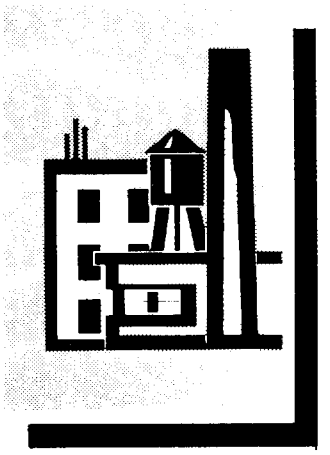
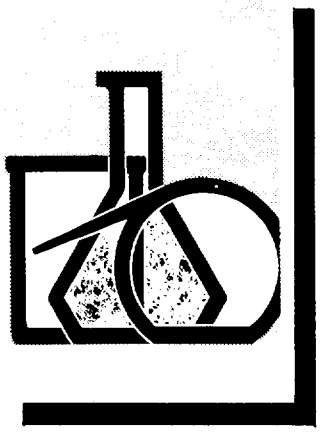
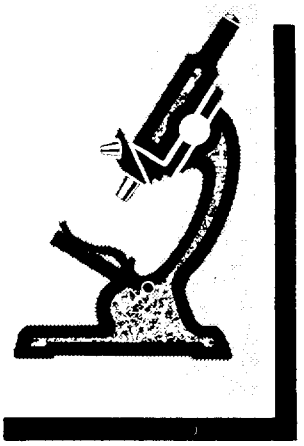
NIOSH

SPECIAL OCCUPATIONAL HAZARD REVIEW with CONTROL RECOMMENDATIONS







Use of Ethylene Oxide as a Sterilant in Medical Facilities

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

SPECIAL OCCUPATIONAL HAZARD REVIEW
WITH
CONTROL RECOMMENDATIONS
FOR THE
USE OF ETHYLENE OXIDE AS A STERILANT IN MEDICAL FACILITIES

prepared by
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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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Center for Disease Control
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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards in their workplace. Pursuant to the fulfillment of this need, the National Institute for Occupational Safety and Health (NIOSH) has developed a strategy of disseminating information about adverse effects of widely used chemical or physical agents intended to assist employers in providing protection for employees from exposure to substances considered to possess carcinogenic, mutagenic, or teratogenic potential. This strategy includes the development of Special Occupational Hazard Reviews which serve to support and complement the other major standards development or hazards documentation activities of the Institute. The purpose of Special Occupational Hazard Reviews is to analyze and document, from a health standpoint, the problems associated with a given industrial chemical, process, or physical agent, and to recommend the implementation of engineering controls and work practices to ameliorate these problems. While Special Occupational Hazard Reviews are not intended to supplant the more comprehensive NIOSH Criteria Documents, nor the brief NIOSH Current Intelligence Bulletins, they are nevertheless prepared in such a way as to assist in the formulation of regulations. Special Occupational Hazard Reviews are disseminated to the occupational health community at large, e.g., trade associations, industries, unions, and members of the scientific community.

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The assistance of Masao Koketsu and Lynn Carssow, Industrial Hygienists with Stanford Research Institute (NIOSH contract No. 210-76-0162), was invaluable in conducting the field survey in medical facilities.

SUMMARY AND CONCLUSIONS

Ethylene oxide (ETO) is used extensively within health care facilities for sterilization of equipment and supplies which are heat sensitive. It is unique for this purpose. Alternative chemicals or processes have, in themselves, serious limitations or health hazards. NIOSH recognizes, therefore, that the continued use of ETO as a gaseous sterilant is highly desirable in many situations. Recent results of tests for mutagenesis have increased the concern for potential health hazards associated with exposure to ETO. In order to assess the potential for exposure and associated hazards, NIOSH has undertaken this Special Occupational Hazard Review. An assessment is made of the evidence for toxic effects of ETO, especially with respect to mutagenic, teratogenic and carcinogenic potentials. Additionally, a limited field survey was conducted by NIOSH to document the use, problems, and potential for human exposure in medical facilities. The results of this survey were in agreement with data made available by the American Hospital Association, the U.S. Army, other Federal agencies, and industrial and professional organizations. Based on this review, measures for control of occupational exposure are recommended.

The acute toxic effects of ETO in man and animals include acute respiratory and eye irritation, skin sensitization, vomiting, and diarrhea. Known chronic effects consist of respiratory irritation and secondary respiratory infection, anemia, and altered behavior.

The observations of (a) heritable alterations in at least 13 different lower biological species following exposure to ETO, (b) alterations in the structure of the genetic material in somatic cells of the rat, and (c) covalent chemical bonding between ETO and DNA support the conclusion that continuous occupational exposure to significant concentrations of ETO may induce an increase in the frequency of mutations in human populations. At present, however, a substantive basis for quantitative evaluation of the genetic risk to exposed human populations does not exist.

No definitive epidemiological studies, and no standard long-term carcinogenesis assays, are available on which to assess carcinogenic potential. Limited tests by skin application or subcutaneous injections in mice did not reveal carcinogenicity. However, the alkylating and mutagenic properties of ETO are sufficient bases for concern about its potential carcinogenicity. Neither animal nor human data are available on which to assess the potential teratogenicity of ETO.

NIOSH recommends that ETO be considered as mutagenic and potentially carcinogenic to humans, and that occupational exposure to it be minimized by eliminating all unnecessary and improper uses of ETO in medical facilities. Whenever alternative sterilization processes are available which do not present similar or more serious hazards to the employee, they should be substituted for ETO sterilization processes whenever possible. Although this review is limited to ETO, concern is also expressed for hazards from such hydration and reaction products of ETO as ethylene glycol and ethylene chlorohydrin, the latter a teratogen to some lower biological species.

This report includes a summary of the airborne ETO concentrations measured within health care facilities as part of the field survey. NIOSH estimates that there are in excess of 10 thousand ETO sterilizers in use in U.S. health care facilities, and that approximately 75 thousand workers are potentially exposed to ETO in those facilities. Reasons for the unnecessary exposure of personnel were found to include: improper or inadequate ventilation of sterilizers, aerators, and working spaces; improper handling and/or storage of sterilized items; untrained workers operating some sterilization equipment; improper operating techniques leading to mishandling of some ETO sterilizing equipment; poor design of the sterilization facility; and, design limitations of the sterilization equipment.

NIOSH recommends, based on the recent results of tests for mutagenesis, that exposure to ETO be controlled so that workers are not exposed to a concentration greater than 135 mg/cu m (75 ppm) determined during a 15-minute sampling period, as a ceiling occupational exposure limit and in addition, with the provision that the time-weighted average (TWA) concentration limit of 90 mg/cu m (50 ppm) for a workday not be exceeded. As additional information on the toxic effects of ETO becomes available, this recommended level for exposures of short duration may be altered. The adequacy of the current U.S. ETO standard, which was based on the data available at the time of promulgation, has not been addressed in this report. Further assessment of other ETO exposure situations, and of the adequacy of the ETO occupational exposure standard will be undertaken during the FY 80 development of a NIOSH criteria document for occupational exposure to epoxides. In the interim, NIOSH strongly recommends that control strategies, such as those described in this document, or others considered to be more applicable to particular local situations, be implemented to assure maximum protection of the health of employees. Good work practices will help to assure their safety.

Where the use of ETO is to be continued, improved techniques of exhausting the gas from the sterilizer, the aerator, and the sterilized items need to be implemented. Gas sterilization should be supervised and the areas into which ETO may escape should be monitored to prevent all unnecessary exposure of personnel. When proper control measures are instituted, the escape of ETO into the environment will be greatly reduced. Under such control, the use of ETO as a gaseous sterilizant in medical facilities can be continued with considerably less risk to the health of occupationally-exposed employees.

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INTRODUCTION

Ethylene oxide (ETO) is a high volume chemical used primarily as an intermediate in the production of ethylene glycol (27% of total consumption), polyethylene terephthalate polyester fiber and film (23%), non-ionic surface-active agents (13%), ethanolamines (9%), with production of di- and tri-ethylene glycol, choline and choline chloride, and other organic chemicals consuming most of the remaining ETO. Although it is estimated that only about 0.02% of the total amount of ETO produced in the U.S. in 1976 was used for sterilization in medical facilities, this amounted to approximately 500,000 kg.

ETO is registered with the U.S. Environmental Protection Agency as a fungicide for fumigation of books, dental, pharmaceutical, medical and scientific equipment and supplies (glass, metals, plastics, rubber or textiles), drugs, leather, motor oil, paper, soil, bedding for experimental animals, clothing, furs, furniture, and transportation vehicles, such as jet aircraft, buses, and railroad passenger cars.

It has been used also to sterilize foodstuffs such as spices, cocoa, flour, dried egg powder, desiccated coconut, dried fruits and dehydrated vegetables (Wesley et al, 1965), and to accelerate the "maturing" of tobacco leaves (Fishbein, 1969). At one time (Stehle et al , 1924), ETO was used briefly as a possible anesthetic agent, but was discarded due to toxic effects.

This Hazard Review Document pertains only to the use of ETO in sterilization of medical supplies and equipment within medical and related facilities. The term "medical facilities" will be used to include hospitals, nursing and "total care" homes, medical, dental and veterinary clinics or facilities, and certain research laboratories affiliated with medical centers.

ETO is manufactured by the catalytic oxidation of ethylene with air (or oxygen) in the presence of a silver catalyst. Since 1972, this has been the only method used in the U.S. Wurtz, in 1859, prepared ETO from ethylene chlorohydrin and potassium hydroxide. Until 1957, the chlorohydrin process was the principal method of manufacturing ETO in the U.S.

In March 1973, the 13 companies which produced ETO in the U.S. and Puerto Rico had a total production of 1,892 million kg. In 1976, the annual U.S. production of ETO had grown to approximately 2,100 million kg, giving to this chemical a position within the top twenty-five chemicals (by volume) produced in the U.S. It is used extensively worldwide, with total production in Japan in 1974 of 415 million kg. European production in 1972 has been estimated at 865 million kg.

The current U.S. standard (OSHA) for occupational exposure to ETO is 50 parts per million (ppm) parts of air, as a time weighted average (TWA) concentration for an 8-hour exposure (CFR 1910.1000), which corresponds approximately to 90 milligrams per cubic meter of air (mg/cu m). The USSR has a standard of 0.5 ppm, (1 mg/cu m), which was adopted in 1966 [Winell, 1975]. Standards of 50 ppm and 20 ppm (36 mg/cu m) are in effect in the Federal Republic of Germany and Sweden, respectively.

While this review includes all known biohazards of ethylene oxide, special emphasis was devoted to its potentials for exerting carcinogenic,

mutagenic, and teratogenic effects. Recent reports of the mutagenic potential of ETO [Embree and Hine, 1975; Ehrenberg et al, 1974], coupled with the "Report of the Secretary's Commission on Pesticides and their Relationship to Environmental Health" [Mrak, DHEW Report, 1969], have prompted a reassessment of the adequacy of the current U.S. occupational exposure standard, as well as a critical appraisal regarding re-registration of the compound by the Environmental Protection Agency (as required under the Federal Insecticide, Fungicide, and Rodenticide Act, FIFRA). This latter action has resulted in a reappraisal by the Department of Health, Education, and Welfare of the use of ETO for sterilization purposes within health care facilities.

During the preparation of this review, a limited field survey of ETO use in medical facilities was conducted by NIOSH in order to better assess the actual occupational exposure situation. A summary of the results of the field survey is presented, and serves as a basis for the recommended control measures. Extensive use was made of information provided by other federal agencies, and from industrial, trade, and professional organizations. In addition, the "Draft Technical Standard and Supporting Documentation for Ethylene Oxide," prepared under the joint NIOSH/OSHA Standards Completion Program, assisted in the preparation of the engineering and control sections of this review. NIOSH was represented on the Ethylene Oxide Subcommittee of the Committee to Coordinate Toxicology and Related Programs (CCTRP), U.S. Department of Health, Education, and Welfare. The Subcommittee met during the period January 30 - March 30, 1977. Certain sections of this NIOSH Special Hazard Review were provided to the CCTRP Subcommittee for inclusion in its Risk/Benefit Analysis of public health uses of ETO (HEW, 1977).

The information and recommendations that follow should aid the U.S. Department of Labor, industrial hygienists, physicians, employers, and architects or other designers of health care facilities in protecting the worker from the hazards of ETO exposure. Furthermore, it will aid the worker in recognizing the hazard.

I. PROPERTIES

This information has been compiled primarily from the Chemical Safety Data Sheet of the Manufacturing Chemists Association, for Ethylene Oxide, (No. SD-38), 1971, with supplementation from other sources.

A. Identification

1. synonyms: 1,2-epoxyethane, oxirane, oxiran, dimethylene oxide, ETO, EO, oxane, dihydrooxirene, oxacyclopropane, oxidoethane, and anprolene
2. CAS number: 75-21-8
3. formula: C2H4O,
4. molecular weight: 44.05

B. Physical/Chemical Properties of ETO

1. appearance and odor: colorless gas or volatile liquid with a characteristic ether-like odor (irritating in high concentrations).
2. boiling point: 10.4 C (50.7 F) at 760 mm Hg
3. melting point: -112.6 C (-170.7 F)
4. specific gravity: 0.8711 (apparent) (20/20 C), (68 F): 0.897 (0/4 C)
5. vapor density: 1.5 (air = 1)
6. vapor pressure at 20 C: 1095 mm Hg
7. solubility: completely miscible with water, alcohol, acetone, benzene, ether, carbon tetrachloride, and most organic solvents. Powerful solvent for fats, oils, greases, waxes, and some rubber formulations.
8. reactivity: (gas and liquid). Highly exothermic and potentially explosive with alkali metal hydroxides, or highly active catalytic surfaces (such as anhydrous chlorides of Fe, Sn and Al, and oxides of Fe and Al), or when heated. Relatively non-corrosive to materials other than certain rubbers. Relatively stable in aqueous solution, and when diluted with CO2 or gaseous halocarbons. An alkylating agent which reacts directly (and virtually irreversibly) with -COOH, -NH2, -SH, and -OH groups. Reacts with the ring nitrogen of purine and pyrimidine bases, and the amino groups of amino acids and proteins.
9. explosive limits: 3 to 100 (% by vol in air).
10. flashpoint: -6C (20 F), (Tag. open cup).

II. USES AND OCCURRENCE IN MEDICAL FACILITIES

The routine use of ETO in medical and related health care facilities is to sterilize heat-sensitive surgical instruments, equipment, and other objects (or fluids) that come in contact with biological tissue (particularly the vascular system), or extracorporeal equipment through which blood may flow. The absence of all microbiological life forms such as viruses, bacteria, yeast, fungi, and especially persistent spore forms is essential in order to prevent infectious diseases in patients and animals.

Complete sterilization by either heat or gaseous agents is essential for many purposes, although varying degrees of disinfection with chemical germicides (which may sharply reduce the populations of many vegetative forms) may be sufficient for some applications.

Heat sterilization is normally the preferred method; however, this method can not always be employed because of the heat-sensitive nature of some items. In addition, ETO gas sterilization is more economical for some applications, such as the industrial sterilization of inexpensive disposable, i.e., single-use, items such as syringes and needles.

A. Characterization of Occupational Exposure During ETO Sterilization Procedures

There is current large-scale industrial use of ETO gas for sterilization of medical supplies and equipment because such use is effective and economical. In addition, alternate methods often are impractical, hazardous, undependable, or uneconomical. Gaseous ETO is generally used industrially for sterilization processing of disposable sterile kits containing items such as disposable syringes and needles, disposable microbiological laboratory supplies, and life-support items such as electronic cardiac "pacemakers," blood oxygenators, and dialysers. An estimated 80% of all such items are processed by ETO gas sterilizaton in the U.S. [CDC, 1977]; many could not be processed, regardless of cost, by any other currently available method [CDC, 1977]. The majority of industrial ETO gas sterilization is performed in less than 50 large (greater than 1,000 cu ft) sterilizers and in approximately the same number of smaller industrial units [HIMA, 1976]. It has been reported that such ETO sterilizers are operated in accord with manufacturers' recommendations, industry safety regulations, state and local fire codes, and provisions of insurance underwriters [HIMA, 1977]. While this review contains information applicable to the few large industrial users of ETO for sterilization, it was primarily intended for medical facility applications (as defined in the Introduction).

There are approximately 8,100 hospitals in the U.S., of which about 7,200 are members of the American Hospital Association (AHA). The AHA estimates that 5,500 to 6,500 of its member hospitals have ETO gas sterilizers [AHA, 1976]. Whereas the majority of these sterilizers are small table top units, it is estimated that 1,000-2,000 large sterilizers (permanent installations with chamber volumes greater than 4 cu ft) are also in use [HIMA, 1977]. Most hospitals have more than one ETO sterilizer. In addition to hospitals, ETO sterilizers are also used in

smaller medical, dental, or veterinary clinics or facilities. While the exact number of sterilizers is not known, NIOSH estimates that it exceeds 10,000 units.

Of the almost 2.1 billion kg of ETO currently produced annually in the U.S. [Chemical & Engineering News, 1976], it is estimated that 500,000 kg (0.02% of the total produced) are used for sterilization within medical facilities [NIOSH, 1977]. This use is increasing.

NIOSH (1977) estimates that approximately 75,000 health care workers employed in sterilizer areas are potentially directly exposed to ETO. In addition, an estimated 25,000 others are "casually" exposed due to improper (or inadequate) venting of sterilizers and aerators, storage (or use) of improperly/incompletely aerated ETO-sterilized items, the physical arrangement of the sterilization facility or workroom (which necessitates passage in close proximity to a gas sterilizer or aerator), and mishandling or failure of the equipment (such as, leaking sterilizer door seals). Thus, the total number of exposed workers in medical and related facilities is estimated to exceed 100,000.

The principal items processed in such hospital "gas" sterilizers are air-powered surgical instruments, anesthesia supplies and equipment, cardiac catheters, endoscopes and other equipment containing lenses intended to be introduced into the human body, humidifiers and nebulizers, implantable body parts, electronic "pacemakers," ophthalmic instruments, x-ray supplies and related equipment, respiratory therapy supplies and equipment, some medications, reusable supplies, thermometers, and equipment contaminated by use in "isolation rooms" (i.e., containing patients with infections). Note some significant differences between the items sterilzied by the "user" and the items sterilized by the "vendor".

ETO is used in sterilizers produced by at least six different manufacturers. In certain small sterilizers it is used full strength, or diluted to a composition of 84% ETO with inert ingredients. In larger sterilizers a non-explosive sterilant mixture is commercially available, either 10% ETO/90% CO2, tradenamed Carboxide (TM), or 12% ETO/88% halocarbon. Halocarbon products, such as Refrigerant-12 (or -11), sold under tradenames such as Freon (TM) or U-con (TM), are used. The Federal standard for occupational exposure to dichlorodifluoromethane (Refrigerant-12) is 1,000 ppm (4,550 mg/cu m) as an 8-hour TWA concentration. No federal exposure limit exists for trichloromonofluoromethane (Refrigerant-11). The impact of the possible removal (for environmental considerations) of certain halocarbon-containing products from general use has not been considered in this report.

B. ETO Residues in Sterilized Medical Equipment

Residues (or byproducts) are produced mainly by two reactions of ETO: (a) from its slow chemical combination with water to form glycols, or (b) from its combination with chloride ion in the presence of water to form the chlorohydrin. Since even dry materials contain some moisture, it is apparent that glycol formation is unavoidable. Moreover, without the presence of some moisture, ETO sterilization cannot be effected. However, traces of glycols have been generally regarded as relatively harmless and permissible for human exposure.

The formation of persistent, toxic ethylene chlorohydrin in foodstuffs fumigated with ETO has been described (Wesley et al, 1965). Chlorohydrins are relatively non-volatile, and are considered highly toxic substances. The Federal standard (CFR 1910.1000) for occupational exposure to ethylene chlorohydrin is 5 ppm parts of air as an 8-hour TWA concentration. Attempts have been made to determine the conditions necessary for elimination of chlorohydrin residues from foods by volatilization and decomposition at elevated temperatures. In general, these attempts have not been successful. Nor would they be applicable for most sterilized medical products, particularly those which are heat sensitive.

While no reference to the formation and levels of ethylene chlorohydrin in medical facilities was found, the possibility that it will be present cannot be ignored.

The use of ETO for sterilization of medical devices and equipment raises a number of significant questions regarding (a) the possible entrapment of ETO in a plastic item that may then exert a toxic effect when placed in contact with living tissue, and (b) the effect of (sorbed) ETO on the physical and chemical properties of the rubber and plastic items. Plastic tubing that has been sterilized with ETO has caused significant hemolysis when placed in contact with human blood (Rose et al, 1953; Clarke et al, 1966; Bain and Lowenstein, 1967). For example, Bain and Lowenstein (1967) reported that when mixed leukocyte cultures were incubated in disposable plastic tubes sterilized with ETO, survival of the cells was severely affected by a toxic residue left on the plastic. The residue was dissipated only after 4 or 5 months' storage at room temperature, whereupon the survival of cells cultured in such stored tubes returned to values similar to those obtained with ultraviolet-sterilized (control) tubes.

O'Leary and Guess (1968), in their study of the toxic properties of medical plastics sterilized with gaseous ETO, presented data demonstrating the ability of ETO to remain entrapped in non-closed systems, such as, surgical tubing, gas washing bottles, plastic syringes, or plastic bottles, at various temperatures above the ETO boiling point. The hemolyzing ability of known amounts of ETO was determined. Freshly gas-sterilized plastic pharmaceutical products were shown quantitatively to produce blood cell hemolysis in proportion to the amount of ETO remaining in the plastic. Additionally, the effects of plasticizers of the ester type upon the sorption of ETO into polyvinyl chloride (PVC) products was also described. The residual ETO could present a hazard in the sterilization of such devices as plastic syringes. For example the residual ETO gas might have toxic effects due to some of its oxidation products.

ETO, if not removed, may be released at a later time (i.e., while under use) and cause hemolysis, erythema, and edema of the tissues. (Clarke et al, 1966; Bain and Lowenstein, 1967; O'Leary and Guess, 1968; Kulkarni et al, 1968; and Sykes, 1964). Other studies relating to the general problem of interaction of ETO with constituents of rubber and plastic have been reported. Downey (1950) demonstrated that the mercaptobenzothiazole vulcanization accelerators found in rubber reacted rapidly with ETO to produce (hydroxyethyl-mercapto)-thioazole, despite the fact that residual ETO concentration in the rubber tubing had been reported to have been dissipated after 5 hours' aeration. Little is known about the

parenteral toxicities of these compounds, or other possible reaction products in ETO-sterilized rubber.

Cunliffe and Wesley (1967) have shown that ethylene chlorohydrin was given off from PVC tubing 6 days after ETO sterilization. Gunther (1965) also demonstrated that high concentrations of ETO can be taken up by polyethylene, gum rubber, and plasticized polyvinylchloride. This re-emphasizes the general problem of entrapment of ETO within sterilized plastics. Reports of local skin irritation from contact with ETO-sterilized plastic items have appeared [ ]. This irritation can become severe if sensitization occurs. Items sterilized with ETO must be properly aerated before application to the human body in order to prevent such adverse reactions.

C. Alternatives to the Use of ETO Sterilization

The reported alternatives to ETO sterilization include: steam, dry heat, steam-formaldehyde, steam at sub-atmospheric pressure, wet pasteurization, radiation (including gamma-ray, X-ray, ultraviolet radiation, and electron beam exposure), liquid glutaraldehyde, liquid or gaseous formaldehyde, propylene oxide, liquid (or gaseous) beta-propiolactone, epichlorohydrin, ethylene imine, glycidaldehyde (i.e., 2,3-epoxy-1-propanal), hypochlorite, peracetic acid, methyl bromide, chloropicrin, and ozone. As a completely different strategy, single use, unsterilized disposable supplies have been considered by some. Although the safety of such items has been questioned, microbial contamination capable of causing disease is rarely present [HEW Rept., 1977].

A number of other chemicals or processes have been used (or considered) for sterilization of medically related items. For various reasons their general use is limited.

III. SUMMARY OF RESULTS OF FIELD STUDIES CONDUCTED IN MEDICAL FACILITIES

In February 1977, NIOSH conducted a limited field survey of hospitals to gain some perspective on situations related to the use of ETO sterilizers that might result in exposure of hospital staff and patients to ETO. The survey involved four hospitals in a metropolitan area, selected to represent both large and small health care facilities. Although a survey limited to only four medical facilities obviously can not be used with confidence as a basis for describing the conditions of the actual wide-spread use of ETO, it nevertheless does present a general impression of the usage of this compound, and some of the potential problems related to its use. The brief summary of the results of the survey presented below is from a more detailed report [Glaser, 1977].

In addition to the data from the NIOSH field survey, information was obtained from other government agencies including EPA, FDA, CDC, and NIH, and from the U.S. Army and U.S. Navy. Information was also made available by the Health Industry Manufacturers Association (HIMA), the American Hospital Association (AHA) and their member group, the American Society for Hospital Central Service Personnel, the Manufacturing Chemists Association (MCA), the Association for the Advancement of Medical Instrumentation (AAMI), the American National Standards Institute (ANSI), the American Society of Hospital Engineers (ASHE), ETO sterilizer and aerator manufacturers, and ETO "gas" manufacturers. From the NIOSH field survey and the above sources, the following account of the use of ETO in medical facilities, and the problems incident to such use, was developed. The results obtained in the NIOSH survey are in agreement with a similar study conducted by the U.S. Army in three of its hospitals (Army, 1977), and with data obtained by a study recently conducted by the American Hospital Assoication (Runnells, 1977).

A. ETO Sterilizer Use, and Number of Workers Potentially Exposed to ETO

The number of gas sterilizers per hospital observed in the survey ranged from 1 to 9 (average of 4), with each hospital having at least one large sterilizer in the Central Supply (CS) area. Smaller sterilizers were installed in one or more of the following locations: Operating Room (OR), Surgery, Cardiac Catheterization Laboratory (Cath Lab), Anesthesiology Department, Ear-Nose-Throat (ENT) Clinic, Dental Clinic, Intensive Care Unit (ICU), Urology Department, and Inhalation Therapy Clinic. Additionally, some hospital-related research facilities have gas sterilizers, used in connection with the banking and transplantation of human tissue and organs (i.e., Tissue Bank), and in veterinary facilities which maintain germ-free (i.e., gnotobiotic) animal colonies. The size of the hospitals in the NIOSH survey varied from 115 beds to 750 (immediately expandable to 1135), with the size of the average hospital being between 460 and 500 beds. Nationally, the number of gas sterilizers per "average" size (i.e., 200-300 beds) hospital appears to be 2. [Runnells, 1977]

The frequency of operation of the large sterilizers (i.e., Central Supply) varies from 3-4 cycles in 24 hours to approximately one cycle every

other day. Sterilizers in other areas generally were operated 2-5 times per week. These frequencies agree with data from other sources.

The number of personnel directly involved in the sterilization process varied widely. Some facilities reported that only a few (3-5) workers actually operate (i.e., load/unload) the sterilizers and aerators, and then generally only one person at a time. Such a situation occurred mostly in the CS and specific research-related areas (such as the Tissue Bank). The Cath Lab or OR technical staff appear to operate the sterilizers on a rotating, random or assigned, basis with a somewhat larger number of people (3-15) directly involved.

While the number of personnel who may be exposed during operation of the sterilizing equipment may be small, many more persons were potentially exposed for a variety of reasons. In one case, access to a main lavatory required that personnel walk directly in front of two large gas sterilizers and a large aerator. In other cases, persons passing between the workroom and stock room had to walk within 2 feet of the fronts of sterilizers located in a small room or area between the CS workroom and the CS stock/storage area. Another sterilizer was located in a small appendage (vestibule) to the OR workroom, adjacent to a doorway to a heavily trafficked hallway. Within a period of less than 15 minutes, more than 30 people were observed passing within 4 feet of the sterilizer and aerator. The aerator vented directly into the workroom, providing additional ETO exposure to workers in that area.

In some facilities, staff from various departments withdrawing sterile supplies from the Central Supply walk directly into the sterilizer or stock areas. ETO can enter stock areas from improper ventilation of aeration areas, or by the placing in stock of incompletely aerated items, resulting in diffusion of ETO into the ambient air.

While the number of potentially exposed persons may be large, depending on the actual physical arrangements, the number most likely to be exposed was estimated to be between 6 and 60 in each of the hospitals included in this study. This range agrees with an estimate obtained from a nation-wide survey of hospital central service/central sterile supply personnel conducted by the American Society for Hospital Central Service Personnel, of the American Hospital Association, in 1977.

B. Potential Exposure Situations Encountered in the Field Study

In addition to the potential for accidental exposures due to the physical arrangements, in a few cases problems were observed in installation, maintenance, and operation that could increase the unnecessary and/or inadvertent exposure of sterilizer operators to ETO. These are:

1. Improper or Inadequate Venting of Sterilizers:

a. Exhaust vent passed through a window and ended within 1 foot of the intake air duct of an air conditioner. While probably very little of the ETO is actually drawn back into the room by the air conditioner intake, it does illustrate a potential source of exposure.

b. An exhaust pipe from a sterilizer discharged into an open floor drain and gave off a cloud of vapors, including ETO, steam, Freon, and possibly other components (such as ethylene chlorohydrin) from the sterilizer into the machinery-room. A local ETO concentration of approximately 8,000 ppm was measured 1 foot above such a drain during a sterilization cycle. High local concentrations of ETO could be significantly reduced by minor modifications of the physical facility. In general, these situations do not result in elevated concentrations of ETO in the operator's breathing zone (BZ), but may contribute to the low background concentration of ETO in the sterilizing area.

c. Incomplete sterilizer flushing prior to opening its door allowed very high concentrations of ETO to enter the room immediately upon opening the door of the sterilizer. This could create a hazardous situation for the operator attending the door. Approximately 1,200 ppm was recorded at one installation immediately upon opening the chamber door.

d. An operator was able to open one sterilizer during use, to add or remove items, even though its chamber contained ETO. This represents, potentially, a very hazardous situation for the equipment operator.

e. Effluent gas from sterilizers and aerators is not treated to destroy all unreacted ETO as well as hazardous byproducts such as ethylene chlorohydrin, so as to render the resulting effluent innocuous. The development of an apparatus (such as a catalytic converter or combustion device) designed to ensure the complete destruction of unreacted ETO at the end of the sterilization procedure should be given high priority to ensure worker safety, as well as to prevent environmental pollution by ETO.

2. Improper Aeration of Sterilized Equipment:

a. With only one notable exception, all aerator cabinets in the medical facilities visited were vented directly into the room in which they were installed, or into the machinery space behind the cabinet. Airborne ETO concentrations of 300 to 500 ppm were not unusual above and behind some aerator cabinets.

b. Aeration was permitted on open shelves in the CS or OR workroom or stock room areas in one facility. Values of 25-50 ppm were measured 1 foot above stored items which had been sterilized more than 24 hours earlier.

c. Sterilized items were stored (following aeration?) in glass cabinets with tightly fitting doors in two facilities visited; an odor of ETO was obvious upon opening one of the cabinets, indicating improper aeration before storage, and lack of venting of the cabinet.

d. Exposure to ETO sterilizer gaseous products is of obvious concern, as some technicians reported skin irritation from contact with recently sterilized items, while others reported that their eyes "watered" while removing items from the sterilizer.

3. Inadequate Room Ventilation:

Ineffective or non-existant room ventilation was noted in some facilities, which allowed the buildup of ETO to a high level within the room. A 10 x 10 x 12 foot unventilated room housed a small sterilizer which was found to have a leaking door gasket. ETO concentration at the BZ near the sterilizer was greater than 1,000 ppm.

4. Malfunctioning or Leaking Equipment:

a. A leaking door seal (gasket) on a sterilizer caused an extremely high value of airborne ETO in a small, non-ventilated and closed room. Results are cited above.

b. ETO leaks were observed at some gas tank valves, threaded fittings, and near some chamber fittings and piping. This could be very serious for personnel entering poorly ventilated machinery spaces. Leaks producing instrument readings ranging from 400 to 3,000 ppm were located.

5. Improper Operating Procedures:

Sterilized items were removed from the sterilizer and transported on carts through a heavily congested hallway to the aerator or storage area. High rates of off-gassing, 200-300 ppm 1 foot above the cart, were noted during the movement of the sterilized items.

C. Measurement of Ambient Levels of ETO

The method used for the sampling and analysis of airborne ETO consisted of the absorption of ETO on charcoal, and gas chromatographic determination following desorption of the ETO with carbon disulfide [NIOSH Standard Completion Set T, 1976].

A series of measurements were obtained at various locations in rooms containing sterilizers and/or aerators, before, during, and after periods of operation of the equipment. Sampling was also conducted in other places of potential exposure, such as hallways, and vent exhaust areas.

In general, the concentrations of ETO in the employee's breathing zone (BZ) were below the current federal (OSHA) standard (CFR 1910.1000) of 50 parts per million (ppm) parts of air as a time weighted average (TWA) over an 8-hour day. General area air samples collected during a 5.5 hour period in front of a bank of two ETO sterilizers and an aerator contained only 1-2 ppm of ETO. However, many values were recorded which were at, or above, the ACGIH tentative Threshold Limit Value (TLV) for short term exposure (i.e. short-term exposure limit, STEL, of 75 ppm for short-time periods of less than 15 minutes). In fact, some very high short-term BZ values were observed, including a peak of 460 ppm within the first minute after opening the sterilizer door, lasting for about 1 minute. Even higher concentrations, for shorter periods, were noted on occasion. Although there is no absolute maximum or "ceiling" value for ETO, one should regard the recommended STEL as a level not to be exceeded.

D. Conclusions

1. The survey revealed a number of conditions which resulted in unnecessary, preventable exposure of hospital staff, and possibly patients, to ETO.

2. Many of the conditons were due to faulty equipment or improper operating procedures. These can be corrected by minor modifications, e.g., venting floor waste drains, replacing leaking sterilizer door seals or pipe joints, and improved work practices, including techniques for removing items from the sterilizer and aerator. In addition, the operator should avoid contact with both ETO gas and liquid which may remain in the flexible connecting lines when changing sterilizer gas cylinders. Protective gloves and goggles are available, and should be worn by personnel changing gas cylinders or cleaning up following an accidental spill. Gas cylinders should be changed in such a manner as not to expose the technician to ETO. Transfer carts should be used to remove sterilized items from large sterilizers, and gloves and forceps should be used whenever possible to remove items from small sterilizers. This will minimize the inhalation of ETO by the operator, and the possibility of dermal contact with ETO.

3. Other conditions resulted from improper installation and ventilation of sterilizers, aerators, or rooms in which such equipment was installed. This may require more extensive modifications such as additional venting ducts, high velocity vacuum pick-up ducts at the sterilizer door, improved room ventilation, and measures to exhaust decontaminated effluent in such a way as to prevent exposure within the hospital. An absolute minimum of 10 air changes per hour should be provided to all rooms containing gas sterilizers, aerators, or stored ETO-sterilized items. Air should not be recirculated in these spaces. Devices which completely destroy all unreacted ETO need to be developed.

4. Modification or engineering re-design of some sterilizer chambers may be necessary to assure effective displacement of the ETO gas following sterilization. It is desirable to have repeated air flushing of the sterilizer before it is opened. A power-operated door-opening device exists on some large sterilizers. It allows the operator to push a button, then walk away, while the sterilizer door slowly opens. If, after a suitable period of time to permit the chamber to "air out," a buzzer could call the operator back to unload the chamber, safer sterilizer operations would result. In lieu of the power door, an alternative might be for the operator, upon completion of the sterilization cycle, to open the chamber door approximately 6 inches and wait 5-15 minutes before removing a load from the sterilizer.

Aerators (which are forced-draft, warm air cabinets) should not vent directly into the room; rather, they should be connected to exhaust ducts to carry effluent out of the work area. Aeration performed under ambient conditions (i.e., in the open, at room temperature and atmospheric pressure) is not generally used, due to the lengthy time required to eliminate ETO "residues" from the sterilized material. In the absence of aerators, removal of ETO from sterilized items should be permitted only in dedicated, well-ventilated areas, such as in hoods.

5. Many items are being sterilized with ETO when they could be processed by other methods, e.g., steam or ultraviolet radiation.

6. Most (but not all) hospitals provide a "standard operating procedures" manual, containing ETO sterilization techniques, and conduct thorough on-the-job training programs including the sterilization procedures with ETO.

7. Medical and Health records of personnel employed in areas in which ETO is used were not maintained in all cases. The keeping of employee medical and health records, as well as occupational exposure records needs to be improved in some medical facilities.

8. Within the past few years, sterilizer and aerator equipment manufacturers appear to be making stronger recommendations in the instruction manuals, and in training aids, courses, seminars, and in advertising as to the proper ventilation, location, use, etc., of sterilizers and aerators. Some early equipment manuals did not contain such recommendations. It is necessary that architects and designers of health care facilities, supervisors of the equipment operators, facility safety staff, industrial hygienists, etc., rigorously follow the recommendations and instructions stated by the equipment manufacturers, to protect the worker from the hazards of ETO exposure.

IV. BIOLOGIC EFFECTS OF EXPOSURE TO ETO

A. Effects in Animals and Lower Biological Systems

1. Acute Toxicity

Acute lethality studies in animals have been performed in four species and by five different routes of exposure. A wide array of responses follow acute exposure to ETO. These include: nausea, salivation, vomiting, diarrhea, lacrimation, nasal discharge, edema of the lungs, gasping, labored breathing, paralysis (particularly of the hind quarters), convulsion, and death. Deaths which occurred shortly after exposure to ETO were attributed primarily to lung edema, whereas delayed deaths often resulted from secondary infection of the lungs along with general systemic intoxication (Patty, 1963).

a. Inhalation

Of the acute lethal studies, the inhalation studies of Jacobson et al (1956) are the most pertinent to occupational exposure. In those experiments, exposures to various ETO concentrations for 4-hour periods resulted in LC50's of 835 ppm for female mice, 1,460 ppm for male rats, and 960 ppm for male dogs. Hine and Rowe (1973) compiled data on inhalation exposures to illustrate the variable lethal response by species, concentration, and duration of exposure. (Table 1). In general, no deaths were reported at ETO exposure levels of 250-280 ppm for rats, guinea pigs, rabbits, cats, and dogs.

b. Oral and Parenteral

LD50's resulting from oral and parenteral exposures ranged between 141 and 631 mg/kg, and are listed in Table 2. Additional support for this range is provided by Patty (1963) who reported LD50's (following intragastric administration of 1 per cent aqueous solutions) of 330 mg/kg for rats, and 270 mg/kg for guinea pigs. Weil et al (1963) reported the single oral LD50 for rats of 330 (range 290-360) mg/kg.

In another study reported by Patty (1963), a single 200 mg/kg dose of ethylene oxide given intragastrically (as a 10 per cent solution in olive oil), killed all 5 rats in the group, whereas all animals survived a dose of 100 mg/kg.

c. Tissue (including eye) Irritation

The results of studies to determine the acute eye and tissue irritant properties of ETO (in aqueous solution) are summarized in Table 3 (Bruch, 1973). The Draize (1965) system of evaluation, consisting of estimates of the highest doses having no overt actions at various sites after various methods of administration, was used in these studies.

Thickening of skin and ecchymoses followed subcutaneous injection in the guinea pig, while mild irritation occurred after intradermal injection and dermal application in the rabbit. No local reactions were observed after intramuscular injections. As illustrated in Table 3, the irritant properties varied with both concentration and total dose.

Ocular Effects:

The cornea and conjunctivae appear to be less sensitive to ETO than the skin of the rabbit. The reactions to the dermal and ocular applications most closely resemble those seen in actual occupational exposures.

Woodard and Woodard (1971) reported slight irritation in the rabbit eye, with lacrimation and conjunctival erythema. In a series of investigations by McDonald et al (1973), ETO in a balanced salt solution was administered by both ocular instillation and injection into the anterior chamber of the rabbit eye. The maximal concentration which did not produce substantial ocular pathology varied with the specific ocular tissue examined and the route of administration, ranging from 0.1% to greater than 20%. (Table 4). Irritant effects observed after acute ocular instillation were discharge, iritis, corneal cloudiness and damage as evidenced by fluorescein staining. Conjunctival congestion, flare, iritis, corneal opacity, and fluorescein staining were observed after administration into the anterior chamber. Injection into the anterior chamber had more effect on the iris, the lens, and the retina than instillation into the conjunctival sac. Conversely, the latter procedure affected the cornea and the conjunctivae more markedly than the former. Neither differential effect is exceptional. (Alcon Submission, 1973)

The irritation potential of a commercial ophthalmic ointment, the components of which were sterilized with ETO, was compared with that of the product prepared from non-sterilized components. The materials were applied to the eye of the rabbit in a 6-hour heavy dosing regimen (0.5 mg/dose at 20-minute intervals for 6 hours), and in a 5-day dosing regimen more comparable to clinical use (0.1 mg/dose, 5 applications/day for 5 days). Minimal conjunctival congestion was seen after the applications of ointment, but no difference was seen between the sterilized and non-sterilized products. (Alcon Submission, 1973)

2. Sub-Chronic Toxicity

a. Oral and Parenteral

ETO was administered to rats by gavage, 5 days/week, for 3 or 4 weeks, (Hollingsworth et al, 1956), and to rats and dogs by daily subcutaneous injections for 30 days (Woodard and Woodard, 1971). The results of these studies are summarized in Table 5. The no-effect levels for the rat were 30 mg/kg by the oral route, and 18 mg/kg by subcutaneous injection.

b. Inhalation

Hollingsworth et al (1956) and Jacobson et al (1956) conducted studies in which various animal species were exposed repeatedly to ETO vapor at concentrations ranging from 100 to 841 ppm. The studies are summarized in Table 6. At 100 ppm there was anemia in 1 of the 3 dogs, and 8 of 30 mice and 3 of 20 rats died during 130 exposures of 6-hour duration. At 113 ppm, no rats (of 40), guinea pigs (of 16), rabbits (of 4), or monkeys (of 2) died during 122 to 157 exposures of 7-hour duration. The male rats did have some depression of their growth. Rats of both sexes exhibited increased lung weight. However, at 204 ppm growth depression was noted, an appreciable number of rats died of secondary respiratory infection, and rabbits and monkeys developed posterior paresis. Rats and guinea pigs exhibited increased lung weights also. At higher concentrations more serious conditions developed, including severe nervous and respiratory effects and degeneration of testicular tubules.

On the basis of these studies, Hine and Rowe (1973) proposed permissible exposure limits of 100 ppm for repeated exposures of 4 hours/day for a 2-week period, and 50 ppm for 7-hour exposures on a continuing basis.

3. Chronic Toxicity

No chronic test data could be found.

NIOSH has been informed that a 2-year vapor inhalation study on rats began on April 27, 1977, at the Carnegie-Mellon Institute of Research, Pittsburgh, Pennsylvania. That study is supported by industry and will include cytogenic, mutagenic, and teratogenic evaluations, and a one-generation reproduction study. A similar 2-year study on mice will also be performed. The National Cancer Institute, National Institutes of Health (NIH) is also supporting long term studies on ETO. The NIH studies are underway at Industrial Bio-Test Laboratories, Northbrook, Illinois.

4. Carcinogenic, Mutagenic, Reproductive, Teratogenic, and Metabolic Studies

a. Carcinogenicity

No standard long-term carcinogenicity bioassays have been reported, although two screening experiments have been conducted. Walpole (1957) subjected 12 "stock" rats to repeated subcutaneous injections of 1 g/kg (bw) ETO in arachis oil. The exact dosing schedule was not reported, although the period of injection was 94 days. The animals were maintained for their lifetimes, during which no local sarcomas or other tumors were observed. In other studies, Van Duuren et al (1965) applied (by brush) 0.1 ml of a 10% solution of ETO in acetone three times each week onto the clipped dorsal skins of 30 female ICR/Ha Swiss mice. The animals were 8 weeks of age at the start of the skin painting, which was continued for

their lifetimes. The median survival time was 493 days; no skin tumors were observed.

Two other studies related to carcinogenicity have been conducted. Jacobson et al (1956) exposed rats, mice, and dogs to 100 ppm of ETO (6 hours/day, 5 days/week) for 6 months. There were no significant pathologic changes suggestive of a carcinogenic response. The only observed effects were decreases in red blood cell count, hemoglobin, and hematocrit in dogs. It is felt by scientists at the National Cancer Institute and the International Agency for Research on Cancer that this study was not conducted for a sufficiently long period to test the possibility that ETO causes cancer. In the other "study" (actually, a retrospective analysis of events), 86 female Swiss-Webster germ-free mice were inadvertently maintained on ETO-treated ground-corncob bedding for 150 days, and were then moved to untreated bedding for the remainder of their lives (maximum lifespan = 900 days). Tumors were observed at various sites in 63 mice. In contrast, no tumors were reported in 83 female mice that had not been exposed to the ETO-treated bedding, but were observed for 100-160 days. (Reyniers et al, 1964). The most common tumors in the exposed group were ovarian, lymphoid (malignant lymphoma), and pulmonary. While the effect is noteworthy, it is not known whether it was due to ethylene oxide, ethylene glycol or some other unknown chemical (or factor).

b. Mutagenicity

Experimental attempts to induce mutations in at least 14 different species through exposure to ETO have been reported. An increased frequency of mutations was observed in 13 of the test species, the exception being a bacteriophage of Escherichia coli [Loveless, 1959].

The data for the species, loci/locus, mutation type, exposure time, exposure route, exposure concentration, and the significant results are summarized in Table 7. The data indicate that several different types of genetic damage may be induced following exposure to ethylene oxide. The induction of point mutations has occurred in both procaryotic and eucaryotic organisms [Table 7]. While the point mutations probably were of the base-pair substitution type in Salmonella typhimurium, the mutational spectra have not been well characterized at the molecular level in other species [Embree, 1975]. In Drosophila melanogaster, the classes of induced mutations included sex-linked lethals, visibles, and "minutes" [Bird, 1952; Fahmy and Fahmy, 1956; Fahmy and Fahmy, 1970; Nakao and Auerbach, 1961]. In plants, the classes of heritable changes include mutations at the chlorophyll and waxy loci and chromosomal abnormalities [Faberge, 1955; Ehrenberg et al, 1956; Ehrenberg et al, 1959; MacKey, 1968; Sulovska et al, 1969; Lindgren and Sulovska, 1969; Roy et al, 1969; Roy and Jana, 1973; Jana and Roy, 1975].

Some evidence suggests that ETO may induce heritable changes in mammals, although no direct observations of such changes, comparable to those observed in lower organisms, have been reported in mammalian systems. Following three 7-hour/day exposures to 250 ppm of ETO, isochromatid and chromatid gaps and breaks were observed in bone-marrow cells sampled 24 hours after the last exposure of the rats [Embree, 1975]. The frequency of gaps and breaks as a function of total exposure time or

total dose was not reported. Following a single oral dose of 9 mg/kg, a significant number (P less than 0.007) of chromosomal abnormalities was observed in the red marrow cells of the femurs of rats. Neither dose-response data nor the rate of return to a normal chromosomal picture was reported [Embree, 1975].

The dose-response relationship for the induction of micronucleated cells in femoral marrow of Long-Evans rats as a function of the concentration of inhaled ETO was studied by Embree (1975), using groups of 5 rats exposed to 0, 10, 25, 50, 250, or 1,000 ppm of ethylene oxide for 4 hours. A statistically significant increase (P less than 0.05) of micronuclei were induced at the 50, 250, and 1,000 ppm levels. While several alkylating agents which are known to induce mutations are also known to induce the formation of micronuclei in bone marrow cells, the biological significance of this adverse effect is poorly defined. These results suggest that the current federal standard of a time-weighted average (TWA) concentration of 50 ppm parts of air for an 8-hour day may not protect exposed employees from all adverse effects resulting from ETO exposure.

The most plausible molecular basis for the induction of heritable changes and other genetic effects following exposure to ethylene oxide is the alkylation of cellular constituents, including deoxyribonucleic acid (DNA). The highly-strained 3-membered ring of the epoxide is broadly reactive toward all classes of cellular nucleophiles. Reactions of ETO with protein [Frankel-Conrat, 1944], and with nucleic acid [Frankel-Conrat, 1961; Ehrenberg et al, 1974] have been measured. The primary identifiable product of the reaction of ETO and DNA was 7-hydroxyethylguanine, although a number of other minor products would also be anticipated. Since the occurrence of these chemical reactions is a consequence of the intrinsic characteristics of the chemical structures, it seems probable that analogous reactions may occur in humans who are occupationally exposed to ETO. These spontaneous reactions result in the formation of covalently altered biomolecules which may possess abnormal functional properties.

In addition to the spontaneous reactions, ETO may also be consumed via detoxifing enzyme-catalysed reactions such as epoxide hydratase and glutathione-S-alkyl tranferase [Arais and Jakoby, 1976]. The rate of consumption of ETO by such enzyme reactions would be a non-linear function of the local concentrations of the substrate. Since the non-catalyzed half-time of the reaction of ETO with water is about 4,200 minutes, whereas the *in vivo* half-life in the mouse is only about 9 minutes [Ehrenberg et al, 1974], it appears that such enzymatic reactions may rapidly detoxify a large fraction of the absorbed doses in mammals. At a minimum, the greatly reduced half-life of ETO *in vivo* suggests a non-linear dose-response relationship for induction of genetic effects in mammals due to the existence of saturable detoxifing mechanisms. Further research is required to establish the relative magnitudes of the competing reactions as functions of the doses and of the exposure times.

The observations of: (a) heritable alterations in at least 13 different species, (b) alterations in the structure of the genetic material in somatic cells of the rat, and (c) a covalent chemical reaction between ETO and DNA, support the conclusion that continuous occupational

exposure to significant concentrations of ETO may induce an increase in the frequency of mutations in human populations.

Embree [1975] and Ehrenberg et al [1974] have attempted to estimate the degree of genetic risk to human populations exposed to ETO by comparing the results with the effects of ionizing radiation, and expressing the result in terms of the "rad-equivalent." Embree's estimate (100 mrad-equivalences/ppm-hr) was based on the frequency of micronuclei in bone marrow following exposure to graded doses of ethylene oxide. At present, the mechanism of generation of micronucleated cells in bone marrow is not known, although it is possible that these cells may arise from either the non-disjunction of the chromosomes during mitosis, or malformation of the spindle. While it is conceivable that somewhat related processes may occur in functionally distinct tissue, such as spermatogonia, neither quantitative nor qualitative evidence is available to indicate the magnitude of the effect in the genetically important cell-types following exposure to ethylene oxide. Consequently, Embree's estimate appears to be highly speculative and with minimal theoretical or experimental basis.

The estimate by Ehrenberg et al [1974] of the risk to humans (reported as 20 mrad-equivalences/ppm-hr) is based on the assumption that the rate and mechanism of induction of mutations affecting chlorophyll in metabolically dormant barley seeds were equivalent to the rate of induction of specific locus mutations in the metabolically active tissues of the testes of mammals. The reliability of this estimate as a quantitative measure of genetic risk to human populations exposed to ETO is open to question. In addition to the obvious physiologic differences between plants and mammals, it should be noted that forward chlorophyll mutations in barley seeds may occur at several hundred loci while the specific locus test is limited to one locus or a small number of loci [Ehrenberg et al, 1974]. Consequently, the relative risk estimated by Ehrenberg et al may be in error by several orders of magnitude. Thus, the estimates of genetic risk by Embree [1975] and Ehrenberg et al [1974] probably do not, by themselves, provide a satisfactory basis for the development of occupational exposure standards. Nevertheless, the observations of induction of heritable changes in a broad spectrum of biological organisms, and of the intrinsic chemical reactivity of ETO with cellular constituents, suggest that ETO may have a significant influence on the spontaneous mutation rates of human populations.

Kalling [1967] briefly reported data, obtained from an experiment performed by Ehrenberg and Hallstrom, on the frequency of pathological mitoses observed in phytohaemaglutinin-stimulated lymphocytes of 7 workers who had been "strongly affected" by ETO following an industrial accident 18 months earlier. Analysis of from 6 to 26 metaphases from each individual suggested an increased frequency of pathological mitoses relative to the frequency in 10 non-exposed workers. Kalling's brief description of the results are insufficient to draw substantive conclusions. However, this report of induction of chromosomal abnormalities in humans is consistant with the observations of Embree [1975] in the rat.

c. Reproductive Effects/Teratogenicity

No data concerning reproductive or teratogenetic effects were found for ETO. Ethylene chlorohydrin (2-chloroethonol), a reaction product of ETO, was shown to cause pronounced teratogenic effects (i.e., anterior hydrophthalmos, a form of buphthalmia) when administered to the developing chicken embryo. The compound was administered in water at pre-incubation (0 hours) or at 96 hours of incubation, at a number of different doses. It should be noted at this point that the limited animal test data on the carcinogenic potential of ethylene chlorohydrin suggests no increased incidence (over controls) when the compound was fed (Ambrose, 1950), or injected subcutaneously (Mason et al, 1971) into rats. Ethylene chlorohydrin is to be tested for effects on reproductive processes by inhalation and by skin painting, under NCI contract.

Studies have shown chromosome aberrations in rat bone marrow cells following exposure to ethylene chlorohydrin (Isakova et al, 1971, and Semenova et al, 1971), and base-pair substitutions (but not frameshift mutations) in Salmonella (Rosenkranz and Wlodkowski, 1974). Ethylene chlorohydrin also induced mutations in bacterium Klebsiella (Voogd and Van Der Vet, 1969).

d. Metabolism.

A comprehensive study designed to isolate and characterize the metabolites of ETO in either lower or higher life forms has not been identified in the literature. However, Frankel-Conrat (1961, 1944) has characterized the spontaneous chemical alkylation of a protein (egg albumin) and viral ribonucleic acid. Brookes and Lawley (1961) characterized the reaction of ETO with guanine. More recently, Ehrenberg et al (1974) have reported the results from several experiments on the fate of inhaled tritium-labeled ETO in mice. The biological half-life was found to be about 9 minutes in the mouse, indicating a rapid metabolic breakdown of the molecule. The second-order rate constants for the reactions of ETO with DNA, and with liver "interphase" protein were found to be 0.9 and 3.3 1/g-hr, respectively. The hydroxyethylated DNA was observed to undergo a slow depurination reaction, a possible pre-mutation lesion, with a half-life of 340 hours. Following inhalation of tritiated ETO, radioactivity (in unidentified chemical form) was found to be associated with proteins isolated from lung, liver, kidney, brain, spleen and testes. Seventy-eight per cent of the absorbed dose was excreted into the urine within 48 hours of the inhalation exposure. Other than the possible isolation of small amounts of 7-hydroxyethyl guanine from the urine, evidence for the alkylation of DNA in vivo was not reported. Since urinary 7-hydroxyethyl guanine may also arise from the alkylation of RNA, the fraction of total absorbed dose which alkylates the genetic material remains to be determined.

The study confirms that ETO is readily absorbed via the respiratory tract and is widely distributed throughout, and reacts with, components of body tissues.

B. Effects in Humans

1. Acute Toxicity:

Zernik (1933) extrapolated results of animal tests to approximate lethal dosages of ETO for man. He estimated that an exposure to 0.5 mg/l (278 ppm) for 1 hour would be objectionable, but that the same concentration for a day would be dangerous. He further speculated that 1.0 mg/l (556 ppm) would be sufficient to cause sickness and death after a number of hours of inhalation. Systemic poisoning due to inhalation exposure to ETO is rare, but 3 cases have been reported in which headache, vomiting, dyspnea, diarrhea, and lymphocytosis occurred (Hine and Rowe, 1963). Hess and Tilton (1950) observed a similar case. The nausea and vomiting may persist for several hours if untreated. There is also evidence that high vapor concentrations can be sufficiently irritating to cause pulmonary edema in man [Thiess, 1963]. Inhalation of high concentrations of ETO for even short exposure periods can produce a general anesthetic effect in addition to coughing, vomiting, and irritation of the eyes and respiratory passages. Early symptoms are irritation of the eyes, nose, and throat and a "peculiar taste"; effects which may be delayed are headache, nausea, vomiting, dyspnea, cyanosis, pulmonary edema, drowsiness, weakness, incoordination, electrocardiographic abnormalities and urinary excretion of bile pigments.

Thiess (1963) reported on his observations in 41 cases of excessive industrial exposure to ETO, mainly due to accidents. The principal effect after excessive exposure to the vapor was vomiting, recurring periodically for hours, accompanied by nausea and headache. Short exposure to high concentrations of ETO resulted in irritation of the respiratory passages leading to bronchitis, pulmonary edema, and emphysema.

At least two additional cases of accidental poisoning in man by ETO appear in the literature. Blackwood and Erskine (1938) reported cases in 6 men who became ill while working in a ship compartment adjacent to one being fumigated with a commercial mixture of 10% ETO/90% CO_2 [Carboxide]. Ten female employees were reported (Anon, 1947) to have been "overcome" by ETO used as a disinfectant in a California food plant. The Department of Public Health of the State of California issued a report on this incident. Attempts at locating the report have been unsuccessful to date. In neither of these events was the concentration of ethylene oxide known. In both, the gross symptoms of the persons affected included headaches, nausea, vomiting, and respiratory irritation. No permanent ill effects were reported.

A number of dermatologic conditions due to exposure to ETO have been reported. These include:

Skin burns occurred in workers after prolonged contact (duration unspecified) with a 1% solution of ETO in water (Sexton and Henson, 1949). Skin contact with solutions of ETO caused characteristic burns on human volunteers. After a latent period of 1 to 5 hours, edema and erythema, progressing to vesiculation with a tendency to coalesce into blebs, and desquamation was followed by complete healing within 21 days, usually without treatment. In some cases, residual brown pigmentation occurred. Application of the pure liquid to the skin caused frostbite (due to rapid

evaporation of the ETO); 3 of the 8 volunteers became sensitized to ETO solutions.

Human experience indicates that extensive blister formation occurs following even brief contact with 40-80% aqueous solutions of ETO. Lesser or greater concentrations produced blisters only after more prolonged contact. ETO has been reported to be retained in rubber and leather for long periods of time, and not to be removable by washing. Wearing contaminated footwear has resulted in serious foot burns (Phillips and Kaye, 1949). Rubber shoes were donned by laboratory workers immediately after the shoes had been sterilized with ETO. Apparently the ETO had dissolved in the rubber and then diffused out to contact the skin. No such incidents occurred when similar articles of clothing were aired until free of ETO before being worn.

Contact of liquid ETO with exposed skin does not cause skin irritation immediately, but blistering of the skin develops after a time if shoes or clothing wet with ETO are not removed promptly. Contact of liquid ETO with the eyes can cause severe burns. A workman exposed to ETO in an unstated manner was reported by McLaughlin (1946) to have suffered a corneal burn, which was said to have healed promptly.

In 1963, Thiess reported that he had observed the effects of an accidental forceful blast of gaseous ETO that struck a nurse in the eye, nose and mouth, from a gas sterilizer that employed a cartridge of ethylene oxide. This caused no immediate discomfort, but within 2 hours one eye became mildly uncomfortable, and one nostril felt sore and obstructed. The only abnormality in the eye at that time was keratitis epithelialis consisting of fine gray dots in the corneal epithelium in the palpebral fissure. These dots stained with fluorescein. In 3 hours the foreign-body type irritation in the affected eye and soreness in one nostril were enough to interfere with working. The foreign-body type of discomfort reached the maximum 9 to 10 hours after the exposure, but by 15 hours pain began to subside, and in 24 hours the eye was entirely normal, both subjectively and by slit-lamp examination. Soreness in the nose persisted a little longer, but at no time was there respiratory distress or alteration of taste or sensation in the mouth.

Another report by Thiess (1963) described an instance of a squirt of liquid ETO into one eye of a patient, treated immediately with copious irrigation with water; this resulted only in irritation of the conjunctivae lasting for 1 day. Thiess quoted Hollingsworth et al (1956) as having observed intense conjunctivitis in rabbit eyes after application of only one drop of ETO. This condition cleared in 4 days.

2. Chronic Effects

a. Case Histories

Exposure to low concentrations of gaseous ETO may cause delayed nausea and vomiting [Hess and Tilton, 1950]. Continuous exposure to even low concentrations will result in a numbing of the sense of smell [Jacobson et al, 1954].

Protracted contact of the gas or the liquid with the skin was observed (Thiess, 1963) to cause toxic dermatitis with large bullae. There appeared to be little or no tendency toward development of allergic dermatitis. Evidence of irritation was seldom seen in the respiratory tract, contrary to what others had reported, and cough was not a warning symptom. The eyes of workers excessively exposed to ETO vapor occasionally showed slight irritation of the conjunctivae, but there were no injuries of the cornea, and no special treatment was felt to be needed. Thiess (1963) observed no lacrimatory effect that could be considered a warning symptom.

Workers have developed severe skin irritation from wearing rubber gloves which had absorbed ETO; redness, edema, blisters and ulceration were observed (Royce and Moore, 1955). There is considerable evidence [Sexton and Henson, 1949, 1950] which suggests that repeated skin contact with dilute or concentrated aqueous solution of ETO results in the development of skin sensitivity of long duration.

The conclusions of Sexton and Henson (1950) are listed:

(1) The magnitude of the skin injury from ETO seems to be influenced and determined by the length of time of contact and the concentration. The most hazardous aqueous dilutions seem to be those in the 50% range.

(2) Pure anhydrous liquid ETO does not cause primary injury to the dry skin of man.

(3) Rapid vaporization of pure liquid ETO sprayed on the skin results in a freezing reaction of the skin.

(4) Repeated skin injury can result in such delayed sensitivity manifestations as the "flare-up" and "spontaneous flare-up" reactions.

Aqueous solutions of ETO in prolonged contact with the skin are well known to be vesicant (owing presumably to the reactivity of ETO with tissue proteins). The volatility of ETO, and the fact that there are rarely circumstances in which considerable concentrations are held in protracted contact with the eye may account in part for the mildness of ocular injuries which have been observed so far. The comparative insensitivity of the cornea to damage by ETO, shown in Tables 3 and 4, undoubtedly plays a part here also. The highly crosslinked structure of collagen quite possibly contributes to this relative insensitivity of the cornea; the high concentration of glutathione present in the cornea may be a factor also in this insensitivity to injury by ETO.

Delayed sensitization reactions have been reported [Shupak, unpublished] in humans, as has one case of anaphylaxis resulting from residues of ETO in renal dialysis equipment (Poothullil et al, 1974).

b. Epidemiologic Studies

Few studies are known which relate directly to long-term exposure to ETO in medical facilities. Correspondence from the Veterans Administration (VA) (Cobis, 1977) indicates a very low incidence of reports of health incidents relating to use of ETO in VA medical facilities. These consist of "1 patient with minor face irritation, and 12 employee incidents, including watering eyes, nausea, and skin irritation." Cobis reported that the "incidents are now being evaluated by the medical staff to see if they can be verified or if there was any sequela." The VA experience is based on an estimated 400,000 sterilization cycles in which ETO was used in 162 hospitals and 7 outpatient clinics over an average of 8.2 years (total of accumulated years is 1,334). The VA estimates that their facilities are processing 5 million packages of sterile supplies in 79,000 sterilization cycles per year (an average of 63.3 packages per cycle).

A small retrospective morbidity study was conducted on a group of 37 employees who were exposed to ETO levels of approximately 5-10 ppm for a period of 5-16 years in an ETO production plant. (Joyner, 1964). The "exposed" group consisted of males between the ages of 29 and 56. Mean exposure to ETO was 10 2/3 years, with only 3 workers exposed for less than 5 years, and 2 workers exposed for more than 15 years. The "control" group was selected from among volunteers who were participants in the periodic physical examination program, with no attempt at selection except to match ages with those of the study group. Mean length of service (in production units) of the control group was 11 2/3 years. No attempt was made to categorize the specific types of chemical exposures (to agents encountered in the petrochemical industry) of the "control" group. The study included a review of medical records (with scoring of such factors as number of visits to the dispensary, days "lost" from work, and number and type of injury reported),and a "problem-oriented" tabulation of specific illnesses diagnosed by the physicians, and comparison of the morbidity rates. In general, the ETO workers had a better health record than the "control" group. While such a study might have detected major toxic effects, the sample size, "control" group, dose levels, duration of exposure and observation period were not sufficient to assess carcinogenic potential or more subtle toxic effects.

A study by Ehrenberg (1967) involved hematologic and chromosomal investigations of a group of personnel of a factory manufacturing and using ETO. Early in 1960, a preliminary hematological investigation was performed. Twenty-eight persons from the part of the factory where leakage of ETO from tube joints, pumps, etc, was possible (and occurred at least occasionally) were investigated, and 26 persons from other departments working with ETO were used as controls. In addition, 3 persons accidentally exposed to high concentrations of ETO were studied; these were included in the "exposed" group. The subjects were males of about the same age (i.e., 45 years). The "exposed" persons had been active in the ETO department for periods of time varying from 2 to 20 years (avg. 15 years).

Since certain differences were found between exposed and control persons, the ventilation of the factory was improved. A second

analysis was undertaken in the following winter (termed "1961 investigation") comprising all male employees of the factory, now classified as follows:

(1) 66 persons not working in contact with ETO (including the 1960 "control group").

(2) 86 persons intermittently working in ETO premises.

(3) 54 persons who had worked in contact with ETO for some period of time.

(4) 37 persons permanently working in the ETO area (including the 1960 "exposed group").

(5) 8 persons exposed to high concentrations of ETO during repair and clean-up operations following a tube break in a factory. Two of the group required immediate hospitalization for respiratory difficulties.

A comparison of exposed and control persons suggested that:

(1) Persons intermittently exposed to ETO during several years exhibited higher absolute lymphocyte counts than did the control group in the initial study population. Following improvement of ventilation this difference became smaller, although it was still significant 1 year later in the same persons. No significant difference between the exposed and the control groups was found after the study population was enlarged, either because the difference found between the groups selected for the first analysis was accidental, or because younger persons with higher lymphocyte counts were introduced into the control group in larger numbers than into the exposed group.

(2) Certain cell abnormalities were found in the exposed group (3 cases of anisocytosis, 1 of leukemia), that did not appear in the control group.

(3) Lower hemoglobin values were found in the exposed group, in addition to a few cases of slight anemia.

(4) Persons exposed accidentally (group 5 of the later study population) for short periods of time to high concentrations of ETO exhibited higher numbers of chromosomal aberrations than a comparable control group.

NIOSH has been informed that Ehrenberg currently has plans to "follow up" members of the study group.

NIOSH is currently initiating a study of approximately 2,500 workers potentially exposed to ETO during its manufacture and/or use. The study will include mortality, morbidity, and reproductive data if possible.

3. Sensitization Response.

Allergic-type reactions have been reported in workers accidently sprayed with ETO in solution (Sexton and Henson, 1949), and in patients exposed to improperly aerated dressings (Hanifin, 1971). ETO (1% solution) was not a contact sensitizer in the occlusive patch test in guinea pigs, nor did a 0.1% ETO solution produce sensitization by the intracutaneous route in this species (Woodard and Woodard, 1971).

In recent skin irritation studies, delayed sensitization of human subjects developed in response to ETO contained in polyvinyl chloride blocks and films, and in vaseline [Shupak, unpublished data]. This finding supports an earlier report of anaphylaxis from products of ETO sterilization of renal dialysis equipment (Poothullil et al, 1974, and Avashia, 1975).

4. Hemolytic Effects.

Hemolysis has been reported (Hirose et al, 1963 and Stanley et al, 1971) with ETO sterilized devices used for blood perfusion, and with devices used for IV administration in patients. Anemia was reported (Woodard and Woodard, 1971) to have developed in dogs in a 30-day subcutaneous toxicity study with ETO in saline solution. Dogs injected with 6-36 mg/kg daily developed anemia; the severity was dose-related. Examinations were performed prior to, and at the end of, 30 days of dosing. Hence, effects occurring earlier would not have been detected. Therefore, a re-examination of the hematologic effects appeared to be in order. Beagle dogs were dosed intravenously with ETO/glucose solution daily for 3 weeks. Doses were increased from 3-60 mg/kg at intervals. Three controls received only glucose. No evidence of anemia was detected (Balazs, 1976). Further clarification of these apparently conflicting results is needed.

Ehrenberg (1967) observed lymphocytosis in workers exposed to ETO.

C. Tabulation of Biologic Effects of ETO

The following tables summarize the bio-effects data described in the earlier section of this report:

1. Summary of Acute Response of Animals to Inhalation Exposure to Ethylene Oxide
2. Acute Toxicity of Ethylene Oxide (Administered in Aqueous Solution) to Mice, Rats, and Rabbits
3. Summary of Tissue Irritation Studies With Ethylene Oxide
4. Maximum Concentration of Ethylene Oxide Not Producing Substantial Ocular Pathology in Rabbits
5. Summary of Subchronic Toxicity of Ethylene Oxide
6. Results of Repeated Inhalation Exposure of Animals to Vapors of Ethylene Oxide
7. Genetic and Allied Effects of Ethylene Oxide

Table 1. Summary of Acute Response of Animals to Inhalation Exposure to Ethylene Oxide

ppm by vol. in air	Exposure Time (hr)	Animal	Results
250-280	8	Guinea pig	Slight respiratory changes; no deaths.
	48	Guinea pig	An occasional death.
560-600	7	Guinea pig, cat, and dog	No deaths
	8	Guinea pig	An occasional death.
	22	Guinea pig and cat	Death during (or following) exposure.
	22	Rabbit and dog	No deaths.
710	4	Dog	0/3 died in 14 d.
1,100	5	Rat, guinea pig, rabbit	Moderate injury, no deaths.
	8	Guinea pig, dog, and rabbit	Slight injury, no deaths.
	8	Rat and cat	Death within 24 hr.
1,300-1,400	8	Guinea pig	Majority died in 1-8 d.
	4	Dog	3/3 died first day.
2,200	1.5	Cat	Injurious, no deaths.
	3	Cat	Death within 24 hr.
	4	Guinea pig	Injurious, few deaths.
	4	Rabbit	Injurious, no deaths.
	4	Dog	Death within 24 hr.
3,000	1	Guinea pig	No deaths.
	3	Guinea pig	Death of majority within 1 to 8 d.
	8	Guinea pig	Death of majority within 24 hr.
4,000*	4	Rat	No deaths (of 6).

Table 1 (Continued). Summary of Acute Response of Animals to Inhalation Exposure to Ethylene Oxide

7,000	20 min	Guinea pig	No evidence of injury.
	1	Guinea pig	Death of majority within 1 to 8 d.
	2.5	Guinea pig	Death within 24 hr.
8,000*	4	Rat	6/6 died.
14,000	10 min	Guinea pig	No evidence of injury.
	20 min	Guinea pig	Majority died in 1 to 8 d.
	1	Guinea pig	Death within 24 hr.
51,000-64,000	5 min	Guinea pig	Majority died in 1 to 8 d.
	10 min	Guinea pig	Death in 24 hr.

Notes: Data compiled by Hine and Rowe (1963) from the studies of Jacobson et al, (1956), Hollingsworth et al, (1956), Waite et al, (1930), and Flury and Zernik, (1931). *Data of Weil et al (1963).

Table 2. Acute Toxicity of Ethylene Oxide (Administered in Aqueous Solution) to Mice, Rats, and Rabbits

Animal	Sex	LD50 (mg/kg) Route of administration			
		Oral	IV	IP	SC
Mouse	M	365	261	178	192
	F	282	261	178	261
Rat	M	242	355	178	141
	F	282	383	153	127
Rabbit	M	631	178	251	200
	F	631	178	251	200

Notes:
(a) Death occurred within 24 hr. in most instances. Toxic signs included ataxia, prostration, labored respiration, and occasional tonic convulsions.
(b) Mouse and rat studies as reported by Bruch (1973). Five animals of each sex were tested at each of six dose levels.
(c) Woodard and Woodard (1971) conducted the study with rabbits, in which one rabbit of each sex was exposed at each of six dose levels.
(d) Injection Route: IV = intravenous, IP = intraperitoneal, SC = Subcutaneous

Table 3. Summary of Tissue Irritation Studies with Ethylene Oxide

Animal Species	Route of Exposure	Maximal concentration tested, % (aq. soln.)	Highest no-effect concentration, %	Total dose of ETO at no-effect level (mg except as noted)
Rabbit	Intramuscular	2	2	10
	Intradermal	2	0.2	0.6%
	Dermal	5	1	5
	Eye	10	2.1	2
Guinea pig	Subcutaneous	5	0.1	0.05%

Notes:
(a) Reference: Woodard and Woodard (1971)
(b) Reactions were scored following a single injection.

Table 4. Maximum Concentration of Ethylene Oxide Not Producing Substantial Ocular Pathology in Rabbits (ETO Administered in Balanced Salt Solution).

Examination type	Concentration (%)	
	6 hr acute ocular instillation (b)	Anterior chamber administration
Macroscopic		
Conjunctiva	0.1	1.0
Biomicroscopic		
Cornea	1.0	1.0
Anterior chamber	5.0	0.1
Iris	1.0	0.1
Lens	5.0	0.1
Microscopic		
Conjunctiva	0.1	1.0
Cornea	1.0	1.0
Iris/Ciliary body	1.0	0.1
Lens	more than 20.0	5.0
Retina	more than 20.0	5.0

Notes:
(a) Based on McDonald et al (1973).
(b) 1 drop of solution applied every 10 min for total of 36 applications in 6 hrs.

Table 5. Summary of Subchronic Toxicity Studies of Ethylene Oxide.

Species	Route of Administration	Highest Level Administered	Effects	No-effect Level
Rat (a)	Oral (gavage) 5 d/wk	100 mg/kg (3 wk)	Loss of wt., gastric irritation, slight liver damage.	30 mg/kg (4 wk)
Rat (b)	Subcutaneous Injection (Daily 30 d)	54 mg/kg	Loss of wt., necrosis, hemorrhage and inflamation at injection site.	18 mg/kg
Dog (b)	Subcutaneous Injection (Daily, 30 d)	54 mg/kg (c)	Severe local inflammatory effects, increased mortality at high level, reduced hemoglobin and hematocrit values at all levels.	not established (d)

Notes:
(a) Hollingsworth et al, (1956)
(b) Woodard and Woodard (1971)
(c) Reduced to 36 mg/kg after 7 days of treatment.
(d) Lowest dose administered was 6 mg/kg.

Table 6. Results of Repeated Inhalation Exposure of Animals to Vapors of Ethylene Oxide

Exposure Regimen						
Conc. ppm (mg/l)	Hrs./ day	No. Exposures (b)	Over No. Days	Mortality (c)	Species	Pathologic Findings
841	7	6	10	10/10	Rat	Gross irritation of the respiratory
(1.51)	7	8	10	8/8	Guinea pig	tract; mice seemed most susceptible.
	7	4	10	1/1	Rabbit	All animals died.
	7	1	10	5/5 F	Mouse	
	7	7	10	1/1 F	Monkey	
357	7	7	9	2/20	Rat	Moderate loss of body weight and severe
(0.64)	7	7	9	4/10 F	Mouse	lung injury in rodents. Secondary
	7	33	48 to 85	10/10	Mouse	respiratory infection the primary cause
	7	38	48 to 85	10/10 F	Rat	of death in rodents. Impaired nervous
	7	38	48 to 85	8/10 M	Rat	function at lumbar and sacral level,
	7	48	48 to 85	1/2	Rabbit	reversible in rat, rabbit, and monkey.
	7	---	---	0/1 F	Monkey	Normal blood urea nitrogen (BUN) in all
	7	123	176	0/16	Guinea Pig	species. Normal hematological values in
	7	38 to 41	60	0/2	Monkey	rats, rabbits, and monkeys. Growth depression
	7	94	140	0/2 M	Monkey	slight increase in lung weight in male guinea pigs, and degeneration of testicular tubules; slight fatty degeneration in cortex of adrenals of females; no nervous system signs. Growth depression. Impairment of function of nervous system: paralysis and muscular atrophy of hind limbs, knee jerk reflexes poor (or non-existent), pain perception poor. Normal pathology upon sacrifice.
290	6	over 6 wk	?	0/3	Dog	Vomiting, occasional tremors, transient
(0.52)						paraplegia, anemia.
204	7	122-157	176-226	22/40	Rat	Appreciable number of rats died of secondary
(0.37)	7	122-157	176-226	1/16	Guinea pig	respiratory infection; growth depression in
	7	122-157	176-226	0/4	Rabbit	rat; posterior paresis in monkey and rabbit;
	7	122-157	176-226	2/10 F	Mouse	increased lung weight in rat and guinea pig.
	7	122-157	176-226	0/2 F	Monkey	Neurologic and muscular atrophy in monkey. Increased liver and kidney weight in F rats. Slight testicular tubal degeneration in rat.

Table 6 (Continued). Results of Repeated Inhalation Exposure of Animals to Vapors of Ethylene Oxide

113	7	122-157	176-226	0/40	Rat	No findings except growth depression in male
(0.20)	7	122-157	176-226	0/16	Guinea pig	rats and increased lung weight of the rats.
	7	122-157	176-226	0/4	Rabbit	
	7	122-157	176-226	0/2	Monkey	
100	6	130	?	3/20	Rat	No clinical signs and no significant findings
(0.18)	6	130	?	8/30	Mouse	except anemia in one dog.
	6	130	?	0/3	Dog	
49	7	127-131	180-184	0/20	Rat	No effect on any of the animals (as judged by
(0.09)	7	127-131	180-184	0/8	Guinea pig	general appearance and behavior, mortality,
	7	127-131	180-184	0/2	Rabbit	growth, final body and organ weight, and gross
	7	127-131	180-184	0/10 F	Mice	and microscopic examination of the tissues).
	7	127-131	54	0/1	Monkey	

Notes:
a) Based on Hollingsworth et al (1956), and Jacobson et al (1956),
b) Exposures usually conducted on a 5 day/week basis.
c) First figure indicates number of animals which died. Second figure indicates number of animals in exposure group. Unless noted otherwise, the second figure is number of animals of each sex present.

Table 7. Genetic and Allied Effects of Ethylene Oxide

Species or Common Name	Locus/Loci (mutation type)	Time & Route	ETO Conc. (Vol. or Dose)	Results and Reference
Tobacco mosaic virus	---	50 hr, gaseous	160 mm pressure pH 5.0 buffer	Approximately 100 ETO residues per single strand RNA molecule. Main product was the 7-hydroxyethyl-guanine adduct (Frankel-Conrat, 1961)
Egg albumin	---	2 day	---	Up to 80 residues of ETO per protein molecule; reacts with carboxy, amino and phenolic residues of proteins; changes isoelectric point and solubility of protein. (Frankel-Conrat, 1944)
T4-Phage of *Escherichia coli*	m and r (forward)	10 min, aqueous	0.10 M	No loss of infective units; no increase in mutation frequency (Loveless, 1959)
Phage lambda in *Escherichia coli*	(prophage induction)	30 min	15mM	lambda-prophage was induced in 1.7% of the treated bacteria (Hussain, et al, 1975)
Salmonella typhimurium TA 1535	histidine (back)	hr (not specified)	---	Increased frequency of base substitution mutations (Embree, 1975)
Escherichia coli	Streptomycin-resistance (forward)	2mM-hr	(2mM-hr)	2 mutants/mM-hr/10(exp. 8) survivors; Swain-Scott s-value reported as 0.96; reaction half-time with H20 about 100 minutes (Hussain, and Osterman-Golkar, 1976)
Neurospora crassa (macroconidia) mold	ad-3A (back)	0.1 to 10 min. aqueous	0.0015 to 0.15M	Under these experimental conditions, the number of mutations per 10(exp. minus 6) survivors could be expressed as 2.61 [(conc)(time)] (exp. 2.69), (Kolmark et al, 1968)
Neurospora crassa	ad-3A (back)	20 min, aqueous suspension	0.14M	Approx. 200-fold increase over spontaneous frequency under optimal conditons; unique "after effect" from ETO (Kilbey et al, 1968)

Table 7 (Continued). Genetic and Allied Effects of Ethylene Oxide

Barley	chlorophyll (forward)	6 d Gas	80% ETO 20% Air	33-fold increased frequency decreased fertility (Ehrenberg, 1956)
Barley	chlorophyll (forward)	?	0.15% Solution	54-fold increased non-monotonic dose-response curve (Ehrenberg, 1959)
Barley	waxy (forward)	24 hr, Gas exposure of pollen	12.5 ppm	Increased mutation rate not given at 12.5 ppm. Statistically significant at 50 ppm (Lindgren et al, 1969)
Barley	chromosomal abnormalities (forward)	10 hr, aqueous	0.20%	Chromosomal aberrations observed in up to 16% of the germinated kernals (Moutschen-Dahmen et al, 1968)
Barley (pollen)	"waxy" (forward)	24 hr, gas	100 ppm	Greater than 10-fold increase in mutational frequency (Sulovska, 1969)
maize, corn	chromosome rearrangement	2 min gas	5% ETO 95% Air	Inherited chromosomal aberrations observed in 1% of the kernels (Faberge, 1955)
Herb (Pterotheca falconeri)	chromosomal abnormalities (forward)	2 hr, aqueous	45 mM.	Chromosomal aberrations observed in up to 65% of the cells (Mehra et al, 1974)
Rice	chlorophyll loci (forward)	2-12 hr, aqueous	0.1-0.6%	Up to 2% chlorophyll mutations at 12 different phenotypes (Roy et al, 1973)
Rice	chlorophyll (forward)	8 hr, aqueous	0.6% (W/V)	Mutations observed up to 14.6% of F-2 generation (Jana et al, 1975)
Rice	chlorophyll (forward)	10 hr, gaseous	0.15% (V/V)	7.2 fold increased frequency; also decrease germination and fertility (Ando, 1968)
T. aestivum wheat	visibles (forward)	aqueous 5 hr,	0.2%	Approximately 10-fold increase in mutation frequency (MacKey, 1968)
Tradescantia	chromosomal abnormalities	gaseous 5 min,	approx. 1%	Up to 5.1% chromatid breaks, "erosions," and gaps (Smith et al, 1954)

Table 7 (Continued). Genetic and Allied Effects of Ethylene Oxide

Drosophila melanogaster Fruit fly	all sex-linked recessive lethals (forward)	Injection (Volume not given)	0.8% solution	Muller-5 Test; 9 lethals in chromosomes tested *vs.* 0 lethals in 494 control chromosomes (Bird, 1952)
Drosophila melanogaster Fruit fly	all sex-linked recessive-lethals; (forward)	Injection	0.10 M. 0.3-0.4 (u)	2 sex-linked recessive lethals per 1,000 chromosomes (Fahmy et al, 1956)
Drosophila melanogaster Fruit fly	"minutes" (small autosomal deletions)	Injection	0.113 M 0.25 ul/animal	Approximate 5-fold increase in frequency of "minutes" (Fahmy et al 1956)
Drosophila melanogaster Fruit fly	sex-linked lethals; translocations (forward)	Injection	0.09 M	Lethals and translocations induced in all stages of spermatogenesis (Nakao et al, 1961)
Rat	chromosomal abnormalities (forward)	Oral	9 mg/kg	Statistically significant increase (P less than .001) in aberrations in femur bone marrow cells (Strekalova, 1971)
Rat	Putative "dominant lethal"	4 hr, Inhalation	1,000 ppm	Significant increase in dead implantations in females mated to treated males at weeks 1, 2, 3 and 5 post-exposure (Embree, 1975)
Rat	---	3 d Inhalation 7 hr/d	250 ppm (450 mg/cu m)	Isochromatid and chromatid gaps and breaks in bone marrow cells sampled 24 hours after last exposure (Embree, 1975)
Human	Chromosomal abnormalities (forward)	approx. 2 hr, gaseous (inhalation & dermal?)	unknown	Exposure from an industrial spill; significant increase (p less than 0.05) in chromosomal aberrations in 7 workers 6 wk after exposure (Ehrenberg et al, 1967)

V. OCCUPATIONAL EXPOSURE LIMITS

The current U.S. standard (OSHA) for occupational exposure to ethylene oxide is 50 parts per million (ppm) parts of air, which corresponds approximately to 90 mg/cu m, as an 8 hour time-weighted average concentration, with no ceiling level stipulated. [29 CFR 1910.1000]. This standard was adopted from the standards established by the American National Standards Institute (ANSI). An identical exposure limit, the Threshold Limit Value (TLV), had been adopted by the American Conference of Governmental Industrial Hygienists (ACGIH, 1957).

The USSR has a standard of 0.5 ppm (1 mg/cu m), which was adopted in 1966 [Winell, 1975]. Occupational exposure standards of 50 ppm and 20 ppm (36 mg/cu m) are recommended by the Federal Republic of Germany and Sweden, respectively [ICF Conf., 1975].

Table 8 lists the federal standard and the ACGIH recommended TLV and short term exposure limits ("STEL") for ETO. The exposure limits for certain hydration and reaction products of ETO, i.e. ethylene chlorohydrin and ethylene glycol, are listed. Also shown for comparison are the exposure levels published by the Federal Republic of Germany, Sweden, and the USSR.

NIOSH recommends, based on the recent results of tests for mutagenesis, that exposure be controlled so that workers are not exposed to ETO at a concentration greater than 135 mg/cu m (75 ppm) determined during a 15-minute sampling period, as a ceiling occupational exposure limit and, in addition, with the provision that the TWA concentration limit of 90 mg/cu m (50 ppm) for a work-day not be exceeded. As additional information on the toxic effects of ETO becomes available, this recommended level for exposures of short duration may be altered. The adequacy of the current U.S. ETO standard, which was based on the data available at the time of promulgation, has not been addressed in this report. Further assessment of other ETO exposure situations, and of the adequacy of the ETO occupational exposure standard will be undertaken during the FY 80 development of the NIOSH Criteria Document on epoxides (including ETO). In the interim, NIOSH strongly recommends that the control strategies presented herein, or others considered to be more applicable to particular local situations, be implemented to assure maximum protection of the health of employees. Good work practices will help to assure their safety.

Table 8. Occupational Exposure Limits for ETO and Some Hydration and Reaction Products

Substance		TWA Values ppm (a)	TWA Values mg/cu m (b)	Tenative Values STEL** ppm	Tenative Values STEL** mg/cu m
Ethylene Oxide	U.S. Federal Std.	50	90		
	ACHIH TLV (Rec.)	50	90	75	135
	German (FRG) Std.	50	90		
	Swedish Std.	20	36		
	USSR level	0.5	1		
Ethylene Chlorohydrin	U.S. Federal Std.	5	16		
	ACGIH TLV (*), (C), skin, (Rec.)	1	3	1	3
	German (FRG) Std.	5	16		
Ethylene Glycol					
particulate	ACGIH TLV	---	10	---	20
vapor	ACGIH TLV	100	250	125	325

Notes and definitions:
For ETO: 1 ppm is approx. equal to 1.80 mg/cu m at 25 C, and 760 mm Hg, 1 mg/l is approx. equal to 556 ppm at 25 c. and 760 mm Hg.
(*) Indicates 1976 additions to the TLV listing.
(C) Threshold Limit Value - Ceiling. The concentration that should not be exceeded even instantaneously.
a) Parts of a vapor or gas per million parts of contaminated air, by vol. at 25 degrees C and 760 mm Hg press.
b) Approximate mg of substance per cu. m . of air.
Rec. = Recommendation.
** "STEL" - Short term exposure limit (recommended by the ACGIH as a "maximal concentration to which workers can be exposed for a period up to 15 minutes continously..." provided that no more than four excursions per day are permitted, with at least 60 minutes between exposure periods..."
TLV = Threshold Limit Value, as proposed by ACGIH.
TWA - Time Weighted Average over 8 hour work shift.
"Skin" notation refers to the potential contributors to the overall exposure by the cutaneous route (including mucous membranes and eye), either by airborne, or more particularly, by direct contact with the substance. Vehicles can alter skin absorption. This designation was intended by the TLV Committee to suggest appropriate measures for the prevention of cutaneous absorption so that the threshold limit is not invalidated.

VI. HAZARDS, CONTROL MEASURES, MEDICAL SURVEILLANCE, AND RECORD KEEPING

A. Hazards and Precautions, Prevention, and Emergency Procedures

1. Fire, Explosion and Reactivity Data

Ethylene oxide is an extremely volatile, flammable liquid with a vapor that forms explosive mixtures with air over a wide range of concentrations (3-100% in air by volume, i.e. 30 thousand ppm and above). Because of its extreme flammability, the following safeguards should be taken in areas where ETO is used as a sterilant:

a. All ignition sources, including static electricity, should be controlled where ETO is in use.

b. Foam, carbon dioxide, or dry chemical fire extinguishers should be readily accessible (a solid stream of water will scatter and spread the fire). If a hose is provided for use against fire, it should be equipped with a fogging nozzle.

c. Where a fan is located in ductwork in which ETO is present in a concentration greater than 7,500 ppm (approximately 25% of the lower flammable limit), the fan blades and appropriate parts of the ventilation system should be made of a nonsparking material. The motor should be explosion-proof.

d. Automatic water spray systems should be provided to cool the sterilizing equipment in case of a nearby fire.

e. Low pressure steam or hot water should be used for heating ETO or mixtures in which ETO is used.

f. ETO not in immediate use in a sterilizing unit should be stored away from heat and strong oxidizers, strong acids, alkalies, anhydrous chlorides of iron, aluminum, or tin, iron oxide, and aluminum oxide.

2. Spill, Leak, and Disposal Procedures

If ETO is spilled or leaks, the following steps should be immediately taken:

a. Evacuate all but those persons necessary for clean-up activities.

b. Remove all ignition sources.

c. Ventilate the area of the spill or leak.

d. If in the gaseous form, stop the flow of gas. If the source of leak is a gas cylinder and the leak cannot be stopped in place, remove the leaking cylinder to a safe place in the open air and repair the leak or allow the cylinder to empty.

e. If in the liquid form, absorb small quantities on paper towels. Evaporate in a safe place (e.g., a fume hood).

ETO should not be allowed to enter a confined space, such as a sewer, because of its toxicity and the possibility of an explosion. Further, in the clean-up of leaks or spills and maintenance or repair operations on contaminated systems or equipment, authorized personnel should be required to wear respirators and other protective clothing (including gloves). (see Section B.2.)

3. Sanitation Practices

Appropriate sanitation practices should be instituted in ETO work areas and should include the following:

a. Clothing which becomes wet with liquid ETO should be removed as soon as possible and placed in sealed containers for storage until it can be discarded (into a decontamination furnace) or decontaiminated for reuse by laundering, steaming, or comparably effective treatment. If laundering is to be performed by a commercial establishment, the manager of that establishment should be informed by the employer at the ETO work area of the hazards of exposure to ETO either in or on contaminated clothing or vaporized into the air, and of the precautions to be taken.

b. Persons involved with handling and/or treatment of ETO-contaminated clothing should be informed of the hazard and should take appropriate precautions.

c. Employees whose skin becomes contaminated with ETO should immediately wash or shower to remove any ETO from the skin.

d. Employees who handle ETO should wash their hands thoroughly before eating, smoking, or using toilet facilities.

B. Recommendations for Control of Hazardous Exposure Situations

1. Posting of Signs

Entrances to areas where ETO is used as a sterilant should be posted with signs indicating:

DANGER:
AUTHORIZED PERSONNEL ONLY
ETHYLENE OXIDE AREA
EXTREMELY FLAMMABLE GAS
MAY BE HARMFUL IF INHALED

Emphasis in any sign should be placed on the possible danger and the restricted nature of the area.

2. Protective Clothing and Respirators

a. Sustained or intermittent skin contact with liquid ETO may produce dermatitis at the site of contact. However, due to the extreme penetrating ability of ETO, and the consequent ineffectiveness of many types of clothing materials to prevent skin contact, the use of any conventional "impervious" clothing is not suggested. There are, however, certain special types of protective clothing which are effective when working with ETO. For example, one of the large ETO manufacturers provides its workers with knitted gloves which have been coated with certain polymers, including polyvinylchloride. In addition, conscientious adherence to appropriate sanitation practices should eliminate most hazards of skin contact with ETO.

b. If ETO splashes into the eye, severe irritation may result. For this reason it is suggested that rubber framed goggles, equipped with approved impact resistant glass or plastic lenses, be worn whenever there is danger of the material coming in contact with the eyes (i.e., in operations which involve transport of bulk containers of ETO from the storage room to the sterilizer unit for installation). Eye wash fountains within easy access from the immediate work area are recommended; they should be so situated that additional contact of the eyes with ETO in vapor form during washing is unlikely.

c. It is suggested that respirators be readily accessible in the event of an emergency situation resulting from an accidental spill or leak of ETO, and for use during subsequent clean-up and disposal procedures. A self-contained breathing apparatus with a full facepiece operated in a pressure-demand or other positive pressure mode is suggested for this purpose.

Respirators (respiratory protective devices) should be those approved under the provisions of 30 CFR 11.

3. Engineering and Other Control Technology

A number of control problems were discovered during the field surveys conducted at several medical facilities which use ETO in sterilizing operations. These problems were addressed in Section III of this report, along with some recommendations for their amelioration. Those, and the following general recommendations should be followed in all medical facilities which use ETO as a sterilant. All equipment should be operated in accordance with manufacturers' recommendations.

a. Sterilization operations involving ETO should be isolated from all non-ETO work areas.

b. ETO work areas, except for outdoor systems, should be maintained under negative pressure, with respect to non-ETO work areas. This may be accomplished by continuous local exhaust ventilation so that air movement is always from non-ETO work areas to ETO work areas. Where a fan is used to affect such air movement, the fan blades and other appropriate parts of the ventilation system should be made of a nonsparking material. Local exhaust pickups should be located at areas where the possibilities for leaks are the greatest (i.e., in close proximity to sterilizing units and aerators). Exhaust air should not be discharged into any work area or into the general environment without decontamination. This may be accomplished using a calalytic converter, or by discharging exhaust air directly to the fire box of a decontamination furnace, with subsequent discharge of this air to the general environment. Sterilizing units and aerators should be closed systems. Elimination of residual ETO from both systems should be accomplished only by ventilation ducts leading directly from the sterilizers and aerators to the decontamination apparatus described above.

c. All equipment (e.g., sterilizing units, gas tanks, and aerators) should be periodically checked for leaky valves, fittings, and gaskets, and for any other malfunctioning parts. Equipment manufacturers' recommendations regarding preventive maintenance should be observed. Further, periodic measurements should be made which demonstrate the

effectiveness of the local exhaust system (e.g., air velocity or static pressure).

d. Tanks of ETO in storage areas should be securely fastened in place and out of the path of traffic.

4. Training in Proper Operational Procedures

Employees operating sterilizer equipment should have received instruction in all parameters of sterilization and aeration procedures. Such training should strictly adhere to equipment manufacturers' installation, operating, routine care, and preventive maintenance instructions. Responsible supervision should be provided.

C. Medical Surveillance, Record Keeping, and Informing Employees of the Hazard

1. Medical Surveillance

Medical surveillance, as described in this section, should be made available to all persons subject to occupational exposure to ETO.

a. Preplacement medical examinations should include at least:

(1) comprehensive medical and work histories with special emphasis directed to symptoms related to eyes, blood, lungs, liver, kidneys, nervous system, and skin.

(2) a comprehensive physical examination, with particular emphasis given to pulmonary, neurologic, hepatic, renal, and ophthalmologic systems, and the skin.

(3) a complete blood count to include at least a white cell count, a differential count, hemoglobin, and hematocrit.

(4) In addition to the medical examination, employees should be counseled by the physician to ensure that each employee is aware that ETO has been shown to induce mutations in experimental animals. The relevancy of these findings in animals to male or female employees has not yet been determined. The findings do indicate, however, that employers and employees should do everything possible to minimize exposure to ETO. If a physician becomes aware of any adverse effects on the reproductive system, any cancers in individuals who have been exposed to ETO, or any abnormal offspring born to parents either or both of whom have been exposed to ETO, the information should be forwarded to the Director, NIOSH, as promptly as possible.

b. Periodic examinations should be made available on an annual basis, and more frequently if indicated by professional medical judgment based on such factors as emergencies and the pre-existing health status of the employee. These examinations should include at least:

(1) interim medical and work histories.

(2) a physical examination as described above for the preplacement examination.

2. Record Keeping and Availability of Records

The employer should keep accurate records on the following:

a. All measurements taken to determine employee exposure to ETO, including:

(1) Dates of measurement
(2) Operations being monitored
(3) Sampling and analytical method used
(4) Numbers, durations, and results of samples taken
(5) Names and airborne exposure concentrations of employees in monitored areas

b. Measurements demonstrating the effectiveness of mechanical ventilation (e.g., air velocity, static pressure, or air volume exchanged), including:

(1) Dates of measurements
(2) Types of measurements taken
(3) Results of measurements

c. Employee medical surveillance, including:

(1) Full name of employee
(2) All information obtained from medical examinations which is pertinent to ETO exposure
(3) Any complaints by the employee relatable to exposure to ETO
(4) Any treatments for exposure to ETO, and the results of that treatment

All of the aforementioned records should be updated at least annually. The employee's medical examination and surveillance records should be made available upon request to designated medical representatives of the Assistant Secretary of Labor for Occupational Safety and Health (OSHA), and the Director of the National Institute for Occupational Safety and Health (NIOSH). Records of environmental and occupational monitoring should be made available upon request to authorized representatives of OSHA and NIOSH. All employees or former employees should have access to the exposure measurement records which indicate their own exposure to ETO. An employee's medical records should be available upon written request to a physician designated by the employee or former employee. Records of all examinations should be held for at least 30 years following the termination of employment.

3. Informing Employees of the Hazard

Each employee, prior to being permitted to work in an ETO sterilizing area, should receive instruction and training on:

a. The nature of the hazards and toxicity of ETO (including those hazards described above), including recognition of the signs and symptoms of acute exposure, and the importance of reporting these immediately to designated health and supervisory personnel.

b. The specific nature of the operation involving ETO which could result in exposure.

c. The purpose for, and operation of, respirator equipment.

d. The purpose for, and application of, decontamination practices.

e. The purpose for, and significance of, emergency practices and procedures, and the employees' specific role in such activities.

f. The purpose for, and nature of, medical examinations, including advantages to the employee of participating in the medical surveillance program.

VII. SAMPLING AND ANALYTICAL METHODS

A. Airborne-ETO Monitoring Techniques and Equipment.

A number of techniques are available for the reliable analytical determination of low concentrations of ETO in air. These include: (1) hydration of ETO (collected in a bubbler) to ethylene glycol followed by oxidation to formaldehyde, which is determined colorimetrically by its reaction with sodium chromotropate (Bolton et al, 1964), and (2) adsorption of the ETO on charcoal, followed by desorption with carbon disulfide, and gas chromatographic determination of the ETO (NIOSH method described in a later section). In addition, instrumentation is available for the direct quantitative determination of the concentration of ETO in air. These direct reading instrumental methods include: a) thermal conductivity detection, b) gas chromatography, c) hydrogen flame-ionization detection, and (d) infrared spectrophotometry.

Other methods (as well as modifications of the above methods), and specific techniques have been described for the determination of airborne ETO concentration. These include: spectrophotometry (Pozzoli et al, 1968), colorimetry (Adler, 1965; Critchfield and Johnson, 1957; Gage, 1957), and volumetric methods (Gunther, 1965; Hollingsworth and Waling, 1955; Lubatti, 1944; and Swan, 1954). Gas chromatography of air residues from fumigated materials has been used for foodstuffs, pharmaceuticals, and surgical equipment (Adler, 1965; Ben-Yehoshua and Krinsky, 1968; Berck, 1965; Brown, 1970; Buquet and Manchon, 1970; Heuser and Scudamore, 1968, 1969; Kulkarni et al, 1968; Manchon and Buquet, 1970). ETO can be determined in cigarette smoke by gas chromatography or mass spectrometry after conversion to ethylene chlorohydrin (Binder and Lindner, 1972; Muramatsu et al, 1968), and in mixtures of lower olefin oxides and aldehydes by gas chromatography (Kaliberdo and Vaabel, 1967). The limits of detection of ETO by spectrophotometry and gas chromatography in these materials are generally of the order of 1 mg/kg.

The method used for the analysis of the ETO samples obtained in the NIOSH field study involved adsorption on charcoal, and gas chromatographic determination following desorption with carbon disulfide. The method, known as NIOSH Analytical Method #S286, is outlined below, and is described in detail in the reference.

B. Principle of the NIOSH Standard Method.

A known volume of air is drawn through a series of two charcoal tubes to trap the ETO vapor present. The two-tube sampling arrangement is necessary to prevent sample migration (and loss) upon storage, and to insure that the front tube is not overloaded during sampling.

The charcoal in each tube is transferred to a 5-ml screw-capped sample container, and the ETO is desorbed with carbon disulfide. An aliquot of the desorbed sample is injected into a gas chromatograph, following which the area of the resulting peak is determined and compared with areas obtained from the injection of "standards" (i.e., known concentrations of ETO).

C. Range of Sensitivity of the Method.

The method was validated over the range of ETO concentrations of 40-176 mg/cu m at a temperature of 26 C and atmospheric pressure of 761 mm Hg, using a 5-liter sample. Under the conditions of recommended sample size (5 liters), the probable useful concentration range of this method is 20-270 mg/cu m at a detector sensitivity that gives nearly full scale deflection of the strip chart recorder for a 1.4-mg ETO sample. 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 front charcoal tube. This capacity varies with the ETO concentration and with the presence of other substances in the sampled air.

The charcoal tube series consists of two separate large tubes; the first tube contains 40 mg of charcoal and the second tube (used as the backup tube) contains 200 mg of charcoal. The charcoal is held in place by glass wool plugs at the tube ends. If a particular atmosphere is suspected of containing a large amount of ETO, an air sample of smaller volume should be taken.

D. Interference.

When the amount of moisture in the air is so great that condensation actually occurs in the tube, organic vapors will not be trapped efficiently; consequently, the breakthrough threshold is decreased.

Any compound which has the same retention time on the chromatography column as ETO under the conditions described in this method has a potential for interfering with the estimation of ETO. A change in the separation conditions, such as column packing or temperature, will generally circumvent the interference problem.

E. Precision and Accuracy.

The coefficient of variation for this method in the range 41-176 mg/cu m is 0.103. This value corresponds to a 9.3 mg/cu m standard deviation at the 90 mg/cu m (present federal standard) level.

Advantages and disadvantages of the method, as well as other aspects of the recommended sampling and analytical method, are described in detail in the reference. (NIOSH, 1977)

APPENDIX

List of Additional Equipment Used in the NIOSH Field Study:

1) Velometer, Alnor Jr. Model 8100. Alnor Instrument Co. 7301 N. Caldwell Avenue, Niles, Illinois, 60648. Ranges: 0-200 fpm on low scale, and 0-800 fpm on high scale.
2) TLV "Sniffer", Portable Gas Detection and Alarm System, Bacharach Instrument Co., Mountain View, California.
3) Century Organic Vapor Analyzer, Model OVA-128, (and portable direct reading gas chromatograph). Century System Corporation, Arkansas City, Kansas. Also, Rustrak portable strip chart recorder (Gulton Industries Inc.).
4) Personal Sampling Pumps, Bendix Model 44, battery operated, Calibrated at a flow rate of 200 cc/min. (Note: Recent experience with the analytical test method indicates that a flow rate of 150-170 cc/min produces best results.)

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