

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 epidemiological studies and studies on mechanisms of carcinogenesis. 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 from studies in humans and sufficient evidence of carcinogenicity from studies in experimental animals. The listing was revised to *known to be a human carcinogen* in the *Ninth Report on Carcinogens* in 2000.

An increased risk of cancer has been demonstrated in epidemiological 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 found similar genetic damage in cells of animals and workers exposed to ethylene oxide. The DNA-damaging activity of ethylene oxide explains its effectiveness as a sterilant, and this same property accounts for its carcinogenic risk to humans.

Cancer Studies in Humans

Several epidemiological studies reported an association between exposure to ethylene oxide and increased risk of leukemia and stomach cancer; however, other studies found no significantly increased risks of cancer (Steenland *et al.* 1991, Teta *et al.* 1993, IARC 1994). In most studies, information on the extent of exposure to ethylene oxide was limited. The types of cancer most frequently reported to be associated with occupational exposure to ethylene oxide were lymphoma and leukemia (IARC 1994). The likelihood of confounding occupational exposures to other chemicals generally is lower for sterilization workers than for chemical synthesis and production workers.

A meta-analysis of 10 distinct cohort studies of workers exposed to ethylene oxide found no association between exposure and risk of pancreatic or brain cancer; however, this analysis suggested associations with non-Hodgkin lymphoma (NHL) and stomach cancer (Shore *et al.* 1993). The largest study of U.S. workers exposed to ethylene oxide at plants producing sterilized medical supplies or spices found no excess mortality from any cause of death; however, males workers had excess mortality from all cancer of the hematopoietic system combined (especially lymphosarcoma, reticulosarcoma, and NHL) (Steenland *et al.* 1991). Risk of mortality from all lymphatic and hematopoietic cancer increased with increasing cumulative exposure to ethylene oxide, and this trend was strengthened when the analysis was restricted to cancer of lymphoid-cell origin (lymphocytic leukemia and NHL combined). Increasing cumulative exposure to ethylene oxide was associated with increased risk of leukemia, but this trend was not statistically significant (Stayner *et al.* 1993). Other studies reported elevated risk of leukemia in workers who had been exposed to ethylene oxide for more than 10 years (Teta *et al.* 1993) and elevated incidence of breast cancer in a cohort of workers who used ethylene oxide as a sterilant (Norman *et al.* 1995).

Studies on Mechanisms of Carcinogenesis

Ethylene oxide is a direct-acting alkylating agent that forms adducts with biological macromolecules, including hemoglobin and DNA. Ethylene oxide caused dose-related increases in the frequency of hemoglobin adducts in exposed humans and rodents. Measurements of hemoglobin adducts (hydroxyethyl histidine and hydroxyethyl valine) have been used to monitor worker exposure to ethylene oxide (IARC 1994). The major DNA adduct of ethylene oxide is *N*7-(2-hydroxyethyl)guanine. Dose-related increases in this adduct, as well as smaller amounts of *O*⁶-(2-hydroxyethyl)guanine and *N*3-(2-hydroxyethyl)adenine, were observed in rodents exposed to ethylene oxide. It has been suggested that background levels of hemoglobin and DNA adducts of ethylene oxide in humans and experimental animals arise from endogenous production of ethylene by intestinal flora or metabolism of unsaturated dietary lipids (Tornqvist 1996).

Ethylene oxide caused genetic damage in all species studied, including prokaryotic, lower eukaryotic, and *in vitro* and *in vivo* mammalian systems. Ethylene oxide caused gene mutations and heritable translocations in germ cells of rodents exposed *in vivo*. In occupationally exposed workers, ethylene oxide caused dose-related increases in the frequencies of chromosomal aberrations, sister chromatid exchange, *hprt* mutations in peripheral lymphocytes, micronucleus formation in erythrocytes, and DNA single-strand breaks in peripheral mononuclear blood cells (Fuchs *et al.* 1994, IARC 1994, Oesch *et al.* 1995, Schulte *et al.* 1995, Major *et al.* 1996). Similar genotoxic effects were 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 end points that are considered to be indicators of chemical carcinogenesis have been observed in both humans and experimental animals exposed to ethylene oxide.

Cancer Studies in Experimental Animals

Inhalation exposure to ethylene oxide caused tumors at several different tissue sites in rodents, including the hematopoietic system in mice and rats; the lung, Harderian gland, mammary gland, and uterus in mice; and the brain and mesothelium in rats (NTP 1987, IARC 1994).

Properties

Ethylene oxide is the simplest epoxy compound, which at room temperature is a colorless gas with a sweet odor. It is miscible with water, alcohol, and most organic solvents and soluble in acetone. Ethylene oxide is flammable and explosive, and incomplete combustion releases carbon monoxide (IARC 1994). Physical and chemical properties of ethylene oxide are listed in the following table.

Property	Information
Molecular weight	44.1 ^a
Specific gravity	0.882 at 10°C/10°C ^a
Melting point	-111°C ^a
Boiling point	10.7°C at 760 mm Hg ^a
Log <i>K</i> _{ow}	-0.3 ^a
Water solubility	1,000 g/L at 25°C ^b
Vapor pressure	1314 mm Hg at 25°C ^a
Vapor density relative to air	1.49 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Ethylene oxide is available commercially in the United States as a high-purity chemical containing no more than 0.03% water, 0.003% aldehydes as acetaldehyde, or 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 2009).

Use

The major use of ethylene oxide in the United States (accounting for over 99% of production) 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. The largest use (about 60%) is to produce ethylene glycol (antifreeze). Other chemicals 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 involve 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 medical and dental surgeries, 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. Before 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, it was produced by the chlorohydrin process, in which ethylene was treated with hypochlorous acid to produce ethylene chlorohydrin, and calcium hydroxide or sodium hydroxide was used to convert ethylene chlorohydrin to ethylene oxide. Essentially all U.S. production of ethylene oxide now uses the direct vapor phase oxidation process, by which ethylene is oxidized 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 25 highest-production-volume chemicals produced in the United States. U.S. production was 4 billion pounds in 1973, 6 billion pounds in 1979, 5 billion pounds in 1987 (ATSDR 1990), 2.6 million metric tons (5.8 billion pounds) in 1992, and 3.4 million metric tons (7.6 billion pounds) in 2002. Peak production of slightly over 4 million metric tons (8.9 billion pounds) was reported in 1999 (CEN 2003). In 2009, 12 U.S. manufacturers (SRI 2009) and 10 U.S. suppliers of ethylene oxide were identified (ChemSources 2009). In 2008, U.S. imports of ethylene oxide were 3 million pounds, and U.S. exports were 1.9 million pounds (USITC 2009).

Exposure

The primary routes of potential human exposure to ethylene oxide are inhalation and ingestion, which may occur through occupational, consumer, or environmental exposure. Exposure by dermal contact is expected to be low under most circumstances. Little information is available on dermal exposure; however, industrial workers whose skin was accidentally exposed to aqueous solutions of ethylene oxide have experienced nausea and vomiting (WHO 1985).

The general population may be exposed to ethylene oxide through use of products that have been sterilized with the compound, such as medical products, food, clothing, cosmetics, beekeeping equip-

ment, 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 exhaust, and some foods and spices; however, few data are available that can be used to estimate exposure levels. Fumigated products may initially contain high levels of ethylene oxide, but it degrades or disperses within a few days. One study found that ethylene oxide levels in most experimentally fumigated commodities were less than 1 ppm after 14 days under normal storage conditions. Concentrations of ethylene oxide in fumigated grains, spices, dates, and peas ranged from 0 to 3.5 ppm after 24 hours. 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 to the environment occur during its storage and handling in industrial facilities, including uncontrolled fugitive emissions or venting with other gases. From 1978 to 1980, 1.3 million to 3 million pounds of ethylene oxide was released to air during ethylene oxide production, and another 143,000 lb was released during storage (ATSDR 1990). Other sources of ethylene oxide emissions to air include its production during combustion of hydrocarbon fuel (including in automobile exhaust), its release from fumigated materials, and losses during disinfection of hospital equipment. Annual releases from fumigated materials were estimated at about 10 million pounds from 1978 to 1980. Estimates of annual releases from commercial sterilization facilities ranged from 1,146 to 44,092 lb per unit (EPA 1993).

Industrial releases of ethylene oxide to water are relatively minor, compared with fugitive air emissions. Although an estimated 800,000 lb of ethylene oxide was 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).

Releases of ethylene oxide to the environment have decreased markedly since 1988, when about 5 million pounds was released, according to the U.S. Environmental Protection Agency's Toxics Release Inventory (TRI 2009). Since 1988, releases to surface water have accounted for 1% or less of total environmental releases, while releases to air have accounted for 93% or more. The remainder of releases have been to underground injection wells, land, and off-site treatment. In 2007, 115 industrial facilities reported environmental releases of ethylene oxide to the environment totalling over 311,000 lb, of which about 93% was released to air, 4% to underground injection, 1% to surface water, and the remainder to off-site treatment and disposal. Occupational exposure to ethylene oxide may occur among workers involved in ethylene oxide production, in the manufacture of its end products, or in its use 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 (e.g., surgical products or single-use medical devices), disposable health-care products, pharmaceutical and veterinary products, spices, and animal feed (IARC 1994).

The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that about 141,000 U.S. workers in 67 nonagricultural industries potentially were exposed to ethylene oxide (NIOSH

1976). In 1977, the National Institute for Occupational Safety and Health estimated that 75,000 health-care workers employed in sterilization areas potentially were exposed to ethylene oxide, and that an additional 25,000 hospital workers in other areas may have been incidentally exposed (NIOSH 1981). The Occupational Safety and Health Administration estimated that in 1983, 80,000 U.S. health-care workers were directly exposed to ethylene oxide, and 144,000 workers in the medical device and related industries were incidentally exposed (NCI 1985). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 270,767 workers, including 120,086 women, potentially were exposed to ethylene oxide (NIOSH 1990).

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 daily average concentrations of 0.5 to 7.3 mg/m³ (0.3 to 4 ppm), with a maximum worst-case peak concentration of 17,500 mg/m³ (9,600 ppm). A review of exposure data collected in 1987 from 11 U.S. ethylene oxide production facilities reported that the highest mean 8-hour time-weighted-average (TWA) concentration was 2.9 mg/m³ (1.6 ppm), with a range of 0.36 to 6.8 mg/m³ (0.20 to 3.8 ppm); mean short-term exposure levels for maintenance workers were as high as 19.6 mg/m³ (10.9 ppm) (IARC 1994).

In industrial and health-care use of ethylene oxide sterilization, workers may be exposed 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; from improper ventilation at the sterilizer door; from an improperly ventilated 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; from 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. Health-care technicians can be exposed to short, concentrated bursts of the gas when the door of a sterilizing machine is opened (Sun 1986). A large survey of 21 companies involved in ethylene oxide sterilization (primarily of medical supplies and spices) conducted from 1976 to 1985 estimated that sterilizer operators were exposed to 8-hour TWA concentrations of 16 ppm before 1978 and 4 to 5 ppm after 1978 (IARC 1994).

A study conducted in Massachusetts hospitals from 1990 to 1992 found that 23% of hospitals exceeded the OSHA action level of 0.5 ppm at least once, 24% exceeded the short-term exposure limit of 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. An evaluation of nine sterilizer control systems in eight hospitals found that control technologies could reduce average ethylene oxide concentrations to less than 0.1 ppm for a full shift and maximum concentrations to within a ceiling limit of 5 ppm (Mortimer and Kercher 1989). Another evaluation found that standard industrial hygiene practices could result in nearly zero exposure to ethylene oxide in hospitals; peak levels were reduced from 500 ppm to less than 2.8 ppm through the use of engineering and administrative controls (Elias *et al.* 1993).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of ethylene oxide on ships and barges.

Department of Transportation (DOT)

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

Environmental Protection Agency (EPA)

Clean Air Act

National Emission Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of ethylene oxide is subject to certain provisions for the control of volatile organic compound emissions.

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

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

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 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 tolerances for residues of ethylene oxide when used as a fumigant on certain herbs and spices, dried vegetables, and walnuts range from 7 to 50 ppm.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of ethylene oxide = U115.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Regulations for ethylene oxide and polymers and copolymers of ethylene oxide used as direct or indirect food additives are prescribed under 21 CFR 172, 173, 175, 176, and 178.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 1 ppm.

Acceptable peak exposure = 5 ppm (15-min excursion).

Comprehensive standards for occupational exposure to ethylene oxide have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 1 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (time-weighted-average workday) = < 0.1 ppm (0.18 mg/m³).

Ceiling recommended exposure limit = 5 ppm (9 mg/m³) (10 min/day).

Immediately dangerous to life and health (IDLH) limit = 800 ppm.

Listed as a potential occupational carcinogen.

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