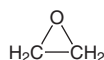


# Ethylene Oxide

## CAS No. 75-21-8

Known to be a human carcinogen

First Listed in the *Fourth Annual Report on Carcinogens* (1985)



### Carcinogenicity

Ethylene oxide is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, including a combination of epidemiological and mechanistic investigations which indicate a causal relationship between exposure to ethylene oxide and human cancer.

Ethylene oxide was first listed in the *Fourth Annual Report on Carcinogens* in 1985 as *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity in humans and sufficient evidence in experimental animals; however, the listing was revised to *known to be a human carcinogen* in the *Ninth Report on Carcinogens* in 2000. Epidemiological evidence demonstrating this risk has come from studies of workers using ethylene oxide as a sterilant for medical devices and spices and in chemical synthesis and production. Evidence for a common mechanism of carcinogenesis in humans and experimental animals comes from studies that have demonstrated similar genetic damage in cells of exposed animals and workers. The DNA damaging activity of ethylene oxide provides its effectiveness as a sterilant, and it is this same property that accounts for its carcinogenic risk to humans.

Several epidemiological studies, some of which were reviewed in support of the 1985 listing of ethylene oxide, reported an association between exposure to ethylene oxide and increased risk of leukemia and stomach cancer; however, other studies found no significant excesses in cancer risk (Steenland *et al.* 1991, Teta *et al.* 1993, IARC 1994). In most studies, information pertaining to the extent of actual ethylene oxide exposure was limited. The most frequently reported association in exposed workers has been for lymphatic and hematopoietic cancer (IARC 1994). A meta-analysis of 10 distinct cohort studies of workers exposed to ethylene oxide found no association between exposure to ethylene oxide and increased risk of pancreatic or brain cancers; however, there was a suggestive risk for non-Hodgkin's lymphoma and for stomach cancer (Shore *et al.* 1993). The largest study of U.S. workers exposed to ethylene oxide at plants producing sterilized medical supplies and spices found no increase in mortality from any cause of death; however, an increase in mortality from all hematopoietic neoplasms, concentrated in the subcategories lymphosarcoma, reticulosarcoma, and non-Hodgkin's lymphoma, was observed among males (Steenland *et al.* 1991). An analysis of the exposure-response data from this study found a positive trend in risk with increasing cumulative exposure to ethylene oxide and mortality from lymphatic and hematopoietic neoplasms. This trend was strengthened when analysis was restricted to neoplasms of lymphoid cell origin (lymphocytic leukemia and non-Hodgkin's lymphoma combined). The relationship between cumulative exposure to ethylene oxide and leukemia was positive, but not significant (Stayner *et al.* 1993).

In the study by Teta *et al.* (1993), leukemia risk was increased in workers exposed for more than 10 years to ethylene oxide. Another study reported an increased incidence of breast cancer in a cohort of workers who used ethylene oxide as a sterilant (Norman *et al.* 1995). The occupational groups most studied are workers who use ethylene oxide as a sterilant and those who work in the production of ethylene oxide and its derivatives. The likelihood of confounding occupational

exposures to other chemicals is generally lower in sterilization workers than in chemical synthesis and production workers.

The evidence that ethylene oxide is a human carcinogen is supported by studies in laboratory animals that have demonstrated that ethylene oxide is carcinogenic at multiple organ sites in rats and mice, likely due to its direct alkylating activity. Sites of tumor induction in mice include the hematopoietic system, lung, harderian gland, mammary gland, and uterus. Sites of tumor induction in rats included the hematopoietic system, brain, and mesothelium (NTP 1987, IARC 1994).

### Additional Information Relevant to Carcinogenicity

Ethylene oxide is a direct-acting alkylating agent that forms adducts with biological macromolecules including hemoglobin and DNA. Measurements of hemoglobin adducts (hydroxyethyl histidine and hydroxyethyl valine) have been used to monitor worker exposure to ethylene oxide. Ethylene oxide causes a dose-related increase in the frequency of hemoglobin adducts in exposed humans and rodents (IARC 1994).

The major DNA adduct of ethylene oxide is *N*<sup>7</sup>-(2-hydroxyethyl)guanine. Dose-related increases in this adduct, as well as smaller amounts of *O*<sup>6</sup>-(2-hydroxyethyl)guanine and *N*<sup>3</sup>-(2-hydroxyethyl)adenine, have been measured in rodents exposed to ethylene oxide. Background levels of hemoglobin and DNA adducts of ethylene oxide in humans and experimental animals have been suggested to arise from endogenous production of ethylene by gut flora or metabolism of unsaturated dietary lipids (Tornqvist 1996).

Ethylene oxide is genotoxic in all species studied, including prokaryotic and lower eukaryotic organisms, as well as *in vitro* and *in vivo* mammalian systems. Ethylene oxide causes gene mutations and heritable translocations in germ cells of exposed rodents. Significant dose-related increases in the frequency of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes, of micronuclei in erythrocytes, of DNA single-strand breaks in peripheral mononuclear blood cells, and of *hprt* mutations in peripheral lymphocytes have been observed in workers occupationally exposed to ethylene oxide (Fuchs *et al.* 1994, IARC 1994, Oesch *et al.* 1995, Schulte *et al.* 1995, Major *et al.* 1996). Similar genotoxic effects have been observed in rodents exposed to ethylene oxide (IARC 1994). For direct-acting mutagenic chemicals, increases in chromosome aberration frequency appear to be a good predictor of increased human cancer risk. Thus, all measurable genotoxic endpoints that are considered to be indicators of chemical carcinogenesis have been observed in both humans and experimental animals exposed to ethylene oxide.

### Properties

Ethylene oxide, the simplest of the cyclic ethers, is a colorless gas at room temperature and normal pressure (Budavari *et al.* 1996). The liquid has a characteristic ether-like odor (HSDB 2003). Ethylene oxide has a molecular weight of 44.1, a melting point of -111°C, and a boiling point of 10.7°C. It has a vapor pressure of 1,314 mm Hg at 25°C and a log octanol-water partition coefficient of 0.30. Ethylene oxide is soluble in water, ethanol, acetone, benzene, diethyl ether, and most organic solvents. It is relatively stable in aqueous solutions or when diluted with carbon dioxide or halocarbons, but it may undergo slow polymerization during storage. Ethylene oxide is highly reactive and potentially explosive when heated or in the presence of alkali metal hydroxides and highly active catalytic surfaces. It reacts readily with acids resulting in ring opening. Vapors may be flammable or explosive if there is inadequate heat dissipation. Incomplete combustion releases carbon monoxide (IARC 1994).

Ethylene oxide is available commercially in the United States as a high-purity chemical that contains a maximum of 0.03% water,



0.003% aldehydes as acetaldehyde, and 0.002% acidity as acetic acid. It has been sold as a mixture with either carbon dioxide or fluorocarbon 12 to reduce its fire hazard (HSDB 2003).

## Use

The major use (more than 99%) of ethylene oxide in the United States is as an intermediate in the production of several industrial chemicals (ATSDR 1990, IARC 1994). The remainder is used in the gaseous form, either alone or combined with nitrogen, carbon dioxide, or dichlorofluoromethane as a sterilizing agent, disinfectant, fumigant, or insecticide. About 60% of the ethylene oxide is used to produce ethylene glycol (antifreeze). Other chemicals that are produced from ethylene oxide include non-ionic surfactants (used in industrial applications, detergents, and dishwashing formulations), glycol ethers, ethanolamines (used in soaps, detergents, and textile chemicals), diethylene glycol, triethylene glycol, polyethylene glycol, and urethane polyols. Although a relatively small percentage of ethylene oxide is used as a fumigant or sterilizing agent, these uses include a variety of facilities, products, and materials, including hospital equipment, medical and dental clinics, research laboratories, foods, furs, clothing, furniture, books, paper, leather, cosmetics, drugs, railroad cars, beehives, and tobacco. Facilities that manufacture sterile disposable medical supplies and medical facilities, including hospitals, medical and dental clinics, and private surgeries for doctors and dentists, account for about 95% of the ethylene oxide used as a fumigant or sterilant. In hospitals, ethylene oxide is used as a gaseous sterilant for heat-sensitive medical items, surgical instruments, and other objects and fluids coming in contact with biological tissues. Prior to 1966, ethylene oxide was used as an intermediate in the production of acrylonitrile.

## Production

Ethylene oxide was first produced in the United States in 1921. Until 1937, ethylene oxide was produced by the chlorohydrin process, in which ethylene was treated with hypochlorous acid to produce ethylene chlorohydrin. Calcium hydroxide or sodium hydroxide was used to convert ethylene chlorohydrin to ethylene oxide. Currently in the United States, essentially all production of ethylene oxide uses the direct vapor phase oxidation process. This process oxidizes ethylene with air or oxygen in the presence of a silver catalyst to produce ethylene oxide. In addition, ethylene oxide is produced naturally as a metabolite of ethylene and has been identified in automobile and diesel exhaust and in tobacco smoke (IARC 1994).

Ethylene oxide is a major industrial chemical and is consistently ranked among the top 25 highest production volume chemicals produced in the United States. Production increased from approximately 4 billion pounds (1.8 billion kilograms) in 1973 to 6 billion pounds (2.7 billion kilograms) in 1979, and then decreased to 5 billion pounds (2.3 billion kilograms) in 1987 (ATSDR 1990). Between 1992 and 2002, ethylene oxide production increased from 2.6 million metric tons (5.8 billion pounds) to 3.4 million metric tons (7.6 billion pounds). Peak production was reported in 1999 at slightly more than 4 million metric tons (8.9 billion pounds) (CEN 2003). Fourteen manufacturers of ethylene oxide were identified in the United States in 2003 (SRI 2003). In 2003, 16 domestic suppliers of ethylene oxide were identified (ChemSources 2003). U.S. imports exceeded exports in 2002, with imports of approximately 32 million pounds (14.5 million kilograms) and exports of approximately 14 million pounds (6.4 million kilograms) (ITA 2003).

## Exposure

The primary routes of potential human exposure to ethylene oxide are inhalation and ingestion, which may occur through occupational, consumer, or environmental exposures. In most circumstances, exposure from skin contact would be low. Little information is

available on skin exposure, but industrial workers accidentally exposed to aqueous solutions contacting the skin have experienced nausea and vomiting (WHO 1985).

Occupational exposure to ethylene oxide may occur among workers involved in ethylene oxide production, in the manufacture of its end products, or in the use of these compounds in hospital and industrial sterilization (ATSDR 1990, IARC 1994). Industrial and health care workers may be exposed to ethylene oxide during sterilization of a variety of products, such as medical equipment and products (surgical products, single-use medical devices, etc.), disposable health care products, pharmaceutical and veterinary products, spices, and animal feed (IARC 1994). Health care technicians can be exposed to quick, concentrated bursts of the gas when the door of a sterilizing machine is opened (Sun 1986).

Several studies have reported on the number of workers potentially exposed to ethylene oxide. In the 1974 National Occupational Hazard Survey, NIOSH estimated that approximately 141,000 U.S. workers in 67 nonagricultural industries were exposed to ethylene oxide. In a 1977 survey, NIOSH estimated that 75,000 health care workers employed in sterilization areas were directly exposed, and an additional 25,000 hospital workers in other areas were incidentally exposed to ethylene oxide. In addition, OSHA estimated in 1983 that 80,000 U.S. health care workers were directly exposed to ethylene oxide, and 144,000 medical device and related industry workers were incidentally exposed (IARC 1985). NIOSH's National Occupational Exposure Survey (NOES), conducted from 1981 to 1983, estimated that 270,767 workers, of which 120,086 were women, were exposed to ethylene oxide in the workplace (NIOSH 1984). No other occupational surveys were identified.

Because ethylene oxide is highly explosive and reactive, the equipment used for its processing generally consists of tightly closed and highly automated systems, which decreases the risk of occupational exposure (NCI 1985). A 1979 survey of U.S. plants producing and using ethylene oxide reported that average daily concentrations were 0.5 to 7.3 mg/m<sup>3</sup> (0.3 to 4 ppm) with a maximum worst-case peak concentration of 17,500 mg/m<sup>3</sup> (9,600 ppm). A review of exposure data collected in 1987 from 11 ethylene oxide production facilities in the United States reported that the highest mean 8-hr time-weighted average concentration (TWA) was 2.9 mg/m<sup>3</sup> (1.6 ppm) with a range of 0.36 to 6.8 mg/m<sup>3</sup> (0.20 to 3.8 ppm); short-term mean exposure levels for maintenance workers were as high as 19.6 mg/m<sup>3</sup> (10.9 ppm) (IARC 1994).

In hospitals, ethylene oxide is used as a gaseous sterilant for heat-sensitive medical items, surgical instruments, and other objects and fluids coming in contact with biological tissues. Worker exposure may occur during changing of pressurized ethylene oxide gas cylinders; from leaking valves, fittings, piping, and sterilizer door gaskets; from opening of the sterilizer door at the end of a cycle; due to improper ventilation at the sterilizer door; from improperly or unventilated air gap between the discharge line and the sewer drain; during removal of items from the sterilizer and transfer of the sterilized load to an aerator; due to improper ventilation of aerators and aeration areas; from incomplete aeration of items; from inadequate general room ventilation; and from passing near sterilizers and aerators during operation. A large exposure survey conducted between 1976 and 1985 of 21 companies involved in ethylene oxide sterilization (primarily medical supplies and spices) estimated that sterilizer operators were exposed to an 8-hr TWA concentration of 16 ppm (29 mg/m<sup>3</sup>) prior to 1978 and 4 to 5 ppm (7 to 9 mg/m<sup>3</sup>) after 1978 (IARC 1994).

A study conducted in Massachusetts hospitals from 1990 to 1992 found that 23% of hospitals exceeded the OSHA action level (0.5 ppm) at least once, 24% exceeded the short-term exposure limit (STEL = 5 ppm), and 33% reported accidental exposures to ethylene oxide in the absence of personal monitoring (LaMontagne and Kelsey



1997). However, other studies have shown that industrial hygiene measures can effectively control ethylene oxide exposure in hospitals and other places where it is used as a sterilant. Mortimer and Kercher (1989) evaluated nine sterilizer control systems in eight hospitals and reported that control technologies could reduce ethylene oxide concentrations to average less than 0.1 ppm for a full shift while not exceeding a ceiling limit of 5 ppm. Elias *et al.* (1993) reported that standard industrial hygiene practices can result in nearly zero exposure to ethylene oxide in hospitals. Peak levels were reduced from 500 ppm to less than 2.8 ppm by using engineering and administrative controls.

The general population may be exposed to ethylene oxide through use of products that have been sterilized with the compound, such as medical products, foods, clothing, cosmetics, beekeeping equipment, and other products (NIOSH 1981, ATSDR 1990). People who live near industrial facilities that produce or use ethylene oxide may be exposed from uncontrolled industrial emissions (see below). Ethylene oxide has been detected in tobacco smoke, automobile exhausts, and in some foods and spices; however, there are few data that can be used to estimate exposure levels. Fumigated products may initially contain high levels of ethylene oxide, but they degrade or disperse within a few days. A study showed that most experimentally fumigated commodities had levels of ethylene oxide below 1 ppm after 14 days in normal storage conditions. Concentrations of ethylene oxide in grains, spices, dates, and peas measured 24 hours after fumigation ranged from 0 to 3.5 ppm. Another study reported concentrations in spices ranging from 53 to 116 ppm after 2 days and about 25 ppm after 26 days (ATSDR 1990).

Industrial releases of ethylene oxide occur during its storage and handling in industrial facilities, including uncontrolled fugitive emissions or venting with other gases. Other sources of releases to the environment include its use as a fumigant and sterilant, automobile exhausts, combustion of hydrocarbon fuels, and cigarette smoke. Between 1978 and 1980, approximately 1.3 to 3 million pounds (0.6 to 1.4 million kilograms) were released to the air during ethylene oxide production with another 143,000 lb (65,000 kg) released during storage (ATSDR 1990). Other sources of ethylene oxide emissions to air include its production from hydrocarbon fuel combustion, its release from fumigated materials, and losses from disinfection of hospital equipment. Releases from fumigated materials were estimated to be about 10 million pounds (4.5 million kilograms) per year from 1978 to 1980. Estimates of releases from commercial sterilization facilities ranged from 1,146 to 44,092 lb (518 to 20,000 kg) per year per unit (EPA 1993).

Industrial releases of ethylene oxide to water are relatively minor compared to fugitive air emissions. Although an estimated 800,000 lb (360,000 kg) of ethylene oxide were discharged annually to wastewater treatment systems in the late 1970s and early 1980s, it was not detected in the treated wastewaters discharged to waterways (ATSDR 1990). Conventional wastewater treatment, including biological treatment, is very effective in removing ethylene oxide from wastewater. No specific solid wastes are produced by the manufacture of ethylene oxide (WHO 1985). Ethylene oxide degrades in water and air with half-lives ranging from a few hours to 15 to 20 days, depending on the environmental conditions. Therefore, even though relatively large amounts of ethylene oxide are released from industrial facilities, it is not a commonly reported environmental contaminant (ATSDR 1990).

EPA's Toxics Release Inventory (TRI) listed 150 industrial facilities that released ethylene oxide to the environment in 2001 (TRI01 2003). The facilities reported total releases of more than 500,000 lb (225,000 kg) in 2001, of which about 95% was released to the air and about 1% was released to surface water. The remainder was transported off site for treatment and disposal. Releases to the environment have decreased markedly since 1988 when about 5 million pounds (2.3 million kilograms) was reported released.

According to TRI, releases to surface water since 1988 have been 1% or less of the total environmental releases while releases to air accounted for 95% or more of the total. Underground injection, releases to land, and off-site treatment accounted for the remainder.

## Regulations

### DOT

Ethylene oxide mixtures are considered hazardous materials and special requirements have been set for marking, labeling, and transporting this material

### EPA

#### Clean Air Act

NESHAP: Listed as a Hazardous Air Pollutant (HAP)

NSPS: Manufacture of substance is subject to certain provisions for the control of Volatile Organic Compound (VOC) emissions

Prevention of Accidental Release: Threshold Quantity (TQ) = 10,000 lb

Urban Air Toxics Strategy: Identified as one of 33 HAPs that present the greatest threat to public health in urban areas

#### Comprehensive Environmental Response, Compensation, and Liability Act

Reportable Quantity (RQ) = 10 lb

#### Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements

Threshold Planning Quantity (TPQ) = 1,000 lb

Reportable Quantity (RQ) = 10 lb

#### Federal Insecticide, Fungicide, and Rodenticide Act

The tolerance for residues of ethylene oxide when used as a fumigant on coconut, walnuts, and spices = 50 ppm

#### Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes in which listing is based wholly or partly on substance -U115

Listed as a Hazardous Constituent of Waste

### OSHA

Acceptable Peak Exposure = 5 ppm (15-minute excursion)

Permissible Exposure Limit (PEL) = 1 ppm

"Comprehensive Standards" for occupational exposure to this substance have been developed

## Guidelines

### ACGIH

Threshold Limit Value - Time-Weighted Average Limit (TLV-TWA) = 1 ppm

### NIOSH

Immediately Dangerous to Life and Health (IDLH) = 800 ppm

Listed as a potential occupational carcinogen

Ceiling Recommended Exposure Limit = 5 ppm (9 mg/m<sup>3</sup>) (10 minutes/day exposure)

Recommended Exposure Limit (time-weighted-average workday) = <0.1 ppm (0.18 mg/m<sup>3</sup>)

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