Vista Chemical Company

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[redacted]
XF: Case Reply

March 11, 1987

VISTA

Ms. Karen Buelow
Johnson Controls Inc.
Battery Division
P.O. Box 591
Milwaukee, WI 53201

Dear Karen:

Enclosed is a current MSDS for Vista PVC Dry Blend. The date of preparation is on the last page, lower left-hand corner.

We are in the process of revising the MSDS format to make this preparation date more prominent and revised sheets will be distributed. Please contact me at 713/531-3445 if you have further questions.

Sincerely,

Thomas G. Grumbles

Thomas G. Grumbles, C.I.H.
Environmental Quality Manager

ajo

Enclosure

VVV 000009139

~~To: [illegible]~~
CF: None

TO: Distribution

FROM: T. G. Grumbles
DATE: March 9, 1987

Interoffice Communication

SUBJ: NEW NRC RECOMMENDATIONS FOR EEGL FOR ETO

VISTA

Enclosed is a copy of the Eto portion of a recent (last week) publication by the NRC. This document finalizes the proposed 20 ppm Emergency Exposure Guidance Level (EEGL). There is a lot of background data presented but the "meat" of the document is on page 57.

There is also a good discussion of the committee's rationale for setting EEGL for carcinogens which could help us in our decision making.

I have requested a copy of the Benzene portion of the document. However, I've been told the proposed 1,000 ppm EEGL for benzene was dropped to 50 ppm in the committee's final recommendation. I'll distribute when I obtain the document. For now I'll ask Mary Jo to model a 50 ppm benzene line in our initial models.

T. G. Grumbles

ajo

Enclosure

Distribution:

M. G. Hayes
S. F. Pitts
E. Taylor
S. R. Ashby
J. P. Warner
LC LAB Safety Director
M. J. Heller
J. R. Drumwright

Emergency and Continuous Exposure Guidance Levels for Selected Airborne Contaminants

Volume 6
Benzene and Ethylene Oxide

Committee on Toxicology
Board on Environmental Studies and Toxicology
Commission on Life Sciences
National Research Council

ETHYLENE OXIDE

BACKGROUND INFORMATION

PHYSICAL AND CHEMICAL PROPERTIES

Synonyms:	Dihydrooxirene, dimethylene oxide, epoxyethane, 1,2-epoxyethane, EO, ethene oxide, EtO, ETOX, oxacyclopropane, oxane, oxidoethane, α,β-oxidoethane, oxirane (IARC, 1985)
CAS number:	75-21-8
Molecular formula:	C_2H_4O
Molecular weight:	44.05
Boiling point:	10.4°C
Freezing point:	-112.6°C
Liquid density:	0.8970 at 0°C
Vapor pressure:	1095 mm Hg at 20°C
Flash point:	-4°F
Flammable limits:	3-100%
Solubility:	Miscible with water, acetone, methanol, ether, benzene, carbon tetrachloride
General characteristics:	Colorless liquid below 10.4°C; at higher temperatures, highly flammable, sweet-smelling gas with median detectable odor concentration of 700 ppm; highly reactive with compounds containing labile hydrogen atoms
Conversion factors:	1 ppm = 1.8 mg/m^3 1 mg/m^3 = 0.55 ppm

OCCURRENCE AND USE

In 1984, U.S. production of ethylene oxide (EtO) was about 5.96 billion pounds (U.S. International Trade Commission, 1985). Its largest use is in the production of the antifreeze constituent ethylene glycol. It also serves as an intermediate in the manufacture of polyethylene terephthalate polyester fiber and film and in the manufacture of diethylene glycol, ethanolamines, choline, and other chemicals. It is used in the manufacture of glycol ethers, which are used as jet fuel additives and in the formulation of coatings, cleaners, automotive

brake fluids, and inks. It is used directly to accelerate the maturing of tobacco leaves. EtO is also used as a fumigant of medical supplies and equipment, cosmetics, clothing, aircraft, spices, and dairy packaging. The National Institute for Occupational Safety and Health (NIOSH) estimated in 1977 that approximately 75,000 workers in U.S. hospitals were commonly exposed for brief but varied periods to EtO at unexpectedly large concentrations (300-3,000 ppm) from sterilizers. Measures recently taken to control release of EtO vapor into the ambient air have reduced the opportunities for workers in hospitals to be exposed to EtO at relatively high concentrations.

SUMMARY OF TOXICITY DATA

EFFECTS ON HUMANS

The Occupational Safety and Health Administration (OSHA) published the final standard for routine occupational exposure to EtO in 1984, including a summary of both animal and human studies on toxicity.

Acute Effects

Early symptoms of inhalation of EtO at high concentrations for even a short period are irritation of the eyes, nose, and throat and a "peculiar taste." Effects that might be delayed are headache, nausea, vomiting, dyspnea, cyanosis, pulmonary edema, drowsiness, weakness, incoordination, electrocardiographic abnormalities, and urinary excretion of bile (Glaser, 1979; Hine et al., 1981).

A variety of case reports describe short-term, acute effects of accidental or occupational exposures to EtO, but none includes followup information about possible long-term health effects of those exposures.

Capellini and Ghezzi (1965) described two workers who were poisoned when accidentally exposed to EtO at high concentrations while packing confectionery products. In one patient, the exposure was associated with neuropsychic excitement, impairment of consciousness, somnolence, and muscle weakness. The second patient experienced gastrointestinal disturbances, including nausea, vomiting, diarrhea, and abdominal pain; laboratory findings suggested hepatic dysfunction. Both patients developed lymphocytosis. Both recovered in 7-10 d, but no followup information is available on possible long-term effects.

Blackwood and Erskine (1938) reported that six men became ill while working in a ship compartment adjacent to one being fumigated with a commercial mixture of 10% EtO/90% CO_2. In another study, 12 female employees were reported to have been "overcome" by EtO used as a disinfectant in a California food plant (Industrial Hygiene Newsletter, 1947). In both instances, headaches, nausea, vomiting, and respiratory irritation were sustained. In a limited period after exposure, no

permanent effects were reported, but long-term followup was not conducted.

In 1963, Thiess reported the effects of an accidental forceful blast of gaseous EtO, from a sterilizer, that struck a nurse in the eye, nose, and mouth. The nurse's nose became painful, and the eye developed epithelial keratitis consisting of fine, gray, fluorescein-staining dots in the corneal epithelium. Discomfort reached a maximum 9-10 h after exposure; by 15 h, the pain began to subside; and by 24 h, the eye was normal by slit-lamp examination. Again, no long-term followup was conducted. Thiess (1963) also reported on a patient who was accidentally squirted in the eye with liquid EtO. The eye was irrigated immediately with copious amounts of water, but became irritated, and the irritation lasted for a day.

In four men, no after-effect of intentional exposure to EtO at 1:400 (2,500 ppm) for an unstated but apparently brief period, other than temporary slight nasal irritation, was observed, whereas definite nasal irritation was noted after 10 s of exposure at 1:80 (12,500 ppm); there was no lacrimation (Walker and Greeson, 1932).

Aqueous solutions of EtO have produced skin burns. EtO is reportedly retained in rubber and leather for long periods. Wearing contaminated footwear has resulted in serious foot burns (Phillips and Kaye, 1949). Redness, edema, blisters, and ulceration of skin have been reported after contact with rubber gloves or leather shoes that had absorbed EtO and had not been properly aerated (Royce and Moore, 1955). These short-term irritant effects were reversible. A reported case of immediate hypersensitivity involved contact urticaria and anaphylaxis after repeated exposure to EtO residues in renal dialysis equipment (Poothullil et al., 1975). As with the other studies noted here, no long-term followup was conducted. The work of Sexton and Henson (1950) suggested that repeated skin contact with aqueous EtO solution results in the development of skin sensitivity.

Some studies of EtO exposures of humans that did include followup examinations indicated that EtO is associated with peripheral neuropathy, chromosomal aberrations, other damage to DNA, some cancers, and increased rates of spontaneous abortion.

Chronic Effects

Neurotoxicity.

Four cases of neurotoxicity were attributed to an EtO sterilizer that leaked for its first 2 mo of operation (Gross et al., 1979). The length of exposure to the leaking sterilizer was 3 wk for patients 1 and 2, 2 wk for patient 3, and 2 mo for patient 4. The peak EtO concentrations were estimated to exceed 700 ppm (greater than that detectable by smell). One exposed person had motor seizures at the end

of the workday, two complained of muscular weakness and had slight sensory decrements, and the fourth was asymptomatic, but had a decreased velocity of conduction of the nerve impulse along peripheral nerves. In all three symptomatic cases, there was marked subjective improvement within 2 wk after termination of exposure. Patients 1, 3, and 4 returned to the work they had been doing. Peripheral nerve conduction in patient 1 was normal throughout, whereas that in patients 2, 3, and 4 was decreased. Patient 2 stopped working with EtO, but sustained permanent peripheral nerve damage. Conduction deficit of the nerve action potential in patients 3 and 4 remained, but they continued to work at lower EtO exposure.

Eight additional workers were examined who were exposed to EtO sterilizers, but were not exposed at the same high concentrations as the four workers exposed to the leaking sterilizer. These eight workers did not develop neurologic abnormalities, but two had increased central corneal thickness with normal endothelial cell counts (Jay et al., 1982). Of the four workers exposed to the leaking sterilizer, three developed cataracts (of whom one required bilateral cataract extractions) and two had increased corneal thickness with normal endothelial cell counts.

Finelli et al. (1983) observed that occupational exposure to EtO at unspecified concentrations for several months resulted in subacute polyneuropathy, with bilateral foot drop and electromyographic denervation potentials as the principal abnormalities in three young men. Two patients were asymptomatic at 7 and 4 mo, and the third had almost fully recovered 6 mo after removal from exposure to EtO.

Kuzuhara et al. (1983) observed sensorimotor polyneuropathy in two workers who had been exposed to EtO at unspecified concentrations repeatedly for several months. Sural nerve biopsies revealed axonal degeneration with mild changes of the myelin sheath. Unmyelinated fibers were also involved. Muscle biopsies showed typical denervation atrophy. Symptoms improved after exposure to EtO terminated.

Chromosomal Effects

Studies of workers exposed to EtO have shown increase in sister chromatid exchanges (SCEs), chromosomal aberrations, and micronuclei.

The lymphocytes in the blood of seven workers who experienced acute symptoms after accidental exposure to EtO at high, but unspecified, concentrations for about 2 h were examined 18 mo after exposure (Kallings, 1967). Greater numbers of chromosomal aberrations (breaks, gaps, and exchanges) were seen in the exposed workers than in 10 unexposed controls from the same factory, but limitations in the design and conduct of the study prevent firm conclusions.

Thiess et al. (1981) studied chromosomal effects in 43 male workers exposed to EtO. The employees were divided into four groups, according

to their periods of exposure: (1) long-term exposure for more than 20 yr, (2) exposure for less than 20 yr, (3) long-term exposure and accident (EtO inhalation or skin contact), and (4) accident (brief high exposure to EtO). The control group comprised male employees from the office staff.

Measurement of the concentrations in various sections of the plant yielded values of up to 3 ppm under conditions of normal operation. However, this figure rose briefly to 1,900 ppm under plant breakdown conditions. In the authors' experience, it is to be expected that workers were subjected to higher exposure in the past.

A significant increase in the chromosomal aberration rate was found only in Group 1. This was confirmed by a control examination carried out a year later. Groups 2, 3, and 4 displayed no significant increases. However, it should be noted that the employees had been in contact with a wide range of substances and products in the course of their occupation, so the increased aberration rate cannot be attributed unequivocally to exposure to a particular substance.

Yager et al. (1983) studied the effect of repeated short-term exposures to EtO on SCEs in 14 hospital workers, compared with 13 control subjects. The cumulative estimated EtO inhalation exposure ranged from 0 to 744 mg. In 30 observed short-term exposures, the mean dose of EtO was 9.6 mg, or 82 ppm averaged over 3.5 min (total dose, 287 ppm•min), even though the estimated time-weighted average concentration was less than 1 ppm. The mean frequency of SCE per cell was significantly higher in workers with EtO exposures exceeding 100 mg (10.69 SCEs per cell) than in those exposed to less than 100 mg (7.76 SCEs per cell) or 13 controls (7.56 SCEs per cell). The authors suggested that the excess SCEs might be attributable to the effect of cumulative unrepaired lesions in the nondividing population of long-lived circulating lymphocytes.

Laurent et al. (1984) analyzed, for SCEs, blood samples from 25 subjects professionally exposed to EtO at high concentrations for 2 yr and from 22 control subjects. The quantity of EtO inhaled during the 2 yr was estimated to be 500-5,800 mg. The exposed group had significantly more SCEs than the control group. Senior workers had the highest mean SCE frequency; that indicates that the effect of exposure to EtO was sufficient to produce genetic effects, was cumulative, and in some cases was persistent.

Stolley et al. (1984) studied SCE frequencies in workers potentially exposed to EtO and compared them with those in unexposed control groups. Three facilities of a company where the previous environmental control of EtO was known to have differed were chosen. Within these worksites, subjects were categorized into high-exposure-potential, low-exposure-potential, and control groups. Worksites I, II, and III, respectively, represented increasing EtO exposure. Blood samples for chromosome studies were drawn at several times over a

period of 24 mo. At worksite III (exposure at 50-200 ppm), large increases in SCEs were seen among those with high exposure potential and persisted for 24 mo. At worksite II (exposure at 5-10 ppm), SCEs in the high-exposure-potential workers were higher than those in the control group. No significant effects were seen among workers at worksite I (exposure at 0.5 ppm).

Richmond et al. (1985), in a study of employees of American Hospital Supply Corporation who had been exposed for 1-10 yr to EtO at 1-40 ppm, observed significant differences in the numbers and types of chromosomal aberrations between EtO-exposed workers and unexposed controls. Quadriradial and triradial chromosomal forms, which are rarely found in unexposed populations, were increased in exposed workers. Increased numbers of SCEs were found in cultured lymphocytes of some, but not all, exposed persons. Significant improvement was not seen during a 4-yr followup, except for moderate reduction in SCEs.

Hogstedt et al. (1983) studied chromosomal aberrations, SCEs, and micronuclei in 28 workers occupationally exposed to EtO and 20 unexposed controls. All 28 exposed persons had been exposed at TWA concentrations not exceeding 1 ppm during the preceding 2.5 yr. Until 2.5 yr before the investigation, 13 had been exposed at higher concentrations, probably 5 ppm. The exposed persons had significantly higher numbers of chromosomal aberrations in lymphocytes and of micronuclei in erythroblasts and polychromatic erythrocytes than the controls. A significant effect of smoking on micronuclei was reported, but there was no increase in SCEs.

Garry and co-workers (1979) studied a group of 12 employees who worked in an EtO sterilization facility. Clinical symptoms of the upper respiratory tract and central nervous system had been reported periodically by many of these employees. Air samples taken over a period of 0.5 h or more revealed a maximal EtO concentration of 36 ppm at a distance of 15 ft from the sterilizer. Concentrations of EtO greater than 1,500 ppm during the purge phase of the sterilization cycle were reported near an open drain. Four symptomatic employees chronically exposed to EtO demonstrated a significantly higher number of SCEs 3 wk and 8 wk after their last known exposure to EtO than a group of 12 employees who worked in an adjacent operating room. Another group of eight EtO-exposed workers with fewer symptoms showed a significant increase in the number of SCEs 9 wk after their last EtO exposure.

Garry et al. (1979) also found that accidental exposure at 1,500 ppm for 5 min increased the incidence of SCEs. From this observation, Garry et al. (1982) postulated that short-term exposure to a high concentration of EtO could increase the number of SCEs in peripheral blood, and they tested this hypothesis by exposing human peripheral blood cells to various concentrations of EtO in vitro. They devised a membrane dosimetry system that was used to expose lymphocytes in peripheral blood to specified amounts of EtO. They observed increased

SCEs in cultured human lymphocytes exposed to EtO at 10-35 μg/ml (in media) for 20 min. A significant dose-response relationship between SCEs and EtO dose was observed up to 35 μg/ml, the highest tested dose. Inasmuch as duration of exposure to EtO was short (20 min), a burst of EtO can increase SCE frequency, and rapid excursions of EtO might be important.

Pero et al. (1981) examined the effects of exposure to EtO on unscheduled DNA synthesis induced by N-acetoxy-2-acetylaminofluorene (NA-AAF)--a measure of repair of damage to DNA--and on chromosomal aberrations in the peripheral lymphocytes of women employed in a Swedish factory that manufactured disposable medical equipment. Seventeen EtO-exposed workers and 11 matched controls working at the same plant were examined. Group 1 consisted of 12 packers exposed to EtO at an average of 0.5-1 ppm throughout each working day for 8 yr. Group 2 was composed of five sterilizer technicians who had been exposed to EtO at 5-10 ppm for 1 hr/d for 0.8-3.0 yr. Numbers of total chromatid gaps and breaks were significantly higher in EtO-exposed groups. The NA-AAF-induced unscheduled DNA synthesis in cultured lymphocytes was negatively correlated with the duration of EtO exposure and the number of chromosomal breaks, indicating an inhibition in vivo of DNA-repair capacity by EtO. These data were verified in vitro by biochemical and autoradiographic studies of EtO-induced unscheduled DNA synthesis in human blood cells. With EtO above 2 mM, unscheduled DNA synthesis was inhibited in lymphocytes, whether they were cultured for 24 h or 122 h after alkylation with EtO.

Pero et al. (1982) also examined the effects of EtO exposure on unscheduled DNA synthesis induced by NA-AAF in cultured peripheral lymphocytes. Blood samples were obtained from five male workers--employed in sterilizing, packing, or truck-driving--who were exposed to EtO at 8-h TWA concentrations of 0.5-1 ppm for 0.3-5 yr. Control samples were obtained from 12 men employed in a nearby facility where no known mutagens were in use; controls were matched with the exposed group for age and smoking history. DNA repair proficiency was significantly lower in the EtO-exposed workers than in controls.

The studies of Pero et al. were criticized on the basis that the workers were exposed to a mixture of EtO and methyl formate. However, it should be noted that the in vitro studies of Pero et al. (1981) were conducted without methyl formate; thus, it is unlikely that methyl formate elicited in vivo effects.

Thus, chromosome studies from a number of EtO-exposed groups have revealed increased numbers of chromosomal aberrations, SCEs in peripheral lymphocytes, and micronuclei in bone marrow progenitor cells (Table 3). These effects reflect the capacity of EtO to bind with DNA molecules and its potential as a cancer hazard.

TABLE 3

Summary of Chromosomal-Effect Studies of Ethylene Oxide in Humans

EtO Exposure	Frequency of Exposure	Results and Comments	Reference
High unspecified exposure for about 2 h	Single	Greater number of chromosomal aberrations in exposed workers than in controls	Ehrenberg and Hallstrom, 1967
82 ppm for 3.5 min	Repeated short-term	Increase in SCEs	Yager et al., 1983
36 ppm (maximum)	Chronic	Increase in SCEs	Garry et al., 1979
1,500 ppm for 5 min	Single	Increase in SCEs	
500-5,800 mg (total exposure)	2 yr	Increase in SCEs	Laurent et al., 1984
50-200 ppm	Chronic	Increase in SCEs	Stolley et al., 1984
Below 5 ppm	Several years	No chromosomal effects when exposure less than 20 yr, increases in chromosomal aberration when exposure more than 20 yr	Thiess et al., 1981
1-40 ppm	1-10 yr	Increase in chromosomal aberrations	Richmond et al., 1985
Less than 5 ppm	Several years	Increases in chromosomal aberrations, SCEs, and micronuclei	Hogstedt et al., 1983
0.5-1 ppm	5 d/wk for 8 yr	Increases in chromosomal aberrations and decreased UDS	Pero et al., 1981
5-10 ppm	1 h/d, 5 d/wk for 0.8-3 yr	Increase in chromosomal aberrations	Pero et al., 1981

Carcinogenicity

Several epidemiologic studies have reported increased incidence of cancers in workers exposed to EtO.

Hogstedt et al. (1979a) reported two cases of leukemia in workers exposed to EtO from newly sterilized boxes. They occurred in a relatively small group (about 230) of Swedish workers exposed for up to 10 yr to EtO at a TWA concentration of 20 ± 10 ppm. Only 0.2 case of leukemia would have been expected. These workers were also exposed to methyl formate. However, no reported evidence links methyl formate with a carcinogenic effect; hence, EtO is the likely causative agent for the increased leukemias.

Hogstedt et al. (1979b) studied mortality and cancer among production workers exposed (1,324 person-yr) not only to EtO, but also to ethylene dichloride, ethylene chlorohydrin, ethylene, and a small amount of bis(2-chloroethyl) ether, maintenance workers with intermittent exposures (1,211 person-yr), and unexposed workers (955 person-yr). The cohort exposed full-time demonstrated a statistically significant excess of cancer of the stomach and of leukemia. Diseases of the circulatory system were also increased. The excess mortality and cancer cannot be attributed to EtO, because of the simultaneous exposures to other chemicals.

Hogstedt et al. (1986) presented additional epidemiologic data that show an association between EtO exposure and cancer. In an additional followup of the Swedish workers, three cases of leukemia were observed in 203 workers exposed intermittently to EtO. In a second plant, four of 175 workers exposed to EtO developed leukemia, but no measure of the concentration of EtO in the air or length of exposure was given. In a third plant, leukemia was observed in one of 355 workers exposed to EtO at 1-8 ppm, but the length of exposure was not given. These findings provide additional evidence of an association between EtO exposure and leukemia. They also reported six cases of stomach cancer, compared with 0.6 case expected.

A limited epidemiologic survey (Morgan et al., 1981) of 767 men who had been employed at a Texaco chemical plant for 5 yr with possible exposure to EtO demonstrated increased risks of cancer of the pancreas and Hodgkin's disease, but had no deaths from leukemia. As in many studies of healthy workers, deaths from all causes were about half the expected (46 observed vs. 80 expected). Exposure of different workers varied, but in most cases was well below 50 ppm for an 8-h TWA. The authors did not reach definitive conclusions, because the study population was small and the observation period short. Further analysis of data from this cohort might use one-sided statistical significance tests.

Other Effects

Spontaneous abortions in a Finnish hospital sterilizing staff were analyzed on the basis of data from a postal questionnaire and a hospital discharge register. Nursing auxiliaries served as controls (Hemminki et al., 1982). Data from questionnaires showed that the frequency of spontaneous abortions was 11.3% for the sterilizing staff and 10.6% for nursing auxiliaries. Members of the sterilizing staff who were involved in sterilization during their pregnancies showed a frequency of spontaneous abortion of 16.9%, compared with 5.6% in the nonexposed. The increased frequency of spontaneous abortion was correlated with exposure to EtO, but not with exposure to glutaraldehyde or to formaldehyde. Exposure to EtO between 1976 and 1981 in Finnish hospitals was at a TWA concentration estimated as ranging from 0.1 to 0.5 ppm, with a peak of 250 ppm. Increased frequency of spontaneous abortion might be due to genotoxic effects of EtO.

In an early study, with slight power to detect a positive effect, Joyner (1964) evaluated the health of 37 workers exposed for an average of 10.6 yr to EtO at estimated mean concentrations of 5-10 ppm, with occasional increases to 56 ppm and peaks of 127 ppm for up to 3 min. No differences in incidence of specific diseases, as evaluated from past and current physical examinations, were found between the exposed and nonexposed populations.

SUMMARY

In sum, the signs and symptoms induced by exposure of humans to EtO vapor at acutely toxic concentrations (above 2,000 ppm) are headache, nausea, vomiting, dyspnea, hematologic abnormalities, and respiratory irritation. Dermal and eye contacts result in skin and corneal burns and possibly sensitization of skin. Longer inhalation exposures at low concentrations are associated with neurotoxicity and chromosomal aberrations. Brief exposures to EtO at high concentrations have also been shown to produce chromosomal effects. Prolonged exposure results in death from leukemia and stomach cancer. Exposure to EtO has also been associated with spontaneous abortions. The value of the epidemiologic studies is confounded, however, by the uncertainty of exposure data and by the presence of exposure to other chemicals.

EFFECTS ON ANIMALS

Acute and Short-Term Exposure

Short-term in vivo animal tests with EtO have produced a panoply of behavioral, hematologic, and other abnormalities.

Table 4 lists 4-h LC_{50}s of EtO vapor for rats, mice, and dogs (Jacobson et al., 1956). For rats, the LC_{50} was 1,460 ppm. A single

TABLE 4

Mortality in Rats, Mice, and Dogs Exposed for 4 h to Ethylene Oxide Vapor at Various Concentrations[a]

Concentration, ppm	Mortality	Mortality at 14 Days, %
Rats (LC_{50}, 1,460 ppm):		
2,298	1 h, 3/10; 1 d, 9/10; 2 d, 10/10	100
1,992	2 h, 5/10; 1 d, 9/10; 4 d, 10/10	100
1,843	1 d, 6/10; 2 d, 9/10	90
1,648	1 d, 2/10; 2 d, 3/10; 4 d, 4/10	40
882	9 d, 1/10;14 d, 2/10	20
Mice (LC_{50}, 835 ppm):		
1,365	During exposure, 2/10; 2 h, 3/10; 1 d, 10/10	100
1,343	During exposure, 4/10; 1 d, 7/10; 3 d, 9/10; 4 d, 10/10	100
960	1 h, 1/10; 1 d, 5/10; 9 d, 6/10; 12 d, 7/10	70
882	1 d, 2/10; 2 d, 3/10	30
860	2 h, 3/10; 1 d, 6/10	60
533	13 d, 1/10	10
Dogs (LC_{50}, 960 ppm:):		
2,830	3 h, 1/3; 5 h, 3/3	100
1,393	1 d, 3/3	100
710	14 d, 0/3	0
327	14 d, 0/3	0

[a] Data from Jacobson et al., 1956.

4-h exposure resulted in frequent movement and preening, clear nasal discharge, lacrimation, diarrhea, gasping, and occasional salivation. Similar signs were observed in mice, except that diarrhea was not noted. The LC_{50} for mice exposed for 4 h was 835 ppm. Dogs exposed at about 2,800 ppm for 4 h showed lacrimation, clear nasal discharge, salivation, vomiting, diarrhea, and convulsions with labored breathing, followed by death. Dogs exposed at about 1,400 ppm showed similar signs, except for diarrhea, convulsions, and respiratory changes. Dogs exposed at about 700 ppm and less showed no toxic signs. The LC_{50} for dogs was 960 ppm. Postmortem examination of rats exposed to EtO showed irritation in the upper respiratory passages and moderate congestion and petechial hemorrhages in the tracheal mucosa. The maximal pulmonary lesion consisted of a minor degree of patchy scattered edema, sometimes involving the peribronchial zones. Secretion around the eyes and nose provided further evidence of the irritant properties of EtO. In dogs, moderate congestion in the lungs and dilation of perivascular lymphatic spaces was noted at necropsy. There was some perivascular edema, but no remarkable changes in other organs or tissues. A constant finding in all species was a gross distension of the stomach.

Experiments of Walker and Greeson (1932) showed that sharp conjunctivitis with blepharitis followed the introduction of a drop of EtO (concentration and vehicle unspecified) into the eyes of rabbits, but the condition subsided rapidly and the eyes were in all cases normal, or practically so, within 4 d. There was no permanent damage to the eyes.

Table 5 summarizes the acute health effects in several species of experimental animals exposed to EtO by various investigators. Exposure to high concentrations of EtO vapor caused irritation of the eyes, respiratory tract, and lungs; convulsive seizures; weakness of the extremities; secondary infection of the lungs; and death from respiratory failure. In guinea pigs, corneal opacity was observed.

Table 6 summarizes effects of repeated exposures to EtO in animals (Hollingsworth et al., 1956; Jacobson et al., 1956, and Lynch et al., 1984a). Inhalation exposure to EtO at concentrations comparable with those which caused acute effects in people caused similar effects in mice, rats, and dogs. Repeated exposures of mice and rats to about 13% of the 4-h single-dose LC_{50}s (Table 4) for 6 or 7 h resulted in significant mortality (26.7% and 55.0%) in these two species.

Mutagenicity and Other Short-Term Tests

EtO has been mutagenic in virtually every test system that has been applied. It reacts with DNA, primarily at the N-7 position of guanine (Brookes and Lawley, 1961; Ehrenberg et al., 1974). It also alkylates other nucleic acid bases when the reaction occurs in vitro. EtO is

TABLE 5

Summary of Acute Effects of Inhalation Exposure of Animals to Ethylene Oxide[a]

Concentration, ppm by vol. in air	Duration of Exposure, h	Species	Results
250-280	8	Guinea pig	Slight respiratory changes, no deaths
	48	Guinea pig	Occasional death
560-600	7	Guinea pig, cat, dog	No deaths
	8	Guinea pig	Occasional death
	22	Guinea pig, cat	Death during or after exposure
	22	Rabbit, 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, rabbit	Slight injury, no deaths
	8	Rat, cat	Death within 24 h
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 h
	4	Guinea pig	Injurious, few deaths
	4	Rabbit	Injurious, no deaths
	4	Dog	Death within 24 h
3,000	1	Guinea pig	No deaths
	3	Guinea pig	Majority died in 1-8 d
	8	Guinea pig	Majority died in 24 h
7,000	0.3	Guinea pig	No evidence of injury
	1	Guinea pig	Majority died in 1-8 d
	2.5	Guinea pig	Death within 24 h
14,000	0.2	Guinea pig	No evidence of injury
	0.3	Guinea pig	Majority died in 1-8 d
	1	Guinea pig	Death within 24 h
51,000-64,000	0.1	Guinea pig	Majority died in 1-8 d
	0.2	Guinea pig	Death within 24 h

[a] Data compiled by Hine et al. (1981), from Jacobson et al. (1956), Hollingsworth et al. (1956), Flury and Zernik (1931), Waite et al., 1930, and Smyth et al. (1941).

TABLE 6

Results of Repeated Inhalation Exposure of Animals to Vapors of Ethylene Oxide[a]

Concentration, ppm	Hours per day	No. of Exposures[b]	Duration, Days	Mortality[c]	Species	Pathologic Findings
841	7	6	10	10/10	Rat	Gross irritation of respiratory tract; mice seemed most susceptible; all animals died
	7	8	10	8/8	Guinea pig	
	7	4	10	1/1	Rabbit	
	7	1	10	5/5F	Mouse	
	7	7	10	1/1F	Monkey	
357	7	7	9	2/20	Rat	Moderate loss of body weight and severe lung injury in rodents
	7	7	9	4/10F	Mouse	
	7	33	48	10/10	Mouse	Secondary respiratory infection primary cause of death in rodents; impaired nervous function at lumbar and sacral levels, reversible in rat, rabbit, monkey; normal blood urea nitrogen in all species; normal hematologic values in rats, rabbits, and monkeys.
	7	38	56	10/10F	Rat	
	7	38	56	8/10M	Rat	
	7	48	70	1/2	Rabbit	
	7	59	85	0/1F	Monkey	
	7	123	176	0/16	Guinea pig	Growth depression and slight increase in lung weight in male guinea pigs, and degeneration of testicular tubules; slight fatty degeneration in cortex of adrenals of females, with no nervous system signs
290	6	6	42	0/3	Dog	Vomiting, occasional tremors, transient paraplegia, anemia
204	7	122-157	176-226	22/40	Rat	Appreciable number of rats died of secondary respiratory infection; growth depression in rat; posterior paresis in monkey and rabbit; increased lung weight in rat and guinea pig; neurologic and muscular atrophy in monkey; increased liver and kidney weight in female rats. Slight testicular tubal degeneration in rat
	7	122-157	176-226	1/16	Guinea pig	
	7	122-157	176-226	0/4	Rabbit	
	7	122-157	176-226	2/10F	Mouse	
	7	122-157	176-226	0/2F	Monkey	

TABLE 6 (continued)

113	7	122-157	176-226	0/40	Rat	No findings except growth depression in male rats and increased lung weight in rats
	7	122-157	176-226	0/16	Guinea pig	
	7	122-157	176-226	0/4	Rabbit	
	7	122-157	176-226	0/2	Monkey	
100	6	130	180	3/20	Rat	No clinical signs and no significant findings except anemia in one dog
	6	130	180	8/30	Mouse	
	6	130	180	0/3	Dog	
49	7	127-131	180-184	0/20	Rat	No effect on any animals (as judged by general appearance and behavior, mortality, growth, final body and organ weight, and gross and microscope examination of tissues)
	7	127-131	180-184	0/8	Guinea pig	
	7	127-131	180-184	0/2	Rabbit	
	7	127-131	180-184	0/10F	Mouse	
	7	127-131	180-184	0/1	Monkey	
50	7	520	728	-	Rat	Decreased body weight after 14 wk exposure. Decreased kidney and brain weights. Median survival time 690 d compared with 720 d in controls. AST (aspartate aminotransferase) was lower than controls. High incidence of proliferative and degenerative lesions of adrenal cortex.
100	7	520	728	-	Rat	Decreased body weight after 9 wk EtO exposure. Decreased kidney and brain weights. Median survival time was 653 d compared with 720 d in controls. AST was lower than controls. High incidence of proliferative and degenerative lesions of adrenal cortex. Higher incidence of skeletal muscle myopathy.

[a] Based on Hollingsworth et al., 1956, Jacobson et al., 1956, and Lynch et al., 1984.
[b] Exposures usually conducted on 5-d/wk basis.
[c] Unless otherwise noted, second figure is number of animals of each sex.

readily converted nonenzymatically to 2-chloroethanol (ethylene chlorohydrin), a derivative with appreciable toxicity, including mutagenicity (Balazs, 1976).

EtO at concentrations of 0.96-95.5 mM was mutagenic when tested with Salmonella typhimurium TA 1535 (Rannug et al., 1976). Studies in Drosophila melanogaster exposed to EtO at 55-175 mM revealed an increase in sex-linked recessive lethal mutations (Bird, 1952).

Embree and Hine (1975) reported an increase in chromosomal aberrations in rat bone marrow cells after exposure of rats to EtO at 250 ppm for 7 h/d for 3 d.

Groups of four male New Zealand white rabbits were exposed to EtO at 10, 50, and 250 ppm for 6 h/d, 5 d/wk, for 12 wk (Yager and Benz, 1982). There was a dose-related increase in the mean number of SCEs per cell in peripheral lymphocytes at 50 and 100 ppm, but not at 10 ppm.

Cynomolgus monkeys exposed to EtO at 50 and 100 ppm for 7 h/d, 5 d/wk, for 2 yr showed increased incidences of SCEs, and chromosomal aberrations (Lynch et al., 1984a).

Kligerman et al. (1983) studied SCEs in male Fischer-344 rats exposed to EtO at 0, 50, 150, and 450 ppm for 6 h/d for 1 or 3 d. EtO induced a concentration-dependent increase in SCEs. The effects at 3 d appeared to be additive. However, no significant dose-dependent increase in chromosomal breakage was observed.

Embree et al. (1977) exposed male rats to EtO for 4 h at 1,000 ppm and mated them each week to groups of two females for 10 wk. The number of postimplantation fetal deaths was significantly higher in the test group than in negative controls. This increase was noted only during the first 5 wk of the experiment and corresponded to the residence time of germinal cells exposed to EtO after meiotic division. The results indicated that EtO produces mutagenic changes in rat germinal cells.

Generoso et al. (1980) reported dominant lethal mutations in mice after intraperitoneal administration of a single dose of EtO at 150 mg/kg. Heritable translocations in male progeny of male mice given EtO intraperitoneally at 0, 30, and 60 mg/kg were also reported with a dose-rate effect.

Generoso et al. (1986) studied the effect of inhaled EtO on dominant lethal mutations in mice. In their dose-response study, male mice were exposed to EtO by inhalation on 4 consecutive days for 6 h/d at 300, 400, and 500 ppm for daily totals of 1,800, 2,400, and 3,000 ppm•h (total exposures, 7,200, 9,600, and 12,000 ppm•h). Quantitation of dominant lethal responses was made on matings that involved sperm exposed as late spermatids and early spermatozoa--the

most sensitive stages. A dose-related increase in dominant lethal mutations was observed; the dose-response curve was nonlinear. In the dose-rate study, exposure of mice at 300 ppm for 6 h/d (total of 1,800•ppm h/d) induced a low incidence of dominant-lethal mutations; however, when the same total exposure was given in only 1.5 h at 1,200 ppm or in 3 h at 600 ppm, markedly higher incidences of dominant lethal responses were observed--an indication of a large dose-rate effect.

Table 7 summarizes mutagenicity and related tests conducted with EtO in experimental systems. EtO is mutagenic and clastogenic in many experimental in vitro and in vivo tests. Moreover, EtO reaches male germinal cells and causes heritable mutations. Both alkylation and mutagenicity have been demonstrated for EtO. The capacity of a chemical to serve as an alkylating agent and to cause mutations in a variety of test systems is widely accepted as indicating that the chemical might have carcinogenic potential.

Carcinogenicity

EtO has been carcinogenic in a number of animal bioassays.

Snellings et al. (1981, 1984) exposed male and female Fischer rats to EtO at 0, 10, 33, and 100 ppm for 6 h/d, 5 d/wk, for 2 yr. They observed a dose-related statistically significant increase in incidence of mononuclear-cell leukemia in female rats. Male rats exposed to EtO also had a higher incidence or an earlier onset of mononuclear-cell leukemias. An increase in mortality from peritoneal mesotheliomas in male rats exposed at 33 and 100 ppm was also observed. Exposure at 100 ppm resulted in an increased incidence of gliomas in rats of both sexes.

Lynch et al. (1984b) exposed groups of 80 male rats and 12 male cynomolgus monkeys to EtO at 0, 50, and 100 ppm for 7 h/d, 5 d/wk, for 2 yr. At 16 mo, the rats became infected with Mycoplasma pulmonis, and many died. The exposure was discontinued for 2 wk to permit the animals to recover, and then exposure was resumed. At sacrifice, significantly higher frequencies of leukemia, mesotheliomas, and gliomas were found in the rats exposed at 100 ppm. None of the monkeys showed evidence of leukemia, but the studies were limited by the number of animals and short duration in their capacity to detect leukemia.

EtO administered to female Sprague-Dawley rats by intragastric intubation in vegetable oil at 7.5 and 30 mg/kg twice a week for nearly 3 yr produced squamous-cell carcinoma of the forestomach (Dunkelberg, 1982).

Subcutaneous injection of EtO dissolved in tricaprylin into NMRI mice weekly at 0.1, 0.3, or 1.0 mg/mouse for at least a year and up to 95 wk led to dose-dependent induction of tumors, mostly fibrosarcomas, at the site of injection (Dunkelberg, 1981).

TABLE 7

Summary of Mutagenicity and Short-Term Tests in Experimental Systems

Test Organism	EtO Concentration	Frequency of Exposure	Results and Comments	Reference
S. typhimurium TA 1535	0.96, 4.77, 9.55, 47.7, 95.5 mM in ethanol	Single	Base-pair substitution mutagen showing dose-response relationship	Rannug et al., 1976
Drosophila melanogaster	55-175 mM in water	Single injection in males	Dominant lethal mutations with dose-response relationship	Bird, 1952
Rat	250 ppm	7 h/d for 3 days	Chromosomal aberrations	Embree and Hin 1975
Rat	1,000 ppm	4 h	Males mated with untreated females for 50 wk after exposure produced increase in ratio of dead implants to total implants	Embree et al., 1977
Rat	50, 150, 450 ppm	6 h/d for 1-3 d	Dose-related increases in SCEs	Kligerman et a 1983
Mice	150 mg/kg	Single	Dominant lethal mutations	Generoso 1 1980
Mice	30, 60 mg/kg	Single	Heritable translocations	
Mice	300, 400, 500 ppm	6 h/d for 4 d	Dose-related increases in dominant lethal mutations	Generoso et al 1986
New Zealand white rabbit	10, 50, 250 ppm	6 h/d, 5 d/wk, for 12 wk	Dose-related increase in SCEs beginning at 50 ppm.	Yager and Benz 1982
Cynomolgus monkey	50 or 100 ppm	7 h/d, 5d/wk for 2 yr	Increased incidence of SCEs and chromosomal aberrations	Lynch et al., 1984b

Lifetime skin-painting studies were conducted on 30 female Swiss mice beginning at the age of 8 wk. Approximately 0.1 ml of a 10% solution of EtO in acetone was applied three times a week to the dorsal skin. The median survival time was only 493 d, but no skin tumors were observed (Van Duuren et al., 1965).

Eighty-six female germ-free, inbred Swiss-Webster mice were accidentally placed on EtO-treated ground-corncob bedding for 150 d and then on untreated bedding for 125-595 d (maximal age at death, 885 d). Sixty-three mice developed tumors at various sites, whereas no tumors were reported in the controls--83 female mice 100-600 d old (Reyniers et al., 1964). At the start of EtO exposure, the animals varied from a few days to about 1.5 yr old. The International Agency for Research on Cancer (IARC, 1976) did not consider this a suitable test for evaluating the carcinogenicity of EtO. Male animals similarly exposed died of hemorrhage while on the EtO-treated bedding. Ethylene glycol, which is produced by hydration of EtO, has been implicated in abnormalities of blood clotting (Allen et al., 1962; Meier et al., 1962), and this action may have been responsible for the hemorrhages.

In a study of limited power (with no controls), 12 rats received subcutaneous injections of EtO in arachis oil at cumulative doses of 1 g/kg (dosing schedule not given) during a period of 94 d. The animals were observed for their lifetimes; no injection-site sarcomas were observed (Walpole, 1958).

The foregoing experimental work on animals (summarized in Table 8) indicated that EtO is carcinogenic in rats, inducing leukemias, mesotheliomas, and gliomas by inhalation and squamous-cell carcinomas of the forestomach by gavage. EtO might also be carcinogenic to mice, producing sarcomas at the site of injection.

Teratogenicity and Reproductive Effects

LaBorde and Kimmel (1980) administered EtO intraperitoneally at 0, 75, and 150 mg/kg to pregnant female CD-1 mice during four different periods of gestation (period I, days 4-6; period II, days 6-8; period III, days 8-10; period IV, days 10-12). Mothers showed signs of toxicity at 150 mg/kg in periods I, III, and IV, but not in period II. At 150 mg/kg, there was a significant reduction in mean fetal body weight, compared with controls, in all treatment periods, and a significant increase in the proportion of malformed fetuses in periods II and IV. Furthermore, approximately 19% of the fetuses in each litter from mothers given 150 mg/kg in period II had malformations, mainly of the cervical and thoracic skeleton.

Snellings et al. (1982a) exposed pregnant Fischer 344 rats to EtO at 0, 10, 33, and 100 ppm for 6 h/d on days 6-15 of gestation. No EtO-related effects on maternal survival, litter size, and number of implantation losses were seen. No teratologic effects on the soft tissues or skeleton were observed.

TABLE 8

Summary of Carcinogenicity Studies on Ethylene Oxide in Experimental Animals

Organism	Route	Dose	Frequency of Exposure	Results and Comments	Reference
Fischer rat	Inhalation	0,10, 33, 100 ppm	6h/d, 5d/wk, for 2 yr	Increased incidence of mononuclear-cell leukemia and glioma in males and females; increased incidence of peritoneal mesotheliomas in males	Snellings et al., 1981, 1984
Fischer rat	Inhalation	0, 50, 100 ppm	7 h/d, 5d/wk, for 2 yr	Increased incidence of leukemia, glioma, and mesothelioma at 100 ppm	Lynch et al., 1984a
Cynomolgus monkey	Inhalation 100 ppm	0, 50, 100 ppm	7 h/d, 5d/wk, for 2 yr	No increase in leukemia	Lynch et al., 1984a
Sprague-Dawley rat	Intragastric intubation	7.5, 30 mg/kg	2 times a week for 3 yr	Increases in squamous-cell carcinoma of forestomach	Dunkelberg, 1982
Swiss mouse	Skin painting	0.1 ml of 10% EtO in acetone	3 times a week for lifetime	No increase in skin tumors	Van Durren et al., 1965
Rat	Subcutaneous	Total dose 1 gm/kg during 94 d	Not specified	No injection site sarcomas	Walpole, 1958
NMRI mice	Subcutaneous	0.1, 0.3, mg/mouse	Once a wk for 95 wk	Dose-dependent increase in fibrosarcomas	Dunkelberg, 1981

Snellings et al. (1982b) conducted a one-generation study to evaluate the reproductive effects of inhalation exposure to EtO. They exposed 30 male and female Fischer rats at either 100, 33, or 10 ppm (6 h/d, 5 d/wk); and these animals were mated, and females were continued on exposure from day 0 through 19 of gestation (6 h/d, 7 d/wk). The major treatment-related adverse effect was significantly fewer pups born per litter after only the highest exposure. There were also fewer implantation sites per pregnant female in the 100-ppm exposure group than in any other group.

Hardin et al. (1983) exposed rats and rabbits to EtO at 150 ppm daily for 7 h before breeding and during gestation. This exposure caused no mortality among nonpregnant or pregnant females of either species. There was statistically significant embryonic and fetal lethality in rats. External, visceral, and skeletal examinations of the offspring revealed no treatment-related morphologic effects, other than an increased incidence of reduced skeletal ossification (primarily of the skull and sternebrae) among the pups of the rats. No evidence of embryonic or fetal toxicity or of developmental defects was detected in EtO-exposed rabbits.

Increased embryonic mortality was reported when male rats were continuously exposed to EtO at 2 ppm for 66 d and then mated to untreated females (Strekalova et al., 1975). This is the only study reporting embryo toxicity at low-dose exposure.

Lynch et al. (1984c) exposed cynomolgus monkeys to EtO by inhalation at 0, 50, and 100 ppm for 7 h/d, 5 d/wk, for 2 yr. The total sperm count and the percentage of motile sperm were reduced in monkeys exposed at 50 or 100 ppm; that suggested an adverse effect on testicular function and perhaps on fertility.

In sum, EtO has adverse reproductive effects in both female and male experimental animals at relatively high dosages and can produce fetal malformations.

SUMMARY

In animals, exposure to ETO vapor at high concentrations causes irritation of the eyes, respiratory tract, and lungs, with convulsive seizures, weakness of the extremities, secondary infection of the lungs, and death from respiratory failure. EtO has also been shown to be teratogenic in mice and to reduce sperm motility in monkeys. EtO was shown to be genotoxic in several in vitro and in vivo systems and was carcinogenic in rats and mice.

PHARMACOKINETICS

Limited information is available on the kinetics of EtO. The oral and intravenous LD_{50}s of EtO in aqueous solution for rats and mice (about

300 mg/kg) are similar, so efficient oral absorption is likely (Glaser, 1979). After exposure of mice to ^{3}H-labeled EtO vapor in air for 75 min, almost all was absorbed. About 90% of the radioactivity was eliminated in 24-48 h. The biologic half-life of EtO was estimated at 9 min. The highest concentrations of residual tritium were recovered from liver and kidney, and most of the residual label was recovered in the protein fraction, presumably after alkylation; some was associated with nucleic acids. These complexes have long half-lives (Ehrenberg et al., 1974). Martis et al. (1982) studied the disposition kinetics of EtO after intravenous administration of 25 and 75 mg/kg to beagles. Plasma concentration of EtO was found to decrease exponentially with a mean rate constant of 0.024 per min and total body clearance of 20.0 ml/kg•min. EtO was found to be metabolized mainly to ethylene glycol, which had a mean plasma half-life of 221 min and a total body clearance of 2.13 ml/kg•min. Between 7 and 24% of intravenously administered EtO was eliminated in the urine as ethylene glycol within 24 h.

INHALATION EXPOSURE LIMITS

Recommended exposure limits for EtO in several countries are summarized in Table 9.

TABLE 9

Recommended Emergency Workplace Exposure Limits for Ethylene Oxide[a]

Type of Limit	Duration	Concentration	Reference
TWA	8 h/d	1 ppm	ACGIH, 1986
Ceiling	7 h/d	10 ppm	Hine et al., 1981
TWA, West Germany	8 h/d	50 ppm	Winell, 1975
TWA, East Germany	8 h/d	50 ppm	Winell, 1975
TWA, Sweden	8 h/d	36 mg/m^3	Winell, 1975
Ceiling, U.S.S.R.	--	1 mg/m^3	Winell, 1975
Ceiling	15 min/d	75 ppm	NIOSH, 1977
TWA	8 h/d	50 ppm	NIOSH, 1977
Ceiling	10 min/d	5 ppm	NIOSH, 1983
TWA	8 h/d	0.1 ppm	NIOSH, 1983
TWA, U.S.	8 h/d	1 ppm	OSHA, 1984

[a] Odor threshold is 700 ppm, but continuous exposure results in olfactory fatigue.

In 1983, the National Institute for Occupational Safety and Health recommended a ceiling of 5 ppm for not more than 10 min in any working day and an 8-h TWA concentration below 0.1 ppm (NIOSH, 1983).

COMMITTEE EVALUATION AND RECOMMENDATIONS

Hine et al. (1981) suggested that injury or death is associated with exposure to EtO at 8,000, 4,000, and 2,000 ppm for 10, 30, and 60 min, respectively, on the basis of animal data; a 1-h exposure at 500 ppm is not likely to produce injury (Figure 1).

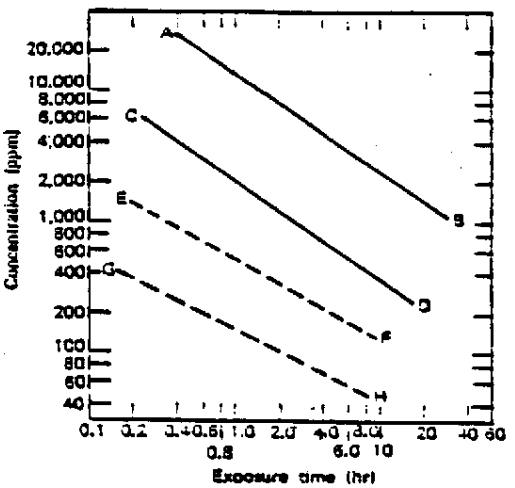

FIGURE 1 Inhalation toxicity of ethylene oxide in air. A-B and C-D, severe injury or death likely. E-F, probable maximum without injury for one exposure. G-H, probable maximum without injury for repeated daily exposures. Reprinted with permission from Hine et al., 1981.

The Committee proposes applying a safety factor of 25 to the 500-ppm no-effect exposure suggested by the data of Hine et al. (1981) for a single exposure, because EtO has been demonstrated to have a wide range of biologic effects in humans and animals, including genotoxicity, carcinogenesis, and teratogenesis. The Committee recommends the following EEGLs:

Time	EEGL
1 h	20 ppm
24 h	1 ppm

Acute LC_{50} data on rats, mice, guinea pigs, rabbits, cats, and dogs show that the mouse is the most sensitive species. The LCt_{50} for 4 h for the mouse was 835 ppm x 4 h = 3,340 ppm•h.

Pregnant Fischer rats exposed at 100 ppm for 6 h/d on days 6-15 of gestation showed no signs of fetotoxicity or teratogenicity (Snellings et al., 1982).

The recommended EEGL of 20 ppm for 1 h compares with an estimated Ct of 6,000 ppm•h for the no-observed-effect exposure reported by Snellings et al. (1982) for fetotoxicity and teratogenicity. The EEGL of 20 ppm for 1 h also compares with an estimated LCt_{50} of 3,340 ppm•h for mice, the most sensitive test animals (Jacobson et al., 1956).

A quantitative risk assessment for EtO (below) indicates that exposure at 20 ppm for 1 h or at 1 ppm for 24 h is estimated to produce a cancer risk no greater than 1×10^{-4}.

QUANTITATIVE CANCER RISK ASSESSMENT

As described earlier, the Committee made a separate assessment of the potential cancer risk associated with exposure to EtO at the EEGL.

EPA (1985) conducted a cancer risk assessment of EtO. It used data of Snellings et al. (1981) in estimating a human cancer risk. EPA estimated that the lifetime probability of cancer from continuous breathing of ETO at 1 ppm in air is 1.9×10^{-1} $(ppm)^{-1}$. According to EPA (1985), extrapolation of risk from human leukemia data results in a highly uncertain risk estimate, because of the small numbers of cases that were observed and expected. However, quantitative comparisons of human and animal inhalation studies do, to the extent possible, support each other (USEPA, 1985).

OSHA (1984) analyses also indicate that the estimates of cancer risk based on human exposure data are as high as or higher than estimates based on animal data. The Committee used both human and animal data for its cancer risk assessment.

QUANTITATIVE ESTIMATE OF THE RISK OF LEUKEMIA IN WORKERS EXPOSED TO EtO BY INHALATION

The Committee evaluated data from four studies (Hogstedt et al., 1979a,b, 1986; Morgan et al., 1981) of occupational groups in making its quantitative assessment of the risks of induction of neoplasms after exposure to EtO.

The results of one occupational study by Hogstedt et al. (1979a) were considered to be the only ones appropriate for estimating the

human risk of developing cancer or other neoplastic disease in association with exposure to EtO. From 1968 to 1977, workers in a small factory in Sweden were exposed to EtO where a mixture of 50% EtO and 50% methyl formate was used to sterilize hospital equipment. Evidence obtained by OSHA (1984) indicated that methyl formate probably does not play a role in the carcinogenic risk. The concentration of EtO in the work area was not estimated until 1977, whereas one of two women who developed leukemia had worked there since 1966 and the other since 1968. Both women, who developed leukemia while working in the storage hall, had worked there for a period of about 10 yr. One man developed leukemia, but was not included in the analysis by Hogstedt et al. (1979a) because he might have had occasional exposures to benzene, as well as EtO.

The two cases of leukemia in women developed between 1972 and 1977. About 70 persons (68 women and two men) worked in the storage hall, where the time-weighted average EtO concentration (due to leakage from sterilized boxes) was 20 ± 10 ppm. At any given time during the 10-yr period 1968-1977, approximately 30 workers were assigned to the storage hall area, for a total exposure to EtO of 30 x 10 = 300 person-work-years. Thus, the average length of occupational exposure to EtO was approximately 300/70 = 4.3 yr at an average concentration of 20 ppm. In fact, one of the cases of leukemia developed after less than 4 yr of exposure in the storage hall. According to Swedish national incidence rates, 0.2 case of leukemia would have been expected among 230 workers at the factory. Thus, the expected number of cases among workers in the storage area would be roughly 70/230 x 0.2 = 0.06, compared with the two cases observed. The observed incidence of two cases of leukemia in this group of 70 workers, excluding the man who had possible exposure to benzene and subtracting the expected 0.06, gives an excess incidence per exposed person of (2 - 0.06)/70 = 0.0277). The median age of this group of workers at the termination of the study was approximately 46.5 yr. Thus, the number of years of possible followup was rather small.

The data were derived largely from exposure of females. Therefore, for these results to be applicable to the general population, one must assume that males and females are equally susceptible to the neoplastigenic effects of EtO for general population estimates. One must also assume that the probability of EtO's producing neoplasms or cancers is the same in the general population as in this group of workers. Various environmental and life-style factors might have altered the incidence of neoplasia in these workers. Obviously, the observed excess incidence of leukemia is unrepresentative, because of the small number of workers involved. An incidence of leukemia as high as 6.1/70 is compatible (with 95% confidence based on the binomial probability distribution) with the observed incidence of 2/70. Thus, a possible way to take into account the uncertainty in the leukemia incidence due to the small number of workers involved would be to use the upper 95% confidence limit of the incidence. The upper 95% confidence limit estimate for the excess incidence of leukemia in these

workers would then be approximately (6.10 - 0.06)/70 = 0.086 (or 8.6%) for an average exposure to EtO at 20 ppm for 4 yr.

Hogstedt et al. (1986) presented additional epidemiologic data that show an association between EtO exposure and cancer. In additional followup of the group of Swedish workers used for the cancer risk assessment performed above, three cases of leukemia were observed in 203 workers exposed to EtO intermittently. In a second plant, four of 175 workers exposed to EtO developed leukemia, but no measure of the concentration of EtO in the air or the length of exposure was given. In a third plant, leukemia was observed in one of 355 workers exposed to EtO at 1-8 ppm, but the length of exposure was not given. These data provide additional evidence of an association between EtO exposure and leukemia, but insufficient information on the concentration of EtO or the length of exposure was provided to permit the quantitative estimate of the risk of leukemia to be modified. The new results appear to be comparable with the risk that two of 70 workers will develop leukemia after an average exposure to EtO at 20 ppm for 4 yr.

QUANTITATIVE ESTIMATE OF THE RISK OF LEUKEMIA IN HUMANS AT THE EEGL

In the Hogstedt et al. (1979a) study, the upper 95% confidence limit of the risk of leukemia was 0.086 for workers exposed to EtO at 20 ppm for 8 h/d, 5 d/wk, 48 wk/yr, for 4 yr, or 7,680 h. If the risk of leukemia is proportional to the total dose received, the upper 95% confidence limit of estimated risk for a 1-h exposure at 20 ppm (i.e., at the EEGL) is estimated to be $0.086/7,680 = 1 \times 10^{-5}$ in round numbers.

The risk of leukemia has been based on observation of a worker population (Hogstedt et al., 1979a) followed for up to 6.5 yr on the average, after exposure to EtO. Because of the relatively short period of observation during the study, more cases of leukemia might appear in these workers, even though they are no longer exposed to EtO. That is, the latent period of leukemia in some workers might exceed the reported period of observation. Thus, it is possible that the estimates of leukemia risk should be revised upward, to allow for the cases of leukemia that might eventually occur in these workers.

The estimated risk of 1×10^{-5} at the EEGL is based on an incidence of leukemia of 8.6% (upper 95% confidence limit) in workers. The Committee does not consider it likely that additional followup or exposure at earlier or later ages could result in a tenfold increase in the incidence of leukemia to 86%. Thus, the estimated risk of leukemia at the EEGL is expected to be less than 1×10^{-4}.

QUANTITATIVE ESTIMATE OF THE RISK OF LEUKEMIA IN RATS EXPOSED TO EtO by INHALATION

Results of two studies in which rats were exposed to EtO by inhalation (Snellings et al., 1981; Lynch et al., 1984b) were considered. The highest risk of leukemia was obtained in female Fischer 344 rats exposed for 6 h/d, 5 d/wk, for 2 yr in the study by Snellings et al. (1981). The proportions of animals with leukemia were 22/166, 14/71, 24/72, and 28/73 at 0, 10, 33, and 100 ppm, respectively. Fitting the multistage dose-response model gave an upper 95% confidence limit for the excess proportion of animals with leukemia of 0.096 at 20 ppm. Assuming equal lifetime neoplastigenic potency of EtO in humans and rats gives the upper 95% confidence limit estimate of 0.096 for humans exposed to EtO at 20 ppm 6 h/d, 5 d/wk, 52 wk/yr, for 70 yr (109,200 h). If the risk of leukemia were proportional to the total dose of EtO, then the estimate of the risk incurred by exposure at 20 ppm for 1 h would be no more than $0.096/109,200 = 8.9 \times 10^{-7}$. On the basis of the results given by Crump and Howe (1984), this estimate of risk needs to be multiplied by a factor of 2.8. This factor allows for increased neoplastigenic sensitivities that might result in connection with age at exposure of a worker 20-60 yr old, assuming that a short-term exposure will affect primarily only one stage of a neoplastigenic process with three to six stages. Thus, the estimate of risk of leukemia from a 1-h exposure to EtO at 20 ppm is less than $2.8 \times 8.9 \times 10^{-7} = 2.5 \times 10^{-6}$.

SUMMARY OF CARCINOGENICITY ANALYSIS

On the basis of the inhalation data on workers in the study by Hogstedt et al. (1979a), a lifetime risk of leukemia of 0.086 (upper 95% confidence limit) was calculated at age 46.5 from an average exposure to EtO at 20 ppm from ages 40 to 44. For the EEGL of 20 ppm for 1 h the estimated risk is 1×10^{-5}, on the basis of the worker experience. Allowing for the short followup and potential increased sensitivity to EtO exposure at earlier or later ages, the risk is not likely to be more than a factor of 10 higher, i.e., the risk is likely to be less than 1×10^{-4}. These estimates of the risk of leukemia assume that the Swedish workers in the study by Hogstedt et al. (1979a)--on 68 women and two men--are reasonably representative of the population. Implied in the calculations is the assumption that the risk of neoplasia is proportional to the total dose of EtO received, regardless of the rate at which it is received.

The maximal estimated risk of 10^{-5} based on the worker experience to date is similar to the estimate based on animal data. Because human data were available for neoplastigenic risk estimation, the Committee used them in estimating the EEGL.

Thus, it is estimated that exposure at the EEGL of 20 ppm for 1 h will, on the basis of noncarcinogenic toxicity, yield a cancer risk no greater than 1×10^{-4}.

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APPENDIX

EEGLs FOR CARCINOGENS

When a substance under evaluation is an animal or human carcinogen, a separate quantitative risk assessment is undertaken in recognition of the fact that even limited exposure to such agents can theoretically increase the risk of cancer (Office of Science and Technology Policy, 1985).

Estimating EEGLs for chemical carcinogens is complicated. Vainio et al. (1985) extracted data from the first 38 volumes of IARC Monographs on chemicals and exposures for which some data on carcinogenicity in humans or sufficient evidence of carcinogenicity in experimental animals existed. In all, 288 chemicals, industrial processes, and complex mixtures fulfilled these criteria. For 30 chemicals or mixtures of chemicals and nine industrial processes, there was sufficient evidence of carcinogenicity in humans; and for 63 chemicals and mixtures of chemicals and five industrial processes, there was evidence that these exposures were probably carcinogenic to humans. For 61 chemicals or groups of chemicals and six industrial processes or occupations, no evaluation of carcinogenicity to humans could be made. For 115 chemicals, there is sufficient evidence of carcinogenicity to experimental animals, but no epidemiologic data are available.

Many experimental investigations involve high-dosage, long-duration exposures to compensate for the small number of animals that are used. Data on short-term or single exposures are virtually nonexistent.

Substances that are carcinogenic in one mammalian species are often carcinogenic in another; species differences in metabolic capacities sometimes account for less than perfect correlations. Further studies are needed to establish which species most closely approximate humans. It would not be surprising to find that this is different for different chemical classes. Quantitative data from humans are sparse. In the absence of human data, it is usually assumed that carcinogenic risk derived from animal data is directly and at least quantitatively applicable to humans. Extrapolation from high-dose animal exposures to low-dose human exposures is often required, and this involves many uncertainties. The shape of the dose-response curve at low doses is generally unknown, especially below the 1% tumor-response range. Repair rates, possible nonlinearities, and other factors involved in low-dose studies are not available. Variations in personal habits,

diet, other exposures, intercurrent disease, and age at first exposure contribute additional uncertainties in predicting human effects. Mathematical models suggest greater precision than exists.

The role of short-term exposures in producing cancer is not clear. On the one hand, any exposure to a carcinogen has the potential to add to the probability of carcinogenic effects, and such exposure should be avoided or at least minimized. Nitrosoureas, for example, are carcinogenic after a single exposure, and hydrazines and other alkylating agents might also have this capacity. On the other hand, the effects of long or repeated exposures could greatly overshadow brief exposures (up to 24 h). Industrial accidents involving brief exposures to vinyl chloride or benzidine might be in that category. A familiar example of strong relation of cancer risk to duration of exposure is tobacco-smoking. Exposure to tobacco products for a day or less, although not carrying zero risk, carries much less risk than chronic smoking and will not be likely to add significantly to the risk of tobacco-related cancer.

The following mathematical approach is applicable for EEGL computations for carcinogens.

1. If an exposure d (usually in parts per million in air) has been computed that, following a lifetime of exposure, is estimated to produce some "acceptable" degree of excess risk of cancer--say, 1×10^{-6}--this has been called a "virtually safe dose" (VSD). Dose d, if not already computed by a regulatory agency, will be computed by COT in accordance with generally accepted procedures used by the major regulatory agencies--i.e., with the multistage no-threshold models for carcinogenesis and the appropriate body weight/surface area adjustments for extrapolating from an animal species to humans.

2. If carcinogenic effect is assumed to be a linear function of the total (cumulative) dose, then for a single 1-day human exposure an acceptable dose (to yield the same total lifetime exposure) would be d x 25,600 (there being approximately 25,600 days in an average lifetime), and the allowable one-day (24 h) dose rate would be

$$d \times 25{,}600.$$

3. Because of uncertainties about which of several stages in the carcinogenic process a material might operate in and because of the likely youth of military persons, it can be shown from data of Crump and Howe (1984) that the maximal additional risk that these considerations contribute is a factor of 2.8. As a conservative approach, the acceptable dose is divided by 2.8, i.e.,

$$\frac{d \times 25{,}600}{2.8}.$$

If a lifetime excess risk, R, is established by DOD (for example at 1×10^{-4}, as has been suggested by the International Council on

Radiation Protection for nuclear power plant workers), then the appropriate EEGL-based risk would be

$$\frac{d \times 25{,}600}{2.8} \times \frac{R}{\text{risk at } d}.$$

(In the example given here, the risk at d was no more than 1×10^{-6}.) If R is 1×10^{-4}, then R(risk at d) = $10^{-4}/10^{-6} = 100$.

4. If a further element of conservatism is required (for example, if animal data need to be translated to human risk), an additional safety factor can be used as a divisor.

The assumption that the carcinogenic response is directly proportional to total dose is likely not to hold for all materials and all tissues that these materials affect. Appropriate mathematical models need to be developed for materials that have other mechanisms for the induction or promotion of cancer. Thus, if a proto-oncogene needs to go through several mutations before it is "turned on" to producing frank cancer cells, the material that leads to the final mutation might show a higher-degree dose-response function than the material producing the first-stage mutation. Knowledge of mechanisms that produce different dose-response curves should, in the future, lead to better material- and mechanism-specific risk-assessment computations.

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