work practices and engineering controls that are designed to prevent or minimize inhalation of and skin and eye contact with them.

Many glycidyl ethers are combustible or flammable liquids, which can present a fire hazard. Many of them may polymerize violently after slight heating, so that precautions should also be taken to prevent fires and explosions. In the event of a fire, media such as water, carbon dioxide, or dry chemicals should be used to extinguish it [3]. Workers must also be protected from the possible hazards of inhaling or ingesting or becoming

contaminated with glycidyl ethers during fires or other emergencies.

To reduce the fire and explosion hazards, smoking and the carrying of open flames or ignition sources should be prohibited in the work area. Electrical wiring should comply with appropriate sections of the National Electrical Code as adopted by OSHA in 29 CFR 1910.309. The tools used to open containers should be of nonsparking materials, and the containers should be bonded and electrically grounded before glycidyl ethers are transferred.

To minimize inhalation of the chemicals, processes should be enclosed whenever possible. When this is not feasible, ventilation systems, such as specifically placed hoods, can be used. Epoxy-based adhesives containing glycidyl ethers should be used only with adequate ventilation.

To prevent the ingestion of glycidyl ethers, food and beverages should not be prepared, dispensed, consumed, or stored in work areas. Employees should be advised to wash their hands before eating or using toilet facilities. Employees should also be cautioned not to touch or rub their eyes with hands that may be contaminated with glycidyl ethers. These general practices, which are discussed in more detail in Chapter V, apply uniformly to the handling, storage, manufacture, and use of all glycidyl ethers.

(g) Monitoring and Recordkeeping Requirements

Workers are not considered to be overexposed to glycidyl ethers if industrial hygiene surveys show that the concentration of airborne glycidyl ethers in the employees' breathing zones are below the recommended ceiling concentrations. However, employee exposures to those glycidyl ethers for which no environmental limits have been recommended should also be

evaluated, and appropriate records of these exposures should be maintained.

Surveys to determine employee exposure should be repeated at least semiannually and within 30 days of any process change likely to result in increases in concentrations of airborne glycidyl ethers. For each ceiling determination, a sufficient number of samples should be taken and analyzed to characterize each employee's exposure during each workshift. Variations in work or production schedules and in employment location and job function should be considered in choosing sampling times, locations, and frequency.

If it is determined that an employee's exposure to a glycidyl ether exceeds the recommended ceiling concentration, control measures should be initiated, the employee should be notified of the exposure and of the control measures being implemented to correct the situation, and the exposure of that employee should be monitored at least once every 30 days. Such monitoring should continue until two consecutive determinations, at least 1 week apart, indicate that exposure no longer exceeds the recommended ceiling concentration. When no ceiling concentration has been recommended, the discovery of any free glycidyl ethers in the workplace should lead to an analysis of engineering controls, work practices, and sanitation procedures to determine that they are operating as effectively as possible, or that those practices and procedures in use are the most efficient ones for preventing access of the glycidyl ethers to the employee.

Records of environmental monitoring, including the basis for the determination that an employee's exposure is below the recommended ceiling concentration, and medical records should be kept for 30 years after termination of employment. The Toxic Substances Control Act of 1976

requires that "Records of...adverse reactions to the health of employees shall be retained for thirty years from the date such reactions were first reported to or known by the person maintaining such records." Because medical examinations will often provide the first recognized evidence of an adverse reaction, whether at the time of the examination or retrospectively, requiring medical records on glycidyl ether workers to be maintained for 30 years seems to be consonant with the Toxic Substances Control Act. Records of environmental exposures should be kept for the same period, to allow correlation of glycidyl ether workers' exposures with changes in their health status.

# VII. RESEARCH NEEDS

By current standards for appraising toxicologic and health hazards, the relevant information available on glycidyl ethers is limited. Dose-response information is especially scarce. No information on the possible carcinogenic and mutagenic hazards of these compounds in humans was found. This scarcity of reported effects is remarkable in light of the widespread use of glycidyl ethers. The number of persons exposed has gone from very few in the 1930's to more than 1,000,000 each year in the 1970's. Many glycidyl ethers are primary irritants, cause allergic reactions, and have the potential to cause cross-sensitization; however, the lack of reports of serious adverse effects in workers exposed to these compounds is encouraging.

The existing data, which come primarily from animal experiments, indicate that some glycidyl ethers are relatively toxic [23,25,27,41,48] and are potentially cytotoxic or mutagenic [6,56,58]. Only a few of the ethers have been assessed for toxicity, even though others, such as CGE, are used in industry. BGE has been shown to be mutagenic [58], and DGE and triethylene glycol diglycidyl ether, at high doses, were tumorigenic and carcinogenic, respectively [51,52]. Further studies of the toxicity of glycidyl ethers should therefore include examination of the carcinogenic, mutagenic, and teratogenic potential of each glycidyl ether that is widely used in industry. Information is especially needed on the effects of these compounds at low doses or concentrations. The similarity in structure of these compounds and the fact that they are potential alkylating agents give

reason for concern about their potential mutagenic and carcinogenic properties.

No epidemiologic studies of workers exposed to glycidyl ethers have been found. There are no existing data on human inhalation exposure to glycidyl ethers. Studies of effects on humans from inhalation exposure that include data on exposure durations and concentrations are needed. Epidemiologic studies that address the problems of sensitization and cross-sensitization, the effects of long-term exposure to the glycidyl ethers, and the influence of age, sex, and other factors on the toxicologic effects of these compounds are also needed. These studies should be designed to investigate eye, respiratory, and skin irritation, in addition to other toxic effects. Although the sensitization potential of some of the glycidyl ethers has been examined in humans [25,27], more research is needed that examines allergic reactions and possible cross-sensitization in glycidyl ether workers with occupational dermatitis.

Sampling and analytical methods have been validated for only four of the glycidyl ethers--BGE [75], IGE [77], AGE [78], and PGE [76]. These methods have not been validated at concentrations as low as the recommended environmental limits, so further refinement of the methods is necessary. No sampling and analytical method has been validated for measuring DGE at the low concentrations at which toxic effects have been reported. Study of the influences of temperature and duration of storage of DGE samples on desorption efficiency may permit the establishment of an improved analytic method for this compound. Other glycidyl ethers, such as resorcinol diglycidyl ether and CGE, are used in industry, and methods of sampling and analysis need to be developed for them. Research to develop continuous

monitoring techniques for the glycidyl ethers would be very desirable. Methods for biologic monitoring should also be developed to permit characterization of accumulated body burden.

Although it appears that there exist in humans two enzymes capable of metabolizing the glycidyl ethers [60,64], little is known about the fate of the ethers in the human body. More information about the metabolism of these compounds and on the toxicology of their metabolites is needed. Pharmacokinetic studies to characterize metabolic pathways would be valuable, especially in the interpretation of experimental data on cytotoxic and mutagenic effects and other aspects of systemic toxicity.

Research related to work practices is also needed. For example, materials impervious to glycidyl ethers and suitable for use in protective clothing, aprons, and gloves need to be identified. Further data on the toxic effects and physical and chemical properties of some of the ethers used in industry are needed, so that appropriate respirator selection guidelines can be developed for them.

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# IX. APPENDIX I

## SAMPLING AND ANALYTICAL METHOD FOR BGE, IGE, AND PGE

The following generalized sampling and analytical method for these glycidyl ethers is adapted from the NIOSH validated methods for these compounds [75,76,77]. If certain parameters are changed, such as solvents and gas-chromatograph operating conditions, it may also be suitable for other glycidyl ethers.

### Principle of the Method

A known volume of air is drawn through a charcoal tube to collect the organic vapors. The charcoal is then transferred to a small, stoppered sample container and desorbed with carbon disulfide. An aliquot of the desorbed sample is injected into a gas chromatograph. The area of the resulting peak is determined and compared with areas obtained from the injection of standards.

### Range and Sensitivity

This method was validated for each glycidyl ether at the limits presented in Table IX-1, but it is capable of measuring much smaller amounts if the desorption efficiency is adequate. Desorption efficiency must be determined over the range used.

TABLE IX-1

RANGE, PRECISION, AND ACCURACY OF THE GAS CHROMATOGRAPH ANALYSIS OF GLYCIDYL ETHERS

| Glycidyl Ether | Temperature (C) and Pressure (mmHg) | Validated Range (mg/cu m) | Probable Range (mg/cu m) | Coefficient of Variation | Standard Deviation* (mg/cu m) | Reference |
|---|---|---|---|---|---|---|
| BGE | 22 at 767 | 133-542 | 30-810 | 0.074 | 20 | 75 |
| IGE | 21 at 763 | 121-484 | 25-720 | 0.067 | 16 | 76 |
| PGE | 22 at 766 | 31-121 | 6-180 | 0.057 | 3.4 | 77 |

*At current OSHA limit

The upper limit of the range of the method is dependent on the adsorptive capacity of the charcoal tube. This capacity varies with the concentration of a particular glycidyl ether and of other substances in the air. Experimental data on breakthrough are listed in Table IX-2.

TABLE IX-2

BREAKTHROUGH DATA FOR CHARCOAL-TUBE SAMPLING OF GLYCIDYL ETHERS

| Glycidyl Ether | Amount in first section (mg) | Influent Test Atmosphere (mg/cu m) | Sampling Rate (liters/min) | Breakthrough Time (min) | Reference |
|---|---|---|---|---|---|
| BGE | 23 | 530 | 0.183 | 240* | 75 |
| IGE | 21 | 480 | 0.183 | 240* | 76 |
| PGE | 25 | 112 | 0.93 | 240* | 77 |

*No breakthrough in time given

Interferences

When the amount of water in the air is so great that condensation actually occurs in the charcoal tube, organic vapors will not be trapped efficiently. Preliminary experiments using toluene indicate that high humidity severely decreases breakthrough volume.

When two or more compounds are known or suspected to be present in the air, such information, including the suspected identities of the compounds, should be transmitted with the sample. It must be emphasized that any compound that has the same retention time as the glycidyl ether at the operating conditions described in this method is an interference. Retention-time data on a single column cannot be considered proof of chemical identity. If the possibility of interference exists, separation conditions (column packing, temperature, etc) must be changed to circumvent the problem.

## Precision and Accuracy

The Coefficients of Variation (CVT) for the analytical and sampling method are listed in Table IX-1. The standard deviation at the OSHA standard level is also included in the table. It should be noted, however, that CVT's and standard deviations at environmental limits recommended in this document are not currently available.

## Advantages and Disadvantages of the Method

The sampling method uses a small, portable sampling device that involves no liquids. Interferences are minimal, and most of those which do occur can be eliminated by altering chromatographic conditions. The tubes are analyzed by means of a quick instrumental method. The method can also be used for the simultaneous analysis of two or more substances suspected to be present in the same sample simply by changing gas-chromatographic conditions from isothermal to a temperature-programmed mode of operation.

One disadvantage of the sampling method is that the amount of sample that can be taken is limited by the number of milligrams that the tube will hold before overloading. When the sample value obtained from the backup section of the charcoal trap exceeds 25% of that found on the front section, the possibility of sample loss exists. The precision of the method is affected by the reproducibility of the pressure drop across the tubes. This drop will affect the flowrate and cause the volume to be imprecise, because the pump is usually calibrated for one tube only.

Apparatus

(a) An approved and calibrated personal sampling pump whose flow can be determined within ±5% at the recommended flowrate.

(b) Charcoal tubes: glass tube with both ends flame sealed, 7-cm long with a 6-mm outer diameter and a 4-mm inner diameter, containing two sections of 20/40 mesh activated charcoal separated by a 2-mm portion of urethane foam. The activated charcoal is prepared from coconut shells and is fired at 600 C prior to packing. The adsorbing section contains 100 mg of charcoal, the backup section 50 mg. A 3-mm portion of urethane foam is placed between the outlet end of the tube and the backup section. A plug of silylated glass wool is placed in front of the adsorbing section. The pressure drop across the tube must be less than 1 inch of mercury at a flowrate of 1 liter/minute.

(c) Gas chromatograph equipped with a flame ionization detector.

(d) Column (10-foot x 1/8-inch stainless steel) packed with 10% FFAP on 80/100 mesh, acid-washed DMCS Chromosorb W.

(e) An electronic integrator or some other suitable method for measuring.

(f) Microliter syringes: 10-$\mu$l, and other convenient sizes for making standards.

(g) Pipets: 0.5-ml delivery pipets or 1.0-ml type graduated in 0.1-ml increments.

(h) Volumetric flasks: 10-ml or convenient sizes for making standard solutions.

(i) Sample containers: 1-ml, with glass stoppers or Teflon-lined caps.

Reagents

(a) BGE, IGE, or PGE, reagent grade.

(b) Carbon disulfide, chromatographic quality.

(c) Nitrogen, purified.

(d) Hydrogen, prepurified.

(e) Filtered compressed air.

Sampling Procedure

(a) Calibration of Personal Pumps. Each personal pump must be calibrated with a representative charcoal tube in the line, as shown in Figure XIV-1. This will minimize errors associated with uncertainties in the sample volume collected.

(b) Collection and Shipping of Samples.

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

(2) 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 position 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 sample size and sampling rate for BGE, PGE, and IGE should be 15 liters sampled at 1 liter/minute. The sampling rates and sample sizes have been changed from those reported for BGE [75] and PGE [77] and the sample size for IGE [76]. This was done to adapt the methods

to sample for ceiling rather than for TWA concentrations. These changes should not affect the collection efficiency of the method and should provide an adequate amount of sample for analysis, but they have yet to be tested.

(6) The temperature and pressure of the atmosphere being sampled should be recorded. If 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 drawn through this tube. This tube should be labeled as a blank.

(9) Capped 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.

Analysis of Samples

All glassware used for the laboratory analysis should be washed with detergent and thoroughly rinsed with tap water and distilled water.

(a) Preparation of Samples. In preparation for analysis, remove the plastic cap used to close the tube after sample collection and remove and discard the glass wool. The charcoal in the first (larger) section is transferred to a 1-ml stoppered sample container. The separating sections

of foam are removed and discarded; the second section is transferred to another container. These two sections are then analyzed separately.

(b) Desorption of Samples. Prior to analysis of BGE, IGE, or PGE, 0.5 ml of carbon disulfide is pipetted into each sample container. (All work with carbon disulfide should be performed in a hood because of its high toxicity.) Desorption should be done for 30 minutes. Tests indicate that this is adequate if the sample is stirred occasionally during this period.

(c) Gas-chromatographic Conditions. The typical operating conditions for the gas chromatograph are listed in Table IX-3.

TABLE IX-3

TYPICAL GAS CHROMATOGRAPH CONDITIONS FOR GLYCIDYL ETHERS

| Glycidyl Ether | Column Packing | Gas Flow (ml/min) | | | Temperature (C) | | | Reference |
|---|---|---|---|---|---|---|---|---|
| | | Carrier Nitrogen (at 60 psig) | Hydrogen* (at 24 psig) | Air* (at 50 psig) | Injector | Manifold | Column | |
| BGE | 10% FFAP on 80/100 mesh, acid-washed DMCS Chromosorb W | 50 | 65 | 500 | 180 | 275 | 130 | 75 |
| IGE | " | " | " | " | 205 | 270 | 115 | 76 |
| PGE | " | " | " | " | 230 | 265 | 90 | 77 |

*Flow to detector

(d) Injection. The first step in the analysis is the injection of the sample into the gas chromatograph. To eliminate difficulties arising from blowback or distillation within the syringe needle, one should employ the solvent-flush injection technique. The 10-$\mu$l syringe is first flushed with solvent several times to wet the barrel and plunger. Draw 3 $\mu$l of solvent into the syringe to increase the accuracy and reproducibility of the injected sample volume. The needle is removed from the solvent, and the plunger is pulled back about 0.2 $\mu$l to separate the solvent flush from the sample with a pocket of air to be used as a marker. The needle is then immersed in the sample, and a 5-$\mu$l aliquot is withdrawn, taking into consideration the volume of the needle, since the sample in the needle will be completely injected. After the needle is removed from the sample and prior to injection, the plunger is pulled back 1.2 $\mu$l to minimize evaporation of the sample from the tip of the needle. Observe that the sample occupies 4.9-5.0 $\mu$l in the barrel of the syringe. Duplicate injections of each sample and standard should be made. No more than a 3% difference in area is to be expected.

(e) Area Measurement. The area of the sample peak is measured by an electronic integrator or some other suitable form of area measurement, and preliminary results are read from a standard curve prepared as discussed below.

Determination of Desorption Efficiency

(a) Importance of Determination. The desorption efficiency of a particular compound can vary from one laboratory to another and also from one batch of charcoal to another. Thus, it is necessary to determine at

least once the percentage of the specific compound that is removed in the desorption process, provided the same batch of charcoal is used.

(b) Procedure for Determination. Activated charcoal equivalent to the amount in the first section of the sampling tube (100 mg) is measured into a 2.5-inch, 4-mm inner diameter glass tube, flame-sealed at one end. This charcoal must be from the same batch as that used in obtaining the samples and can be obtained from unused charcoal tubes. The open end is capped with Parafilm. A known amount of the glycidyl ether is injected directly into the activated charcoal with a microliter syringe, and the tube is capped with more Parafilm. The amount injected is equivalent to that present in a 15-liter liter air sample for BGE, IGE, and PGE, respectively, at the selected level. Six tubes at each of three levels (0.5, 1, and 2 times the recommended standard) are prepared in this manner and allowed to stand at least overnight to assure complete adsorption of the glycidyl ether onto the charcoal. These tubes are referred to as the samples. A parallel blank tube is also prepared. The sample and blank tubes are desorbed and analyzed in exactly the same manner as the sampling tube described in Analysis of Samples. Two or three standards are prepared by injecting the same volume of compound into 0.5 ml of carbon disulfide with the same syringe used in the preparation of the samples. (All work with carbon disulfide should be performed in a hood because of its high toxicity.) These are analyzed with the samples. The desorption efficiency (DE) equals the average weight in mg recovered from the tube divided by the weight in mg added to the tube, or:

$$DE = \frac{\text{Average weight (mg) recovered}}{\text{Weight (mg) added}}$$

The desorption efficiency is dependent on the amount of glycidyl ether collected on the charcoal. The desorption efficiency is plotted against the weight of glycidyl ether found.

## Calibration and Standards

It is convenient to express concentrations of standards in terms of mg/0.5 ml of carbon disulfide, because samples are desorbed in this amount of carbon disulfide. The density of the glycidyl ether is used to convert mg into μl for easy measurement with a microliter syringe. A series of standards, varying in concentration over the range of interest, is prepared and analyzed under the same gas-chromatographic conditions and during the same time period as the unknown samples. Curves are established by plotting concentration in mg/0.5 ml vs peak area. Note: Since no internal standard is used in the method, standard solutions must be analyzed at the same time that the analysis of samples is done. This will minimize the effect of known day-to-day variations and variations during the same day in the gas-chromatographic detector response.

## Calculations

The weight in mg corresponding to each peak area is read from the standard curve. No volume corrections are needed, because the standard curve is based on mg/0.5 ml of carbon disulfide and the volume of sample injected is identical with the volume of the standards injected.
Corrections for the blank must be made for each sample:

$$\text{mg} = \text{mg sample} - \text{mg blank}$$

where:

mg sample = mg found in front section of sample tube

mg blank = mg found in front section of blank tube

A similar procedure is followed for the backup sections.

Add the weights found in the front and backup sections to get the total weight in the sample.

Read the desorption efficiency from the curve for the amount found in the front section. Divide the total weight by this desorption efficiency to obtain the corrected mg/sample.

$$\text{Corrected mg/sample} = \frac{\text{Total weight}}{\text{DE}}$$

Determine the volume (in liters) of air sampled at ambient conditions based on the appropriate information, such as flowrate in liters/minute multiplied by sampling time. If a pump using a rotameter for flowrate control was used for sample collection, a pressure and temperature correction must be made for the indicated flowrate when the pump was calibrated under substantially different conditions than those that exist during sampling. The expression for the correction is:

$$\text{Corrected volume} = f \times t\left(\sqrt{\frac{P1}{P2} \times \frac{T2}{T1}}\right)$$

where:

f = flowrate during sampling
t = sampling time
P1 = pressure during calibration of samplimg (mmHg)
P2 = pressure of air sampled (mmHg)
T1 = temperature during calibration of sampling pump (K)
T2 = temperature of air sampled (K)

The concentration of the glycidyl ether in the air sampled can be expressed in mg/cu m.

$$\text{mg/cu m} = \frac{\text{Corrected mg x 1,000 (liter/cu m)}}{\text{Air volume sampled (liters)}}$$

Another method of expressing concentration is ppm:

$$\text{ppm} = \text{mg/cu m} \times \frac{24.45}{MW} \times \frac{760}{P} \times \frac{T + 273}{298}$$

where:

P = pressure (mmHg) of air sampled
T = temperature (C) of air sampled
24.45 = molar volume (liters/mole) at 25 C and 760 mmHg
MW = molecular weight (g/mole) of the glycidyl ether
760 = standard pressure (mmHg)
298 = standard temperature (K)

# X. APPENDIX II

## SAMPLING AND ANALYTICAL METHOD FOR AGE

The following method for AGE is adapted from the draft report of the NIOSH validated method [78]. If certain parameters are changed, such as the solvent and the gas-chromatographic operating conditions, it may be suitable for other glycidyl ethers.

### Principle of the Method

A known volume of air is drawn through a Tenax-GC resin tube to trap the organic vapors present. The sampling tube consists of a front adsorbing section and a backup section. The resin in each tube is transferred to a vial and the AGE is desorbed with diethyl ether and analyzed by gas chromatography.

### Range and Sensitivity

This method was validated over the range of 19-87 mg/cu m at an atmospheric temperature of 17 C and atmospheric pressure of 752 mmHg using a 3-liter sample volume. This sample volume is based on two-thirds of the 5% breakthrough capacity determined at 90% relative humidity when sampling a test atmosphere at 2 times the OSHA standard (45 mg/cu m). This method is capable of measuring much smaller amounts if the desorption efficiency is adequate. Desorption efficiency must be determined over the range used.

The upper limit of the range of the method is dependent on the adsorptive capacity of the Tenax-GC resin tube. This capacity can vary with the concentrations of AGE and other substances in the air.

Interferences

When two or more compounds are known or suspected to be present in the air, such information, including the suspected identities of the compounds, should be transmitted with the sample. It must be emphasized that any compound that has the same retention time as AGE at the operating conditions described in this method is an interference. Retention-time data on a single column cannot be considered as proof of chemical identity. If the possibility of interference exists, separation conditions (column packing, temperature, etc) must be changed to circumvent the problem.

Precision and Accuracy

The Coefficient of Variation (CVT) for the total analytical and sampling method in the range of 19-87 mg/cu m was 0.058. This value corresponds to a 2.6 mg/cu m standard deviation at the OSHA standard level (45 mg/cu m).

On the average, the concentrations obtained at the OSHA standard level (22 mg/cu m) using the overall sampling and analytical method were 0.5% lower than the "true" concentrations in a limited number of laboratory experiments. Any difference between the "found" and "true" concentrations may not represent a bias in the sampling and analytical method but rather a random variation from the experimentally determined "true" concentration. Therefore, no recovery correction should be applied to the final result.

The data are based on validation experiments using the internal standard method.

Advantages and Disadvantages

The sampling device is small, portable, and involves no liquids. Interferences are minimal, and most of those which do occur can be eliminated by altering chromatographic conditions. The tubes are analyzed by means of a quick, instrumental method.

One disadvantage of the method is that the amount of sample that can be taken is limited by the number of mg that the tube will hold before overloading. When an atmosphere at 90% relative humidity containing 92 mg/cu m of AGE was sampled at 0.8 liter/minute, 5% breakthrough was observed after 15 minutes (capacity = 12 liters or 1.1 mg). The sample size recommended is less than the 5% breakthrough capacity at 90% relative humidity for a test atmosphere at 2 times the OSHA standard (90 mg/cu m) to minimize the probability of overloading the sampling tube.

The precision of the method is affected by the reproducibility of the pressure drop across the tubes. This drop will affect the flowrate and cause the volume to be imprecise, because the pump is usually calibrated for one tube only.

Apparatus

(a) A calibrated personal sampling pump whose flow can be determined within ±5% at the recommended flowrate.

(b) Resin tubes. Glass tube with both ends flame-sealed, 10-cm long with 8-mm outer diameter and 6-mm inner diameter, containing two sections of 35/60 mesh Tenax-GC resin. The adsorbing section contains 100 mg of resin, the backup section 50 mg. A small wad of silylated glass wool is placed between the front adsorbing section and the backup section; a plug of silylated glass wool is also placed in front of the adsorbing section and at the end of the backup section. Since the pressure drop across the tube must be less than 25 mmHg at a flowrate of 1 liter/minute, it is necessary to avoid overpacking with glass wool.

(c) Gas chromatograph equipped with a flame ionization detector.

(d) Column (20-foot x 1/8-inch stainless steel) packed with 10% FFAP stationary phase on 100/120 mesh Supelcoport.

(e) An electronic integrator or some other suitable means of measuring peak areas.

(f) Sample containers with Teflon-lined caps, 5-ml.

(g) Microliter syringes, 10-$\mu$l and 500-$\mu$l, and other convenient sizes for making standards and for taking sample aliquots for dilution.

(h) Pipets, 2-ml, delivery type.

(i) Volumetric flasks, 1-ml and 10-ml or convenient sizes for making standard solutions and dilution of samples.

Reagents

(a) Diethyl ether, anhydrous.

(b) AGE, 99%.

(c) Isoamyl alcohol or other suitable internal standard. The appropriate solution of the internal standard is prepared in ether.

(d) Hexane. This is used to prepare solutions of AGE for preparing the analytical samples for desorption efficiency determination.

(e) Nitrogen, purified.

(f) Hydrogen, prepurified.

(g) Air, filtered compressed.

Sampling Procedure

(a) Calibration of Personal Pumps. Each personal pump must be calibrated with a representative Tenax-GC resin tube in line, as shown in Figure XIV-1. This will minimize errors associated with uncertanties in the sample volume collected.

(b) Collection and Shipping of Samples.

(1) Immediately before sampling, break the two ends of the resin tube to provide an opening at least one-half the internal diameter of the tube (3 mm).

(2) The section containing 50 mg of resin is used as a backup and should be positioned nearest the sampling pump.

(3) The resin tube series should be placed in a vertical position during sampling to minimize channeling through the resin.

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

(5) A sample size of 3 liters is recommended. Sample at a flowrate of 0.2 liter/minute for 15 minutes. The flowrate should be known with an accuracy of at least ±5%.

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

(7) The resin tube should be labeled appropriately and capped with plastic caps. Under no circumstances should rubber caps be used.

(8) With each batch of 10 samples, one resin tube that has been handled in the same manner as the sample tubes (break, seal, and transport), except that no air is sampled through it, should be submitted. This tube should be labeled as a blank.

(9) Capped resin tubes should be packed tightly and padded before they are shipped to minimize breakage during shipping.

Analysis of Samples

All glassware used for the laboratory analysis should be washed with detergent and thoroughly rinsed with tap water and distilled water.

(a) Preparation of Samples. In preparation for analysis, remove the plastic caps used to cover tube after sample collection, and remove and discard the glass wool. The resin in the front 100-mg section is transferred to a 5-ml screw-capped sample container. The separating section of glass wool is removed and discarded. The second 50-mg section is transferred to another container. These two sections are analyzed separately.

(b) Desorption of Sample. Prior to analysis, 2.0 ml of ether is pipetted into each sample container. Samples should be desorbed for 30 minutes. Tests indicate that this is adequate if the sample is agitated

occasionally during this period. The sample vials should be capped as soon as the solvent is added to minimize volatilization. For the internal standard method, desorb using 2.0 ml of internal standard solution in ether.

(c) Gas-chromatographic Conditions. The typical operating conditions for the gas chromatograph are:

(1) Nitrogen carrier gas flow, 30 ml/minute (60 psig).

(2) Hydrogen gas flow to detector, 30 ml/minute (25 psig).

(3) Air flow to detector, 300 ml/minute (60 psig).

(4) Injector temperature, 200 C.

(5) Manifold temperature (detector), 280 C.

(6) Column temperature, 150 C.

A retention time of approximately 10.0 minutes is to be expected for the analyte using these conditions and the recommended column. The internal standard elutes between ether and the AGE.

(d) Injection of Samples. A 2-$\mu$l aliquot of the sample solution is injected into the gas chromatograph. The solvent-flush method or other suitable alternative, such as an automatic sample injector, can be used provided that duplicate injections of a solution agree well. No more than a 3% difference in area is to be expected.

(e) Measurement of Area. The area of the sample peak is measured by an electronic integrator or some other suitable form of area measurement, and preliminary results are read from a standard curve.

Determination of Desorption Efficiency

(a) Importance of Determination. The desorption efficiency of a particular compound can vary from one laboratory to another and also from

one batch of Tenax-GC to another. Thus, it is necessary to determine the percentage of the specific compound that is removed in the desorption process for the particular batch of resin used for sample collection and over the concentration range of interest. The desorption efficiency must be at least 75% at the OSHA standard level.

(b) Preparation for Determination. Desorption efficiency must be determined over the sample concentration range of interest. To determine the sample concentration range that should be tested, the samples are analyzed first. Then the analytical samples are prepared based on the relative amount of AGE found in the samples. The desorption efficiency must be determined at least twice for each concentration of AGE found in the samples.

The analytical samples are prepared as follows: Tenax-GC, equivalent to the amount in the front section (100 mg), is measured into a 5-ml screw-capped vial. This resin must be from the same batch as that used in obtaining the samples.

A known amount of a solution of AGE in hexane (spiking solution) is injected directly into the resin by means of a microliter syringe. Adjust the concentration of the spiking solution so that no more than a 10-$\mu$l aliquot is used to prepare the analytical samples.

For the validation studies conducted to determine the precision and accuracy of this method, six analytical samples at each of the three concentration levels (0.5, 1, and 2 times the OSHA standard of 45 mg/cu m) were prepared by adding an amount of AGE equivalent to that present in a 3-liter sample at the selected level. A stock solution containing 67.34 mg of AGE/ml of hexane was prepared. One-, 2-, and 4-$\mu$l aliquots of the

solution were added to Tenax-GC resin tubes to produce solutions of 0.5, 1, and 2 times the OSHA standard level. The analytical samples were allowed to stand at least overnight to assure complete adsorption of the analyte onto the resin. A parallel blank tube was treated in the same manner except that no sample was added to it.

The procedure described can be used to prepare the analytical samples that are analyzed to determine desorption efficiency over the concentration range of interest.

(c) Procedure for Determination. The analytical samples and the blank are desorbed and analyzed as described in Analysis of Samples. Calibration standards are prepared by adding the appropriate volume of spiking solution to 2.0 ml of ether with the same syringe used in the preparation of the samples. Standards should be prepared at the same time that the sample analysis is done and should be analyzed with the samples.

If the internal standard method is used, prepare calibration standards by using 2.0 ml of ether containing a known amount of the internal standard.

The desorption efficiency (DE) equals the average weight in $\mu g$ recovered from the tube divided by the weight in $\mu g$ added to the tube, or:

$$DE = \frac{\text{Average weight } (\mu g) \text{ recovered}}{\text{Weight } (\mu g) \text{ added}}$$

The desorption efficiency may be dependent on the amount of AGE collected on the resin. Plot the desorption efficiency against the weight of AGE found. This curve is used to correct for adsorption losses.

Calibration and Standards

(a) Add 2.0 ml of ether (or 2.0 ml of internal standard solution in ether) to a 5-ml vial. The same solution of AGE in hexane may be used to prepare calibration standards, or microliter aliquots of pure AGE could be diluted to the appropriate volume for the standard concentration range of interest. The concentration of standards can be expressed in terms of μg of AGE/2.0 ml of ether.

(b) A series of standards, varying in concentration over the range of interest, is prepared as described above and analyzed under the same gas-chromatographic conditions and during the same time period as the unknown samples. Curves are established by plotting peak area (ordinate) against sample concentration in μg/2.0 ml.

For the internal standard method, use ether containing a predetermined amount of the internal standard. The internal standard concentration used was approximately 70% of the concentration at 44 mg/cu m. The area ratio of the AGE to that of the internal standard is plotted against the AGE concentration in μg/2.0 ml.

Note: Whether the external standard or internal standard method is used, standard solutions should be analyzed at the same time the sample analysis is done. This will minimize the effect of variations in the gas-chromatographic detector response.

Calculations

Read the weight, in μg, corresponding to each peak area from the standard curve. No volume corrections are needed, because the standard curve is based on μg/2.0 ml of ether, and the volume of sample injected is identical with the volume of the standards injected.

Corrections for the blank must be made for each sample:

$$\mu g = \mu g \text{ sample} - \mu g \text{ blank}$$

where:

$\mu g$ sample = $\mu g$ found in front (100-mg) sample section
$\mu g$ blank = $\mu g$ found in front (100-mg) blank section

A similar procedure is followed for the backup (50-mg) section.

Read the desorption efficiency from the curve for the amount found in the front section of the tube. Divide the total weight by this desorption efficiency to obtain the corrected $\mu g$/sample.

$$\text{Corrected } \mu g/\text{sample} = \frac{\text{Weight } (\mu g) \text{ of front section}}{DE}$$

Add the amounts present in the front and backup sections for the same sample to determine the total weight in the sample.

(e) Determine the volume in liters of air sampled at ambient conditions based on the appropriate information, such as flowrate in liters/minute multiplied by sampling time. If a pump using a rotameter for flowrate control was used for sample collection, a pressure and temperature correction must be made for the indicated flowrate. The expression for this correction is:

$$\text{Corrected volume} = f \times t\left(\sqrt{\frac{P1}{P2} \times \frac{T2}{T1}}\right)$$

where:

f = flowrate during sampling
t = sampling time
P1 = pressure during calibration of sampling pump (mmHg)
P2 = pressure of air sampled (mmHg)
T1 = temperature during calibration of sampling pump (K)
T2 = temperature of air sampled (K)

The concentration of the AGE in the air sampled can be expressed in mg/cu m, which is numerically equal to $\mu$g/liter:

$$\text{mg/cu m} = \frac{\text{Corrected g}}{\text{Air volume sampled (liters)}}$$

Another method of expressing concentration is ppm (corrected to standard conditions of 25 C and 760 mmHg):

$$\text{ppm} = \text{mg/cu m} \times \frac{24.45}{MW} \times \frac{760}{P} \times \frac{T + 273}{298}$$

where:

P = pressure (mmHg) of air sampled
T = temperature (C) of air sampled
24.45 = molar volume (liters/mole) at 25 C and 760 mmHg
MW = molecular weight of AGE
760 = standard pressure (mmHg)
298 = standard temperature (K)

# XI. APPENDIX III

## SAMPLING AND ANALYTICAL METHOD FOR DGE

This sampling and analytical method is adapted from a method tested by NIOSH [79]. It was found unsuitable for determining DGE at the current Federal standard of 2.8 mg/cu m because recovery of DGE from the sampling tubes was unacceptably low. However, it is believed that, with immediate desorption of samples as described below, this method can be used to measure DGE in air at the recommended concentration limit of 1.0 mg/cu m.

### Principle of the Method

A known volume of air is drawn through a charcoal tube to collect organic vapors. The sample is immediately desorbed with methylene chloride and analyzed by gas chromatography. The area of the resulting peak is determined and compared with areas obtained from the injection of standards.

### Range and Sensitivity

The range and sensitivity of this method is dependent on the decomposition of the DGE on the charcoal prior to analysis. If decomposition time is minimized, the recovery of DGE from the samples should be adequate to analyze for the compound at the recommended standard.

## Interferences

When the amount of water in the air is so great that condensation actually occurs in the charcoal tube, organic vapors will not be trapped efficiently. When two or more compounds are known or suspected to be present in the air, such information, including the suspected identities of the compounds, should be transmitted with the sample. It must be emphasized that any compound that has the same retention time as DGE at the operating conditions described in this method is an interference. Retention-time data on a single column cannot be considered proof of chemical identity. If the possibility of interference exists, separation conditions (column packing, temperature, etc) must be changed to circumvent the problem.

## Precision and Accuracy

The Coefficient of Variation (CVT) and standard deviation at half the current Federal standard (1.5 mg/cu m) for DGE using this method were 0.081 and 0.090, respectively [79]. While the CVT and standard deviation for this method have not been determined at the recommended limit of 1.0 mg/cu m, it is likely that the method as modified will be able to detect DGE at this limit given a standard deviation of 0.1.

## Advantages and Disadvantages of the Method

The sampling method uses a small, portable sampling device that involves no liquids. Interferences are minimal, and most of those that do occur can be eliminated by altering chromatographic conditions. The tubes

are analyzed by means of a quick instrumental method. The method can also be used for the simultaneous analysis of two or more substances suspected to be present in the same sample simply by changing gas-chromatographic conditions from isothermal to a temperature-programmed mode of operation.

The major disadvantage of this method is the necessity for immediate desorption of samples and the attendant problems of breakage, spillage, and evaporation associated with transporting liquid samples to the analytical laboratory.

Another disadvantage is that the amount of sample that can be taken is limited by the number of milligrams that the tube will hold before overloading. When the sample value obtained from the backup section of the charcoal trap exceeds 25% of that found on the front section, the possibility of sample loss exists. The precision of the method is affected by the reproducibility of the pressure drop across the tubes. This drop will affect the flowrate and cause the volume to be imprecise, because the pump is usually calibrated for one tube only.

Apparatus

(a) An approved and calibrated personal sampling pump whose flow can be determined within ±5% at the recommended flowrate.

(b) Charcoal tubes: glass tube with both ends flame sealed, 7-cm-long with a 6-mm outer diameter and a 4-mm inner diameter, containing two sections of 20/40-mesh activated charcoal separated by a 2-mm portion of urethane foam. The activated charcoal is prepared from coconut shells and is fired at 600 C prior to packing. The adsorbing section contains 100 mg

of charcoal, the backup section 50 mg. A 3-mm portion of urethane foam is placed between the outlet end of the tube and the backup section. A plug of silylated glass wool is placed in front of the adsorbing section. The pressure drop across the tube must be less than 1 inch of mercury at a flowrate of 1 liter/minute.

(c) Glass vials with Teflon-lined screw caps, for desorbing and shipping samples.

(d) Gas chromatograph equipped with a flame ionization detector.

(e) Column (10-foot x 1/8-inch stainless steel) packed with 5% Carbowax 20M on 80/100-mesh acid-washed DMCS Chromosorb W.

(f) An electronic integrator or some other suitable method for measuring.

(g) Microliter syringes: 10-$\mu$l, and other convenient sizes for making standards.

(h) Pipets: 0.5-ml delivery pipets or 1.0-ml type graduated in 0.1-ml increments.

(i) Volumetric flasks: 10-ml or convenient sizes for making standard solutions.

Reagents

(a) DGE, reagent grade.

(b) Methylene chloride, chromatographic quality.

(c) Nitrogen, purified.

(d) Hydrogen, prepurified.

(e) Filtered compressed air.

Sampling Procedure

(a) Calibration of Personal Pumps. Each personal pump must be calibrated with a representative charcoal tube in the line, as shown in Figure XIV-1. This will minimize errors associated with uncertainties in the sample volume collected.

(b) Collection and Shipping of Samples.

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

(2) 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 position 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 temperature and pressure of the atmosphere being sampled should be recorded. If pressure reading is not available, record the elevation.

(6) The charcoal in the front and back section of the tube should be transferred to separate glass vials immediately after sampling. One milliliter of methylene chloride should be added to each vial, and they should be capped with Teflon-lined screw caps.

(7) One tube should be handled in the same manner as the sample tube (break, desorb, and transport), except that no air is drawn through this tube. An intact charcoal tube should also be shipped to the laboratory with the samples.

(8) Capped vials should be packed tightly and padded before they are shipped to minimize breakage during shipping.

Analysis of Samples

(a) Gas-chromatographic Conditions. The typical operating conditions for the gas chromatograph are:

(1) Nitrogen carrier gas flow, 50 ml/minute (60 psig).

(2) Hydrogen gas flow to detector, 65 ml/minute (24 psig).

(3) Air flow to detector, 500 ml/minute (50 psig).

(4) Injector temperature, 220 C.

(5) Manifold temperature (detector), 275 C.

(6) Column temperature, 205 C

(b) Injection. The first step in the analysis is the injection of the sample into the gas chromatograph. To eliminate difficulties arising from blowback or distillation within the syringe needle, one should employ the solvent-flush injection technique. The 10-$\mu$l syringe is first flushed with solvent several times to wet the barrel and plunger. Draw 3 $\mu$l of solvent into the syringe to increase the accuracy and reproducibility of the injected sample volume. The needle is removed from the solvent, and the plunger is pulled back about 0.2 $\mu$l to separate the solvent flush from the sample with a pocket of air to be used as a marker. The needle is then immersed in the sample, and a 5-$\mu$l aliquot is withdrawn, taking into consideration the volume of the needle, since the sample in the needle will be completely injected. After the needle is removed from the sample and prior to injection, the plunger is pulled back 1.2 $\mu$l to minimize evaporation of the sample from the tip of the needle. Observe that the

sample occupies 4.9-5.0 μl in the barrel of the syringe. Duplicate injections of each sample and standard should be made. No more than a 3% difference in area is to be expected.

(c) Area Measurement. The area of the sample peak is measured by an electronic integrator or some other suitable form of area measurement, and preliminary results are read from a standard curve prepared as discussed below.

Determination of Desorption Efficiency

(a) Importance of Determination. The desorption efficiency of a particular compound can vary from one laboratory to another and also from one batch of charcoal to another. Thus, it is necessary to determine at least once the percentage of the specific compound that is removed in the desorption process, provided the same batch of charcoal is used.

(b) Procedure for Determination. Activated charcoal equivalent to the amount in the first section of the sampling tube (100 mg) is measured into a 2.5-inch, 4-mm inner diameter glass tube, flame-sealed at one end. This charcoal must be from the same batch as that used in obtaining the samples and can be obtained from unused charcoal tubes. The open end is capped with Parafilm. A known amount of DGE is injected directly into the activated charcoal with a microliter syringe, and the tube is capped with more Parafilm. The amount injected is equivalent to that present in an air sample at the selected level. Six tubes at each of three levels (0.5, 1, and 2 times the standard) are prepared in this manner and allowed to stand at least overnight to assure complete adsorption of the DGE onto the

charcoal. These tubes are referred to as the samples. A parallel blank tube is also prepared. The sample and blank tubes are desorbed and analyzed in exactly the same manner as the sampling tube. Two or three standards are prepared by injecting the same volume of compound into 1.0 ml of methylene chloride with the same syringe used in the preparation of the samples. These are analyzed with the samples. The desorption efficiency (DE) equals the average weight in mg recovered from the tube divided by the weight in mg added to the tube, or:

$$DE = \frac{\text{Average weight (mg) recovered}}{\text{Weight (mg) added}}$$

The desorption efficiency is dependent on the amount of DGE collected on the charcoal. The desorption efficiency is plotted against the weight of DGE found.

Calibrations and Standards

It is convenient to express concentrations of standards in terms of mg/ml of methylene chloride, because samples are desorbed in this amount of methylene chloride. The density of DGE is used to convert mg into $\mu$l for easy measurement with a microliter syringe. A series of standards, varying in concentration over the range of interest, is prepared and analyzed under the same gas-chromatographic conditions and during the same time period as the unknown samples. Curves are established by plotting concentration in mg/ml versus peak area. Note: Since no internal standard is used in the method, standard solutions must be analyzed at the same time that the analysis of samples is done. This will minimize the effect of known day-to-day variations and variations during the same day in the gas-chromatographic detector response.

Calculations

The weight in mg corresponding to each peak area is read from the standard curve. No volume corrections are needed, because the standard curve is based on mg/ml of methylene chloride and the volume of sample injected is identical to the volume of the standards injected.

Corrections for the blank must be made for each sample:

$$mg = mg\ sample - mg\ blank$$

where:

mg sample = mg found in front section of sample tube

mg blank = mg found in front section of blank tube

A similar procedure is followed for the backup sections.

Add the weights found in the front and backup sections to get the total weight in the sample.

Read the desorption efficiency from the curve for the amount found in the front section. Divide the total weight by this desorption efficiency to obtain the corrected mg/sample.

$$\text{Corrected mg/sample} = \frac{\text{Total weight}}{DE}$$

Determine the volume (in liters) of air sampled at ambient conditions based on the appropriate information, such as flowrate in liters/minute multiplied by sampling time. If a pump using a rotameter for flowrate control was used for sample collection, a pressure and temperature correction must be made for the indicated flowrate when the pump was

calibrated under substantially different conditions than those that exist during sampling. The expression for the correction is:

$$\text{Corrected volume} = f \times t\left(\sqrt{\frac{P1}{P2} \times \frac{T2}{T1}}\right)$$

where:

f = flowrate during sampling
t = sampling time
P1 = pressure during calibration of sampling (mmHg)
P2 = pressure of air sampled (mmHg)
T1 = temperature during calibration of sampling pump (K)
T2 = temperature of air sampled (K)

The concentration of DGE in the air sampled can be expressed in mg/cu m.

$$\text{mg/cu m} = \frac{\text{Corrected mg} \times 1{,}000 \text{ (liters/cu m)}}{\text{Air volume sampled (liters)}}$$

Another method of expressing concentration is ppm:

$$\text{ppm} = \text{mg/cu m} \times \frac{24.45}{130} \times \frac{760}{P} \times \frac{T + 273}{298}$$

where:

P = pressure (mmHg) of air sampled
T = temperature (C) of air sampled
24.45 = molar volume (liters/mole) at 25 C and 760 mmHg
130 = molecular weight (g/mole) of DGE
760 = standard pressure (mmHg)
298 = standard temperature (K)

## XII. APPENDIX IV

## MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted 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. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted 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) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which 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, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

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) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% 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, eg, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the

American National Standards Institute Inc. Flashpoint, shock sensitivity, or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) 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 (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 F (21.1 C); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) 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 firefighting 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."

(e) 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 LD50 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 which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed employees.

(f) 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.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect employees 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.

(h) 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 US Bureau of Mines approval class, ie, "Supplied air," "Organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.

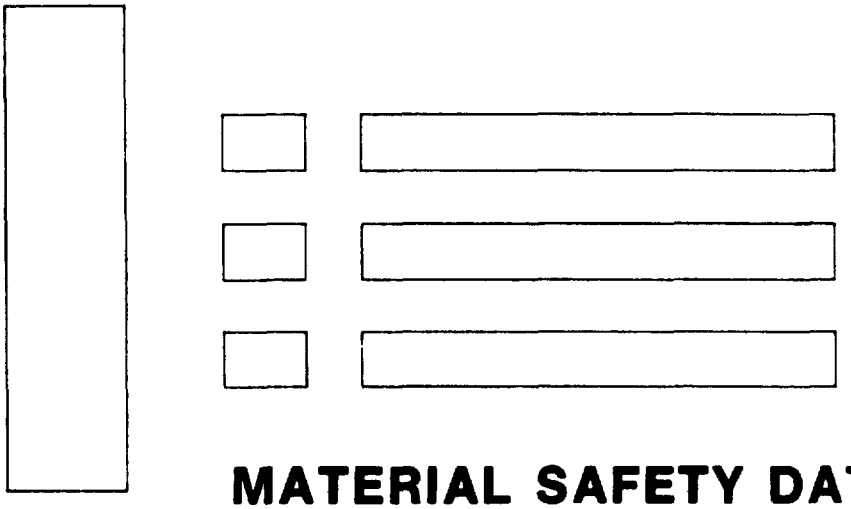
(i) Section IX. Special Precautions

"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.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to employees 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 employees. 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 employees.



# MATERIAL SAFETY DATA SHEET

| I PRODUCT IDENTIFICATION | |
|---|---|
| MANUFACTURER'S NAME | REGULAR TELEPHONE NO<br>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 | | | |

## 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

## 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

## IX SPECIAL PRECAUTIONS

PRECAUTIONARY
STATEMENTS

OTHER HANDLING AND
STORAGE REQUIREMENTS

PREPARED BY _____

ADDRESS _____

DATE _____

# XIII. APPENDIX V

## REACTIVITY OF THE GLYCIDYL ETHERS

The epoxide group is very reactive and there are several types of chemical reactions in which it will take part. Because glycidyl ethers contain the epoxide group, they would be expected to undergo the types of reactions that have been demonstrated for this moiety. Some reactions that have significance for biologic systems are summarized in Figure XIII-1 [6,98]:

(a) In the presence of hydrogen ions, the epoxide behaves as an ionized, very reactive radical and is capable of multiple additive reactions on the electronegative radicals. The epoxide ring is cleaved, and an alcohol (hydroxyl group) is formed.

(b) With organic acids, the alcohol is formed and an esterification takes place.

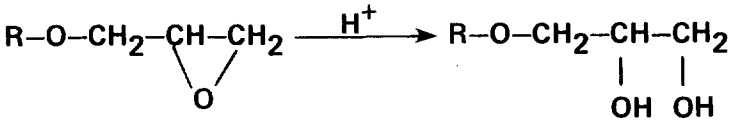
(c) Phenols react to form the alcohol and the aromatic ring attaches through the ether linkage.

(d) Some nucleophilic compounds react directly on the epoxide, cleaving the ring and making the oxygen electronegative. If the R group is nucleophilic, the effect is stronger.

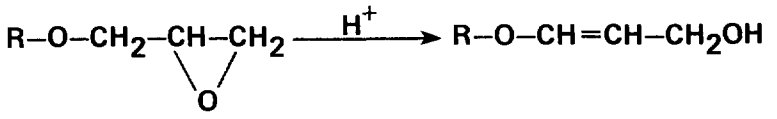
(e) The epoxides are also described as alkylating agents or electrophilic agents, which are postulated to form a carbonium ion in which the positive charge resides on one of the carbon atoms [6]. The carbonium ion reacts with water or with nucleophilic compounds such as proteins and nucleic acids [6].

(a) Alcohol Formation

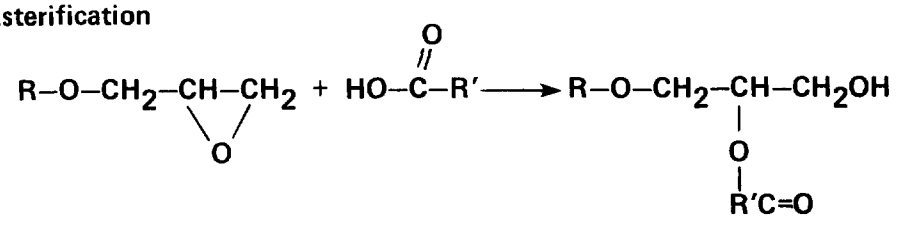
aqueous



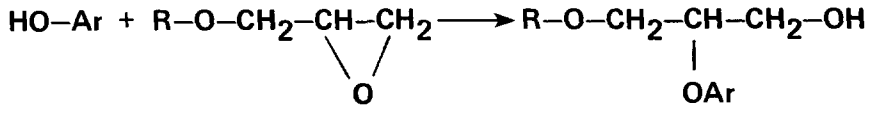
nonaqueous



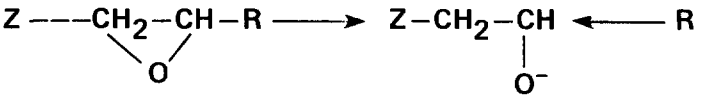
(b) Esterification



(c) Phenolic Reaction



(d) Reaction with Nucleophilic Substance (Z)



(e) Carbonium Ion Formation

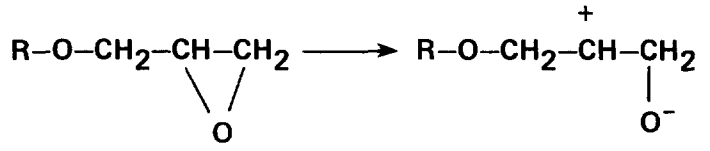


FIGURE XIII-1

BIOLOGICALLY IMPORTANT REACTIONS OF EPOXIDES

Adapted from references 6,98

Experimental evidence also indicates that glycidyl ethers are very reactive biologically. They have been used for tumor inhibition because of their alkylating properties [52]. They have produced chromosomal aberrations in plants [6,53-55], and Hine et al [41,48] have demonstrated their radiomimetic effects on blood cells. BGE has been shown to be mutagenic in mammals [58], and all glycidyl ethers tested have shown some mutagenic activity in bacterial systems [49,57,58]. However, very high doses were generally required to produce these effects and attempts to find consistent structure-activity relationships among various glycidyl ethers have met with little success [48,56].

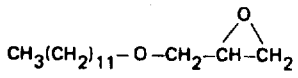
## XIV. TABLES AND FIGURE

### TABLE XIV-1

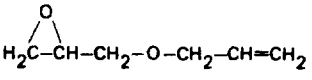
### SYNONYMS AND STRUCTURAL FORMULAS FOR SOME GLYCIDYL ETHERS

---

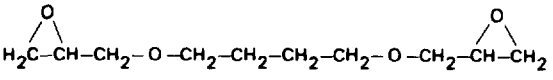
Alkyl glycidyl ether (C12)
*Oxirane, (methoxydodecyl)-
Lauryl glycidyl ether
Aliphatic glycidyl ether



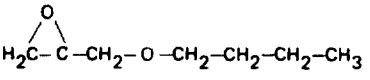
Allyl glycidyl ether (AGE)
*Oxirane, [(2-propenyloxy)methyl]-
Allyl 2,3-epoxypropyl ether
1,2-Epoxy-3-allyloxypropane



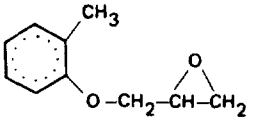
1,4-Butanediol diglycidyl ether
*Oxirane, 2,2'[1,4-butanediol bis(oxymethylene]bis-
Butane-1,4-diol diglycidyl ether
1,4-Bis-(2,3-epoxypropoxy)butane



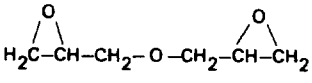
n-Butyl glycidyl ether (BGE)
*Oxirane, (butoxymethyl)-
Glyceryl butyl ether
1-Butoxy-2,3-epoxypropane
Butyl 2,3-epoxypropyl ether
2,3-Epoxypropyl ether of butanol-1



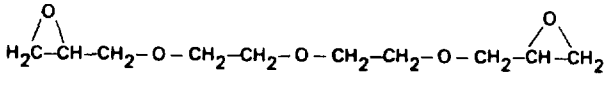
o-Cresyl glycidyl ether (CGE)
*Oxirane, [(2-methylphenoxy)methyl]-
Glycidyl o-tolyl ether
2,3-Epoxypropyl-o-tolyl ether



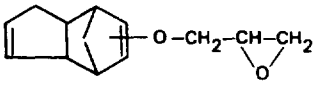
Di(2,3-epoxypropyl) ether (DGE)
*Oxirane, 2,2'[oxy-bis(methylene)]bis-
Diglycidyl ether
Bis(2,3-epoxypropyl) ether
Glycidyl ether
Diallyl ether dioxide



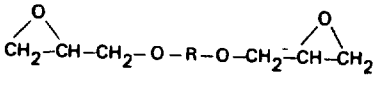
Diethylene glycol diglycidyl ether



Dicyclopentadiene glycidyl ether



Diglycidyl ether of substituted glycerin



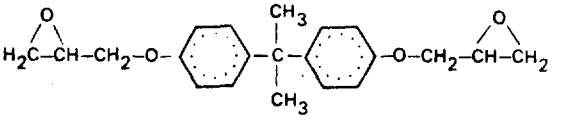
R = aliphatic radicals (average mw 100)

TABLE XIV-1 (CONTINUED)

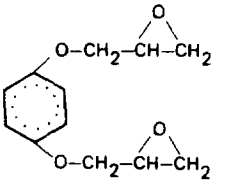
SYNONYMS AND STRUCTURAL FORMULAS FOR SOME GLYCIDYL ETHERS

---

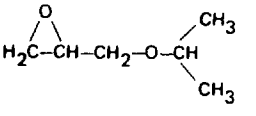
Diphenylol propane diglycidyl ether
*Oxirane, 2,2'-[(1-methylethylidene) bis(4,1-phenylene oxymethylene)]bis-
Diglycidyl ether of bisphenol A
2,2-Bis[p-(2,3-epoxypropoxy)phenyl]-propane
2,2-Bis(4-hydroxyphenyl)propane diglycidyl ether
Diomethane diglycidyl ether
2,2-Bis[p-(glycidoxy)phenyl]propane



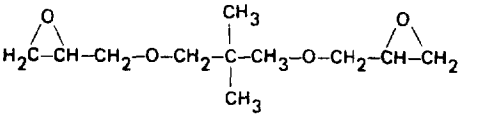
Hydroquinone diglycidyl ether
*Oxirane, 2,2'-[1,4-phenylene) bis(oxymethylene)]bis-
Hydroquinone bis(2,3-epoxypropyl)ether
1,4-Bis(2,3-epoxypropoxy)benzene



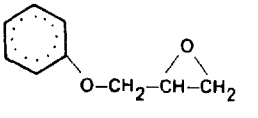
Isopropyl glycidyl ether (IGE)
*Oxirane, [(1-methylethoxy)methyl]-3-Isopropoxy-1,2-epoxy propane
(Isopropoxymethyl)oxirane



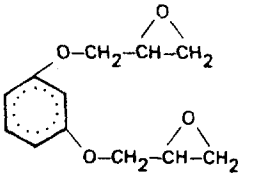
Neopentyl glycol diglycidyl ether
*Oxirane, 2,2'[1,3-(2,2-dimethyl) propane diyl bis(oxymethylene'] bis-



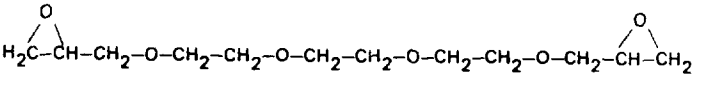
Phenyl glycidyl ether (PGE)
*Oxirane, (phenoxymethyl)-
Gamma-phenoxypropylene oxide
Phenoxypropenoxide
2,3-Epoxypropyl phenyl ether



Resorcinol diglycidyl ether
*Oxirane, 2,2'-[1,3-phenylene bis(oxymethylene)]2 bis-
1,3-Bis(2,3-epoxypropoxy)benzene
Resorcinol bis-2,3-epoxypropyl ether



Triethylene glycol diglycidyl ether
Ethoglucid
Etoglucid
Epodyl



---

*IUPAC name

TABLE XIV-2

PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED GLYCIDYL ETHERS

| | |
|---|---|
| **Allyl Glycidyl Ether** | |
| Empirical formula | C6H10O2 |
| Formula weight | 114.14 |
| Appearance and odor | Colorless liquid; characteristic but not unpleasant odor |
| Boiling point | 153.9 C (760 mmHg ) |
| Freezing point | Forms glass at -100 C |
| Vapor density (air = 1) | 3.32 (25 C) |
| Specific gravity (water = 1.0 at 4 C) | 0.9698 (20 C) |
| Vapor pressure | 4.7 mmHg (25 C) |
| % in saturated air | 0.62 (25 C) |
| Refractive index | 1.4348 (20 C) |
| Solubility | |
| In water | 14.1% |
| In other solvents | Miscible with acetone, toluene, and octane |
| Flashpoint | 57.2 C |
| Conversion factors (760 mmHg and 25 C) | 1 mg/cu m = 0.214 ppm<br>1 ppm = 4.67 mg/cu m |
| **n-Butyl Glycidyl Ether** | |
| Empirical formula | C7H14O2 |
| Formula weight | 130.21 |

TABLE XIV-2 (CONTINUED)

PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED GLYCIDYL ETHERS

| | |
|---|---|
| **n-Butyl Glycidyl Ether (continued)** | |
| Appearance and odor | Colorless liquid; slight, irritant odor |
| Boiling point | 164 C (760 mmHg) |
| Vapor density (air = 1) | 3.78 (25 C) |
| Specific gravity (water = 1 at 4 C) | 0.9087 (25 C) |
| Vapor pressure | 3.2 mmHg (25 C) |
| % in saturated air | 0.42 (25 C) |
| Solubility | 2% in water (20 C) |
| Conversion factors (760 mmHg and 25 C) | 1 mg/cu m = 0.188 ppm<br>1 ppm = 5.32 mg/cu m |
| **o-Cresyl Glycidyl Ether** | |
| Empirical formula | C10H12O2 |
| Formula weight | 164.21 |
| Flashpoint | 121.1 C |
| Viscosity C 25 C | 20 cps |
| Epoxide equivalent weight | 180 |
| Conversion factors (760 mm Hg and 25 C) | 1 mg/cu m = 0.149 ppm<br>1 ppm = 6.72 mg/cu m |

TABLE XIV-2 (CONTINUED)

PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED GLYCIDYL ETHERS

Di(2,3-epoxypropyl) Ether

| | |
|---|---|
| Empirical formula | C6H1003 |
| Formula weight | 130.1 |
| Appearance and odor | Colorless liquid; pronounced, irritant odor |
| Boiling point | 260 C (760 mmHg) |
| Vapor density (air = 1) | 3.78 (25 C) |
| Specific gravity (water = 1.0 at 4 C) | 1.262 (25 C) |
| Vapor pressure | 0.09 mmHg (25 C) |
| % in saturated air | 0.0121 (25 C) |
| Flashpoint | 64 C |
| Conversion factors (760 mmHg and 25 C) | 1 mg/cu m = 0.188 ppm<br>1 ppm = 5.32 mg/cu m |

TABLE XIV-2 (CONTINUED)

PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED GLYCIDYL ETHERS

| | |
|---|---|
| **Isopropyl Glycidyl Ether** | |
| Empirical formula | $C_6H_{12}O_2$ |
| Formula weight | 116.16 |
| Appearance | Colorless liquid |
| Boiling point | 137 C (760 mmHg) |
| Vapor density | 4.15 (25 C) |
| Specific gravity (water = 1.0 at 4 C) | 0.9186 (20 C) |
| Vapor pressure | 9.4 mmHg (25 C) |
| % in saturated air | 1.237 (25 C) |
| Solubility | |
| In water | 18.8% |
| In other solvents | Soluble in ketones and alcohols |
| Conversion factors (760 mmHg and 25 C) | 1 mg/cu m = 0.210 ppm<br>1 ppm = 4.75 mg/cu m |
| **Phenyl Glycidyl Ether** | |
| Empirical formula | $C_9H_{10}O_2$ |
| Formula weight | 150.17 |
| Appearance | Colorless liquid |
| Boiling point | 245 C (760 mmHg) |
| Melting point | 3.5 C |
| Vapor density (air = 1) | 4.37 (25 C) |
| Specific gravity (water = 1.0 at 4 C) | 1.1092 (20 C) |

TABLE XIV-2 (CONTINUED)

PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED GLYCIDYL ETHERS

| | |
|---|---|
| **Phenyl Glycidyl Ether (continued)** | |
| Vapor pressure | 0.01 mmHg (25 C) |
| Refractive index | 1.5314 |
| % in saturated air | 0.0013 (25 C) |
| Solubility | |
| In water | 0.24% |
| In other solvents | 12.9% in octane; completely soluble in acetone and toluene |
| Conversion factors (760 mmHg and 25 C) | 1 mg/cu m = 0.163 ppm<br>1 ppm = 6.14 mg/cu m |
| **Resorcinol Diglycidyl Ether** | |
| Empirical formula | C12H1404 |
| Formula weight | 222.24 |
| Appearance and odor | Colorless solid; slight, phenolic odor |
| Boiling points | 150-160 C (0.05 mmHg)<br>208-210 C (12 mmHg) |
| Melting point | 32-33 C |
| Vapor density (air = 1) | 7.95 |
| Specific gravity (water = 1.0 at 4 C) | 1.2183 (20 C) |
| Refractive index | 1.5409 (20 C) |
| Conversion factors (760 mmHg and 4 C) | 1 mg/cu m = 0.110 ppm<br>1 ppm = 9.09 mg/cu m |

TABLE XIV-2 (CONTINUED)

PHYSICAL AND CHEMICAL PROPERTIES OF SELECTED GLYCIDYL ETHERS

| Triethylene Glycol Diglycidyl Ether | |
|---|---|
| Empirical formula | C12H2206 |
| Formula Weight | 262.31 |
| Appearance | Liquid |
| Boiling points | 133-149 C (0.1 mmHg)<br>195-197 C (2 mmHg) |
| Melting point | -15 to -11 C |
| Specific gravity (water = 1.0 at 4 C) | 1.1312 (20 C) |
| Refractive index | 1.4622 (20 C) |
| Solubility | Miscible with water |
| Flashpoint | 79.4 C |
| Conversion factors (760 mmHg and 25 C) | 1 mg/cu m = 0.093 ppm<br>1 ppm = 10.73 mg/cu m |

Adapted from references 1-5

TABLE XIV-3

OCCUPATIONS WITH POTENTIAL EXPOSURE TO GLYCIDYL ETHERS

| |
|---|
| Adhesive makers and users |
| Automobile workers |
| Cable makers |
| Casting and molding workers |
| Custom-blended epoxy resin system production workers |
| Dental laboratory technicians |
| Dentists |
| Electrical appliance production workers |
| Electronic equipment production workers |
| Flooring makers |
| Laminators |
| Glycidyl ether production workers |
| Nurses |
| Paintmakers |
| Physicians |
| Polyglycidyl ether production workers |
| Soft drink canners |
| Telephone production workers |
| Telephone installers |

Adapted from references 17,19-22

TABLE XIV-4

ACUTE TOXICITY OF GLYCIDYL ETHERS

| Compound | LD50 (g/kg) | | | | | | LC50 (mg/cu m) | | Reference |
|---|---|---|---|---|---|---|---|---|---|
| | Oral | | | SC | Dermal | | 8-hr | 4-hr | |
| | Rat | Mouse | Rabbit | Mouse | Rat | Rabbit | Rat | Mouse | |
| AGE | 1.60 | 0.39 | - | - | - | 2.55 | 3,120 | 1,260 | 23 |
| BGE | 3.43 | - | - | - | - | 2.26 | - | - | 32 |
| " | 2.26 | 1.53 | - | - | - | 4.93 | 5,480 | >18,600 | 23 |
| " | 2.05 | - | - | - | - | 2.52 | - | - | 37 |
| " | 2.5 | - | - | - | - | - | - | - | 30 |
| CGE | - | - | - | 0.96 | - | - | - | - | 36 |
| DGE | 0.45 | 0.17 | - | - | - | 1.5 | >1,060 | 160 | 23 |
| IGE | 4.20 | 1.30 | - | - | - | 9.65 | 5,220 | 7,120 | 23 |
| PGE | 3.85 | 1.40 | - | - | - | 2.99 | >60 | >60 | 23 |
| " | 4.26 | - | - | - | - | 1.50 | - | - | 34 |
| " | 2.6-3.8 | - | - | - | 2.16 | - | - | - | 35 |
| " | - | - | - | 0.76 | - | - | - | - | 36 |
| Alkyl glycidyl ether (C8-C10) | 9.4 | - | - | - | - | - | - | - | 30 |
| Alkyl glycidyl ether (C12-C14) | 17.1 | - | - | - | - | - | - | - | 30 |
| Butanediol diglycidyl ether | 2.98 | - | - | - | - | 1.3 | - | - | 32 |
| Diphenylol propane diglycidyl ether | 21.6 | - | - | - | - | >22 | - | - | 37 |
| Resorcinol diglycidyl ether | 2.57 | 0.98 | 1.24 | - | - | - | - | - | 33 |

TABLE XIV-5

DEGREE OF IRRITATION* PRODUCED IN RABBITS
BY TOPICAL APPLICATION OF UNDILUTED GLYCIDYL ETHERS

| Compound | Skin | | Eyes | Reference |
|---|---|---|---|---|
| | Single Application (24 hr) | Repeated Application (1 hr x 5-7 d) | Single Application | |
| AGE | Moderate (4.0/8) | Moderate (3.8/8) | Severe (72/110) | 23 |
| BGE | Severe (8.0/8) | -- | Moderate (23.2/110) | 30 |
| " | Moderate (2.8/8) | Moderate (3.8/8) | Mild (4/110) | 23 |
| " | Moderate (5/10) | -- | Mild (4/10) | 32 |
| " | Mild | -- | Moderate (5/10) | 37 |
| " | " | -- | -- | 42 |
| DGE | Severe (7.5/8) | Severe (6.5/8) | Severe (74/110) | 23, 41 |
| IGE | Moderate (4.3/8) | Moderate (2.2/8) | Moderate (40/110) | 23 |
| PGE | Severe | -- | Severe** | 35 |
| " | Moderate (5/10) | -- | Mild-Moderate (2/10) | 37, 34 |
| " | Mild (0.7/8) | Moderate (5.2/8) | Mild (8/110) | 23 |
| Alkyl glycidyl ether (C8-C10) | Moderate (3.3/8) | -- | Mild (11.7/110) | 30 |

TABLE XIV-5 (CONTINUED)

DEGREE OF IRRITATION* PRODUCED IN RABBITS
BY TOPICAL APPLICATION OF UNDILUTED GLYCIDYL ETHERS

| Compound | Skin | | Eyes | Reference |
|---|---|---|---|---|
| | Single Application (24 hr) | Repeated Application (1 hr x 5-7 d) | Single Application | |
| Alkyl glycidyl ether (C12-C14) | Moderate (3.4/8) | -- | Mild | 30 |
| Butanediol diglycidyl ether | Moderate (5/10) | -- | Moderate (5/10) | 32 |
| Resorcinol diglycidyl ether | Moderate (5.0/8) | Severe*** (8.0/8) | Moderate (45/110) | 33 |

*Numerical scores are based on the method described by Draize [43] and by Smyth et al [34]. Maximum severity is indicated by a score of 8 for skin irritation and 110 for eye irritation in the Draize system, and by a score of 10 for both skin and eyes in the method of Smyth et al.
**Severe hyperemia of the cornea, disappearing within 96 hr
***Applied for 7 hr x 7 d

TABLE XIV-6

MUTAGENIC ACTIVITY OF GLYCIDYL ETHERS

| Compound | Bacterial | | | Mammalian | | | Reference |
|---|---|---|---|---|---|---|---|
| | Ames Test | Body-Fluid Analysis | Host-Mediated Assay | DNA Repair | Micronucleus Test | Dominant Lethal | |
| AGE | +(0)* | n.d.** | n.d. | n.d. | n.d. | n.d. | 57 |
| BGE | +(-) | n.d. | n.d. | n.d. | n.d. | n.d. | 57 |
| " | +(-) | - | - | + | - | + | 58 |
| CGE | +(-) | + | - | + | - | - | 58 |
| DGE | +(-) | n.d. | n.d. | n.d. | n.d. | n.d. | 57 |
| PGE | +(-) | n.d. | n.d. | n.d. | n.d. | - | 49 |
| Alkyl glycidyl ether (C12-C14) | -(+) | - | ?*** | - | - | - | 58 |
| Dicyclopentadiene glycidyl ether | +(0) | - | - | - | - | - | 58 |
| Diglycidyl ether of substituted glycerine | +(0) | n.d. | n.d. | n.d. | n.d. | n.d. | 57 |
| Diphenylol propane diglycidyl ether | -(+) | n.d. | n.d. | n.d. | n.d. | n.d. | 57 |
| " | +(+) | - | - | ? | - | - | 58 |
| Neopentyl glycol diglycidyl ether | +(0) | + | ? | + | - | ? | 58 |

*Character in paretheses indicates the effect of adding rat liver homogenate to the assay: (+) = increased mutagenic activity; (-) = decreased activity; (0) = no effect.
**n.d. = Compound not tested in this system
***? = Inconclusive or nonsignificant positive results

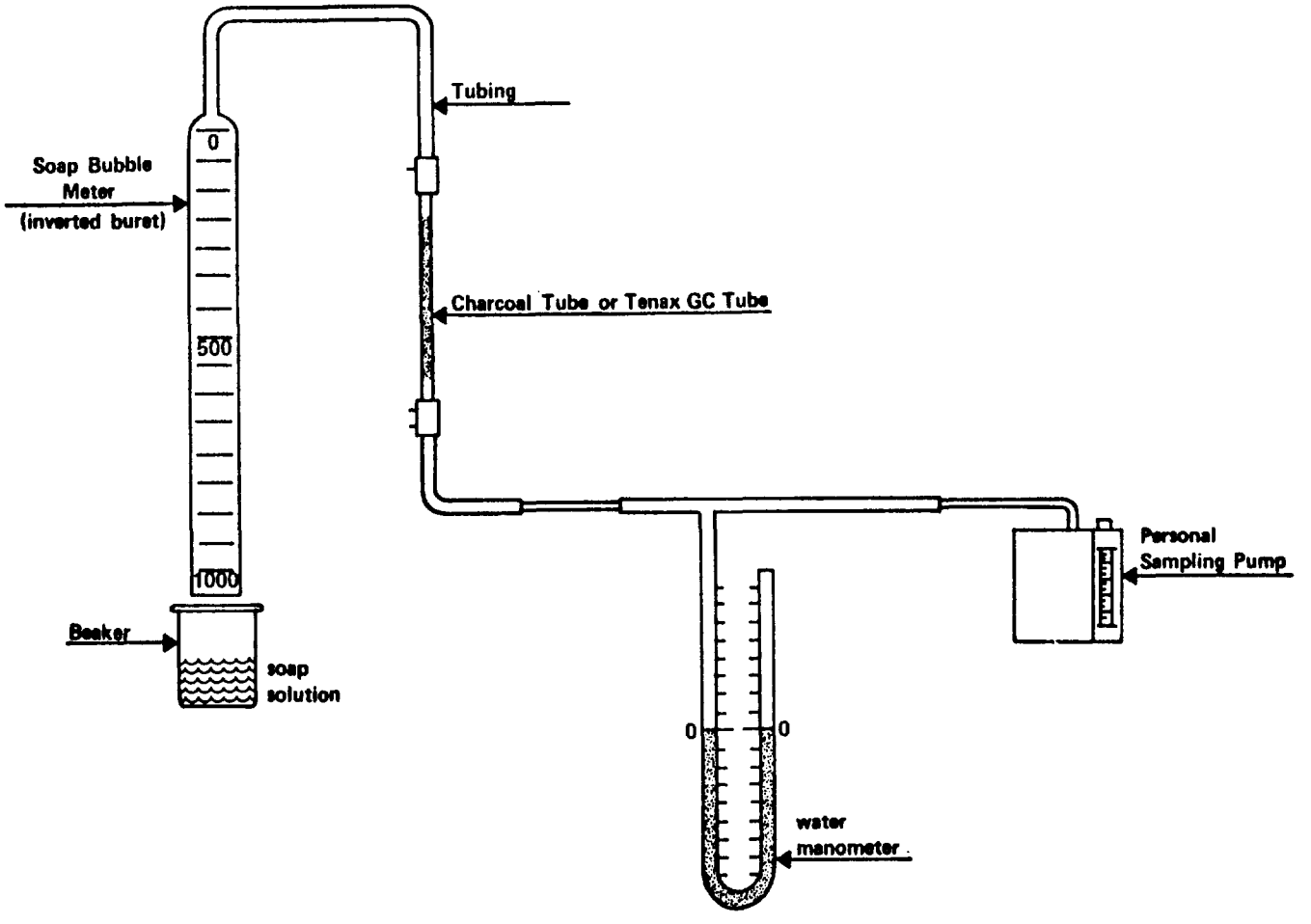



FIGURE XIV-1

CALIBRATION SETUP FOR PERSONAL SAMPLING PUMP
WITH CHARCOAL OR TENAX-GC TUBE



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