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Ethylene Oxide: An Overview of Toxicologic and Epidemiologic Research

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Ethylene oxide (EtO) is a reactive epoxide and potent biocide. It is used widely in gas sterilization of hospital equipment. An estimated 75,000 health care workers in the United States have potential exposure. EtO binds covalently to deoxyribonucleic acid (DNA) and has been shown in 13 species to cause point *mutations*. Apparently, as a consequence of its alkylating ability, EtO exposure can result in *chromosomal damage*. In monkeys EtO exposure produces increased frequencies of sister chromatid exchanges (SCEs) and chromosomal aberrations. In man, five cytogenetic studies have shown dose-related increased frequencies of either SCE or chromosomal aberrations; in one study SCEs developed after regular exposures lasting less than five minutes per day. EtO is a *reproductive toxin*. In adult male rats, exposure produces decreased fertility, increased fetal deaths, and heritable chromosomal translocations. In pregnant female rats and rabbits, exposure causes increased fetal losses, and in one study in pregnant mice exposure was associated with increased numbers of malformed fetuses. In male monkeys EtO causes dose-related reductions in sperm count and sperm motility. In pregnant women, one study suggests that brief occupational exposure twice daily in concentrations of 20 ppm or above was associated with increased spontaneous abortions. EtO is *carcinogenic* to animals. In rats it causes dose-related increases in mononuclear cell leukemias, peritoneal mesotheliomas, and cerebral gliomas. In man, exposure has been associated in two epidemiologic studies with increased leukemias: 3 leukemias observed versus 0.2 expected in one study, and 2 observed versus 0.14 expected in the other; two additional small studies of limited power found no excess leukemias. *Quantitative risk assessment* indicates that from 634 to 1,093 excess deaths from

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cancer will occur per 10,000 workers exposed to EtO at 50 ppm over a working lifetime, and that 12 to 23 excess cancer deaths will occur per 10,000 workers exposed at 1 ppm. The National Institute for Occupational Safety and Health (NIOSH) recommends that EtO be regarded as a potential human carcinogen. NIOSH has recommended that eight-hour time-weighted average exposure to EtO be less than 0.1 ppm and that short-term peak exposure not exceed 5 ppm for more than ten minutes per working day.

Key words: ethylene oxide, mutation, chromosomal damage, sister chromatid exchange, reproductive toxicity, cancer epidemiology

INTRODUCTION

Ethylene oxide (EtO) is a colorless, flammable gas, with a characteristic ether-like odor, and is the simplest of the epoxide compounds (Fig. 1). Because of its reactive nature, EtO is a major industrial chemical. With an annual production of approximately 6.1 billion lbs, it is one of the 25 chemical compounds with greatest annual production volume in the United States [NIOSH, 1981].

EXPOSURES

Most EtO is consumed in the chemical plants where it is produced. It is used in the manufacture of such compounds as ethylene glycol. Because EtO is highly explosive, the equipment containing it in chemical process plants generally consists of tightly closed and highly automated systems. This equipment is often located outdoors, and except during maintenance, workers have minimal opportunity for exposure. Air samples collected in process areas of six chemical production plants indicated that EtO concentrations were, with few exceptions, less than 1 ppm [Koketsu, 1978].

Approximately 0.24 percent of the annual US production of EtO (approximately 7 million kg) is used in the health care industries [Phillips et al, 1978]—primarily in the manufacture of medical products, and secondarily for gas sterilization in hospitals [Glaser, 1977]. An estimated 75,000 health care workers in the United States have potential occupational exposure to EtO [NIOSH, 1981]. Occupational exposures to EtO tend to be higher in health instrument manufacture and in hospitals than in the chemical process industries. In a limited field survey of hospitals, conducted in 1978, the National Institute for Occupational Safety and Health (NIOSH) found that EtO concentrations near malfunctioning or improperly designed equipment may reach concentrations of hundreds of ppm for brief periods. Time-weighted average (TWA) breathing zone air concentrations in hospitals were, however, generally well below

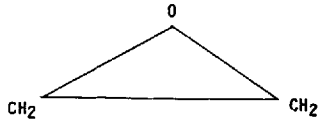

Fig. 1. Structural formula of ethylene oxide.

the current permissible exposure limit of 50 ppm [Koketsu, 1978]. Yager et al [1983] have emphasized that the exposures of hospital workers to EtO tend to be of a short-term and intermittent nature.

MUTAGENIC AND CYTOGENTIC EFFECTS

EtO is a potent alkylating agent. It binds irreversibly to deoxyribonucleic acid (DNA) [Ehrenberg, 1981]. It causes mutations, primarily of the base-pair substitution variety, in a wide variety of plant, submammalian and mammalian species including viruses, Salmonella typhimurium, Escherichia coli, Neurospora crassa, barley, rice, wheat, Tradescantia paludosa, Drosophila melanogaster, and mice [NIOSH, 1981].

As an apparent consequence of its ability to alkylate DNA, EtO produces a spectrum of chromosomal damage in both experimental animals and man. In a cytogenetic study of cynomolgus monkeys, conducted by the National Institute for Occupational Safety and Health (NIOSH) [Lynch et al, 1982], the monkeys were exposed to 0 ppm, 50 ppm, or 100 ppm of EtO for seven hours per day, five days per week for 24 months. After 24 months, the peripheral lymphocytes of the monkeys were examined to determine the frequency of sister chromatid exchanges (SCEs) and chromosomal aberrations. The frequency of SCEs was found to increase in a dose-related fashion, such that in animals exposed at 50 ppm they occurred 1.8 times more frequently than in unexposed controls, and in those exposed at 100 ppm they occurred 3.1 times more frequently. The frequency of chromosomal aberrations also increased significantly in relation to dose.

In another cytogenetic study, Yager and Benz [1982] examined SCE frequency in the peripheral lymphocytes of New Zealand white rabbits exposed to EtO at airborne concentrations of 0, 10, 50, or 250 ppm, six hours per day, five days per week for 12 weeks. Additional rabbits were injected with mitomycin C, a known mutagen, to serve as positive controls. A dose-related increase in the frequency of SCEs was noted at exposures of 50 ppm and of 250 ppm, but was not evident in animals exposed at 10 ppm (Table I). The frequency of SCEs increased with duration of exposure. Two weeks after cessation of exposure, the frequency of SCEs had fallen from 9.5 per cell to background (7.7 per cell) in the rabbits exposed at 50 ppm, and from 13.2 per cell to 10.8 per cell in those exposed at 250 ppm.

To evaluate the chromosomal changes induced by EtO in man, Garry et al [1979], studied SCE frequency in twelve hospital sterilization workers exposed

TABLE I. Frequency of Sister Chromatid Exchanges (SCE) in Lymphocytes of Rabbits Exposed to Ethylene Oxide*

	Mean SCEs per cell by duration of exposure		Mean SCEs per cell by interval since last exposure	
Exposure group	7 Weeks	12 Weeks	2 Weeks	7 Weeks
Unexposed	8.7	7.3	8.0	8.7
EtO–10 ppm	7.7	7.9	7.8	7.7
EtO–50 ppm	8.9	9.5	7.7	9.0
EtO–250 ppm	11.3	13.2	10.8	9.8
Mitomycin C—positive control	14.9	14.9	14.9	14.9

*From Yager and Benz [1982].

occupationally to EtO. Their SCE frequencies were compared to those of nonexposed hospital workers. Four of the exposed individuals complained of respiratory irritation, and they were observed to have the highest SCE frequencies (9.7 per cell versus 6.0 per cell in unexposed controls). Their SCE frequencies remained significantly increased compared to controls at three weeks and also at eight weeks after last known exposure. No potentially confounding factors such as cigarette smoking, medications, or illness were found to have accounted for the elevated frequency of SCEs. The maximum measured peak exposure (duration of sampling unspecified) was 36 ppm in an area air sample.

In a second human cytogenetic study, Ehrenberg et al [1981] reported that the incidence of chromosomal aberrations in the peripheral lymphocytes of seven workers remained elevated for as long as 18 months following an accidental one-time exposure to EtO at a concentration of approximately 1,500 ppm for a period of two hours.

Abrahams [1980] reported the results of a cytogenic study of 75 workers in nine health instrument manufacturing facilities. Average EtO exposure was reported to be below the permissible exposure limit of 50 ppm, although peak exposures may have exceeded 75 ppm. Thirty-seven nonexposed workers at the same facilities served as controls. Exposed workers had statistically significant increases in SCEs and also in chromosomal abnormalities (including quadriradial chromosomes) compared to controls.

Hermann [1982], in a preliminary report of a human cytogenetic study, compared SCE frequencies in workers unexposed to EtO with those in workers whose eight-hour time-weighted average exposures to EtO were less than 1 ppm, 1–10 ppm, or 5–200 ppm. All exposed workers were employed in sterilizing areas at health instrument manufacturing facilities. In each of the two most heavily exposed groups, Hermann observed statistically significant elevations in SCE frequencies (15 and 32 per cells, respectively, versus 9 per cell in controls). Those elevations were still apparent six months after cessation of exposure.

In another human cytogenetic study, Högstedt et al [1983] evaluated the frequency of chromosomal aberrations, sister-chromatid exchanges, and micronucleus formation in 28 workers exposed to EtO in two medical supply sterilization facilities. At one facility, environmental data indicated that previous EtO exposures had ranged from 0.3 to 7.6 ppm. At the time of biological sample collection in 1978, all exposed workers were exposed to less than 1 ppm. At the second plant EtO exposures had been limited to less than 0.5 ppm for all but two employees. These two employees' exposures ranged between 1 and 2 ppm. Thirty controls were identified from among unexposed employees from the same facilities and from a group of bus drivers.

Högstedt indicated that a statistically significant increase in the frequency of chromosomal aberrations and gaps was associated with EtO exposure. They reported that this effect was evident when the effects of confounder variables (age, smoking, etc) were controlled. They also reported a statistically significant increase in the frequency of micronuclei in erythroblasts and of polychromatic erythrocytes in the bone marrow of exposed subjects as compared to controls. No significant association was observed between EtO exposure and the frequency of either SCE or of micronuclei in lymphocytes. Although the results of this study are generally consistent with those of other recent reports, their interpretation is made difficult by the fact that the cytogenetic techniques employed differed in several important aspects from the methodologies generally employed in such studies [Archer et al, 1981].

In the most recently reported human cytogenetic study, Yager et al [1983], examined SCE rates in a group of 14 hospital workers exposed to EtO for an average of 3.6 minutes per sterilizing task. The workers were stated to have performed the task between six and 120 times during the six-month study period. They observed an exposure-related increase in frequency of SCE both in relation to EtO exposure and also in relation to cigarette smoking (Table II). There appeared to be some evidence for positive interaction between EtO exposure and cigarette smoking in the etiology of SCEs.

To study the effect of EtO exposure on DNA repair mechanisms in man, Pero et al [1982] examined the effects of EtO exposure on unscheduled DNA synthesis. Peripheral lymphocytes were obtained from five men exposed occupationally to EtO in health equipment manufacture. Their EtO exposures ranged from 0.5 to 1 ppm (time-weighted average exposure) for periods of four months to five years (mean 2.9 years); lymphocytes were also obtained from 12 unexposed men who worked in a nearby factory and who were matched to the exposed workers in age and smoking status. A significant decrease in the repair proficiency index (p less than 0.01) was observed in the exposed workers as compared to the unexposed controls. That finding was interpreted as constituting further evidence for the genotoxicity of EtO to man and as indicating that genotoxicity is evident even at very low levels of occupational exposure.

Taken collectively, these cytogenetic studies demonstrate that EtO is genotoxic to man. These findings are consistent with previous reports of genetic and chromosomal damage induced by EtO in experimental species. Although the full biological significance of this cytogenetic toxicity of EtO to man is not yet clear, the recent rapid accumulation of evidence suggesting a pervasive link between chromosomal damage and human neoplasia [Yunis, 1983] requires that these findings be accorded careful consideration.

REPRODUCTIVE EFFECTS

In experimental animals, EtO is toxic to reproductive function in both males and females. Although EtO may exert its reproductive toxicity through several mechanisms, the induction of dominant lethal mutations has been the mechanism most convincingly demonstrated.

In male mice exposed to EtO, a positive dose-response relationship has been found between the level of EtO exposure and the occurrence of sterility [Generoso et al, 1980]. In the same study a positive dose-response relationship was noted between

TABLE II. Occurrence of Sister Chromatid Exchanges (SCE) in Lymphocytes of Hospital Workers by EtO Exposure and Smoking Status*

	Mean SCEs/cell	
	Nonsmokers	Smokers
Not exposed	7.04 (±1.00)	7.98 (±0.92)
EtO exposed	8.27 (±2.06)	9.09 (±2.00)

*From Yager et al [1983].

EtO exposure and the incidence of heritable translocations. The frequency of translocations increased from 0% in the offspring of unexposed controls to 1.3% in offspring of mice administered EtO at 20 mg/kg/day and to 9.4% in offspring of mice administered EtO at 60 mg/kg/day.

In male mice injected with EtO in a single intravenous dose of 150 mg/kg body weight, an increase was noted in the frequency of dominant lethal mutations [Generoso et al, 1980]. Dominant lethal mutations are genetic alterations in the sperm that cause death in the offspring. Their occurrence is manifested by a decrease in the number of living embryos per litter and an increase in fetal resorptions. Those effects were most noticeable among females impregnated 2.5 to 7.5 days after exposure of the male mice. Dominant lethal mutations have also been noted in mice, [Appelgren et al, 1977] and in rats [Embree et al, 1977] following single-dose inhalation exposure to EtO at a concentration of 1,000 ppm for four hours. In those latter studies [Embree et al, 1977] a significant increase in postimplantation fetal deaths persisted for five weeks following exposure and then disappeared.

Further evidence for the reproductive toxicity of EtO is provided by a one-generation reproductive study, in which both male and female rats were exposed to EtO by inhalation at concentrations of 10, 33 or 100 ppm, six hours per day, five days per week for 12 weeks prior to mating and for six hours per day, seven days per week for two weeks during and after mating [Snellings et al, 1983]. In the rats exposed at 100 ppm, litter size was significantly reduced; there were fewer implantation sites per pregnant female, and the ratio of the number of live fetuses to the number of implantation sites was decreased. Also a dose-related decrease in fertility was observed in the rats exposed at 33 ppm and at 100 ppm. These findings support the concept that the observed effects are the result of dominant lethal mutations.

LaBorde and Kimmel [1980] have reported recently that EtO is teratogenic to mice. They found a significant increase in the incidence of malformed fetuses, principally with aberrations of the cervical vertebrae, when EtO was administered intravenously in a single dose of 75 or 150 mg/kg to pregnant mice during days 6–8 or days 10–12 of gestation. Those findings have not been replicated in studies conducted in rabbits and in rats [Hardin et al, 1983; NIEHS, 1983].

The effect of EtO on the sperm of cynomolgus monkeys was examined in studies recently conducted by NIOSH [Lynch et al, 1983]. The data from this study show that exposure to EtO in concentrations of 50 ppm and 100 ppm, seven hours per day, five days per week, for 24 months resulted in decreased sperm count and sperm motility, but did not increase the percentage of morphologically abnormal sperm.

A retrospective study of the reproductive toxicity of EtO exposure to hospital sterilizing staff has recently been reported by Hemminki et al [1982] in Finland. These authors examined the frequency of spontaneous abortions in female sterilizing staff exposed to EtO in the years 1951 through 1981 and compared their miscarriage rate with those of (1) sterilizing staff unexposed to EtO and (2) unexposed controls, mainly nursing auxiliaries. They found that the miscarriage rate was significantly higher in exposed than in unexposed hospital staff (Table III). Although documentation of exposure to EtO in Finnish hospitals was not undertaken until 1976, little change in exposure patterns is reported to have occurred over the years prior to 1976. It appears that most workers had no more than one or two short-term EtO exposures per day, and that the concentration of EtO in those short-term peak exposures was 20

TABLE III. Spontaneous Abortion Rates Among Sterilizing Staff Exposed to EtO and Nursing Auxiliaries (Controls)*

	Total No. of pregnancies	Spontaneous abortion rate	
		Crude (%)	Adjusted (%)[a]
Sterilizing staff	1,443	11.3	9.7
Exposed during pregnancy	545	16.7[b]	15.1[b]
Exposure uncertain	293	12.3[b]	11.3[b]
Not exposed during pregnancy	605	6.0	4.6
Controls	1,179	10.6	10.5

*From Hemminki et al [1982].
[a]Rates adjusted for age, parity, decade of reported pregnancy, coffee and alcohol consumption, and smoking habits.
[b]$p < 0.001$ (exposed versus nonexposed pregnancies).

ppm or more. In this study, some misclassification of pregnancies according to exposure appears to have been possible [Gordon and Meinhardt, 1983]. Also, unexposed hospital staff had a miscarriage rate intermediate between those of EtO-exposed and unexposed sterilizing staff; the basis of that finding is unexplained. Nevertheless, the results of the study by Hemminki et al [1982] are suggestive of a toxic effect of EtO on human reproduction. Clearly, these findings need to be corroborated and their implications explored further.

CARCINOGENIC EFFECTS

Animal studies have demonstrated clearly that EtO is carcinogenic.

In a chronic inhalation bioassay study, conducted at the Bushy Run Research Center [Snellings et al, 1981], male and female Fischer 344 rats were exposed to EtO at airborne concentrations of 10, 33, or 100 ppm for six hours per day, five days per week, for two years. Two other groups of animals served as untreated controls. Each group consisted initially of 120 animals of each sex. Based on histologic evaluation, this study concluded that the incidence of mononuclear cell leukemia was significantly increased in a dose-related fashion in female rats exposed to EtO. Also a dose-related increase in peritoneal mesotheliomas was reported in males exposed to EtO. In addition, further analysis at a later date of the neuropathological specimens from this study indicates that a dose-related increase in the incidence of cerebral gliomas was present in the exposed rats.

NIOSH has recently completed a similar inhalation study in which groups of 80 male Fischer 344 rats and 12 male cynomolgus monkeys were exposed to EtO for seven hours/day, five days/week for two years at dose levels of 0, 50, or 100 ppm [Lynch et al, 1982]. This investigation also found dose-related increases in the frequency of mononuclear cell leukemia, peritoneal mesothelioma, and cerebral glioma in the exposed rats.

Dunkelberg [1982] reported that the intragastric administration of EtO to female Sprague-Dawley rats produced a dose-dependent increased incidence of squamous cell carcinomas of the forestomach. EtO was given at a dose of either 7.5 or 30 mg/kg body weight twice a week for nearly three years. At the low dose level, 8 (16%)

of 50 animals developed tumors; at the high dose, 31 (62%) of 50 rats developed tumors.

In a preliminary assessment of the carcinogenicity of EtO to man, Hogstedt et al [1979a], reported three cases of leukemia that occurred between 1972 and 1977 in a relatively small group of Swedish workers exposed to EtO. From Swedish national statistics, 0.2 cases of leukemia would have been expected in the group. The TWA exposure to EtO was estimated to have been between 10 and 30 ppm.

In a follow-up cohort mortality study, Hogstedt et al [1979b] examined the cancer experience of 89 production workers who had worked for at least one year in an EtO manufacturing plant, who had participated in a medical examination at that plant in 1960–61, and who had accumulated at least 10 years' experience since initial employment in the facility. The cancer experience of 86 maintenance employees intermittently exposed to EtO and of 66 men with no potential exposure to EtO was also considered.

The production workers were reported to have had a number of chemical exposures in addition to EtO. These included ethylene glycol, surfactants, cellulose ethers, chloroform, chlorinated acetals, chloral, DDT, ethylene dichloride, ethylene chlorohydrin, and bis (2-chloroethyl) ether. The average EtO exposure was stated to have been under 14 ppm, with occasional higher peaks.

Hogstedt et al [1979b] found significant increases in mortality in the production workers as compared to Swedish national rates for total cancers (9 observed/3.4 expected), for stomach cancer (3/0.4), for leukemia (2/0.14) and for diseases of the circulatory system (12/6.3); the observed-to-expected ratio for leukemia represents a 14-fold increase. No significant excess mortality was observed for any of these causes in the two unexposed groups of workers. A similar pattern of increased mortality was observed in a subcohort of the production workers who had accumulated at least ten years' exposure to EtO and 20 years' latency since first exposure.

A reportedly negative mortality study of workers exposed to EtO has been described by Morgan et al [1981]. They found no indication of an increased risk in total or site-specific cancer mortality, including leukemia. The authors indicated, however, that due to the small size of their study population, they would have expected only 0.14 leukemia deaths based on national rates and could have detected only a greater than a 10-fold increase in risk of leukemia. Also the study population included persons with only potential exposure to EtO, and no analysis was conducted by duration of induction-latency. This study should therefore more properly be described as inconclusive rather than as negative.

In a recent review [OSHA, 1983] of these studies of the human carcinogenicity of EtO, the Occupational Safety and Health Administration, US Department of Labor, observed:

> Taken singularly, the two studies by Hogstedt [1979a,b] and the study by Morgan et al [1981] are not remarkable. They attempted to characterize relatively rare events in small populations and might be disregarded because of small numbers regardless of statistical significance. Taken together with all their limitations, however, OSHA believes they suggest that exposure to EtO may increase the risk of malignancies, particularly leukemia.

Subsequent to that commentary, data from a fourth epidemiologic study by Thiess et al [1982] have become available. In this small retrospective cohort evaluation, the mortality experience of 602 chemical workers from nine facilities was compared to that of several general reference populations and to that of another worker population with potential exposure to styrene. The 602 workers in this population were exposed not only to EtO, but also to propylene oxide and to a variety of other chemicals including butylene oxide, dioxane, epichlorohydrin, dichloropropane, ethylene chlorohydrin, cyclohexylamine, formaldehyde, benzene, and phenol. The study period covered the years 1928 to 1980, during which time dramatic changes in the working environment undoubtedly occurred.

The analysis by Thiess et al [1982] demonstrated a nonsignificant excess in death caused by stomach cancer (4 observed/2.667 expected) and by tumors of the hematopoietic and lymphatic tissue (2 observed/1.158 expected) compared to general rates from the Federal Republic of Germany. When the analysis was further restricted to consider only the experience of the 351 workers who had accrued at least ten years of life since initial employment, nonsignificant excesses of deaths were observed for malignant tumors of the brain (one observed) and for myeloid leukemia (one observed). Analysis of mortality rates in this study population in relation to those observed in the workers exposed to styrene indicated that mortality from all malignant tumors was 46% greater in this population.

The study by Thiess et al [1982], like the one reported by Morgan et al [1981], is limited in that it can detect only relatively large increases in cause-specific death risk, owing to its small study population. Using the statistical power calculation procedures presented by Beaumont and Breslow [1981], we determined that only a five-fold or greater increased risk of death owing to hematopoietic malignancy could have been detected in this population (assuming a level of significance of 0.05 for a one-sided hypothesis) with 80% power. Consequently, the results of this study are inherently inconclusive.

NEUROLOGIC TOXICITY

EtO exposure has been associated with neurological effects in both animals and man. Impairment of sensory and motor function and muscle atrophy (wasting and weakening of the hind limbs), were observed in rats, rabbits, and monkeys exposed to 357 ppm EtO over a period of 48–85 days [Hollingsworth et al, 1956]. Also a study of rats exposed to 400 ppm of EtO for six weeks noted that during the last two weeks of the exposure period, the rats moved about on their front feet only, dragging their hindquarters [Jacobson et al, 1956].

There are also reports of human exposure to EtO associated with neurological effects. Gross et al [1979] linked workplace exposure to EtO with peripheral neuropathy. They reported four cases of clinically confirmed neuropathy among workers exposed to a leaking sterilizing chamber for a period of two weeks to two months. Levels of EtO were not monitored but were thought to have been greater than 700 ppm.

QUANTITATIVE RISK ASSESSMENT

To evaluate in quantitative fashion the relationship between EtO exposure and human malignancy, OSHA has recently conducted a quantitative risk assessment

[OSHA, 1983]. This assessment was based on data from the chronic inhalation bioassay study in Fisher 344 rats undertaken at the Bushy Run Research Center. The assessment was performed using a computer program (GLOBAL 82) that extrapolates animal data on chemical carcinogenesis to the situation of low-dose human response. The program assumes (1) a linear, no-threshold dose-response relationship between exposure at low doses and death from malignancy and (2) that absorption of EtO for both rats and humans is 100%. In the extrapolation, data from male rats were fitted to both a multistage as well as to a one-hit model of carcinogenesis; data from female rats were fitted to a multistage model.

The assessment found, as a maximum likelihood estimate, that if 10,000 workers were exposed to EtO for a working lifetime at a dose of 50 ppm, then between 634 and 1,093 excess deaths from cancer would be expected to occur; the estimate varied with the model used and the source of the data (Table IV). At exposure for a working lifetime at 1 ppm, between 12 and 23 excess cancer deaths were projected per 10,000 workers, and at 0.1 ppm between 1.2 and 2.3 excess cancer deaths were projected.

EVALUATION AND RECOMMENDATIONS

We conclude on the basis of our evaluation of the available data that—

- EtO is a mutagen;
- EtO is capable of causing damage to the chromosomes of plant species, animal species, and man;
- EtO is toxic to reproductive function in both males and females of several animal species;
- EtO is possibly toxic to human reproductive function (based on results of a single study);
- EtO is a proven animal carcinogen, causing dose-related increases in the incidence of leukemia, peritoneal mesothelioma, and cerebral glioma;
- there is evidence, albeit limited, for the carcinogenicity of EtO in man.

TABLE IV. Excess Lifetime Risk of Cancer per 10,000 Workers From Exposure to Ethylene Oxide*

Exposure	Multistage[a]		One hit[b]		Multistage[c]	
(ppm)	MLE[d]	UCL[e]	MLE	UCL	MLE	UCL
50	634	1,008	746	1,018	1,093	1,524
10	118	211	154	213	229	326
5	58	106	77	107	115	164
1	12	21	15	21	23	33
0.5	6	11	8	11	12	16

*Extra risk per 10,000 workers. Lifetime exposure is assumed to be eight hours per day, five days per week, 46 weeks per year for 45 years in a 54-year life span since initial exposure.
[a]Extrapolated from male rats.
[b]Extrapolated from male rats.
[c]Extrapolated from female rats.
[d]Maximum likelihood estimate of excess risk.
[e]95% upper confidence limit on excess risk.

These findings, and the striking similarities between the numerous animal and human studies, reinforce the assessment made previously by NIOSH [1981] that EtO must be regarded as a potential human carcinogen.

No safe level of exposure to carcinogens has been demonstrated for man. However, the probability of developing cancer is likely to be reduced through decreasing exposure. In light of these principles, and given the findings of the foregoing quantitative risk assessment [OSHA, 1983], we have recommended that the eight-hour time weighted average (TWA) permissible exposure limit for EtO be set lower than 0.1 ppm. Even at an exposure to 0.1 ppm, according to the currently available risk assessments (with their limitations) [OSHA, 1983], mortality from excess cancer is not completely eliminated. Therefore, for maximum protection of health, the legal standard should be set below that limit.

In addition, because of the observations that even brief exposures to EtO are associated with an increased frequency of SCEs [Yager et al, 1983] and possibly of spontaneous abortions [Hemminki et al, 1982], we recommend that a short-term exposure standard for occupational exposure to EtO be adopted. We recommend that such a standard allow a worker to be exposed to no more than 5 ppm EtO for more than ten minutes in any working day.

These recommended exposure levels will not eliminate completely the risk of developing cancer as a consequence of occupational exposure to EtO. Adherence to these recommendations will, however, if a linear model is assumed to be applicable, reduce by 99.8% the risk of developing cancer that exists at the current legal exposure standard of 50 ppm.

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