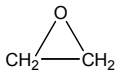
ETHYLENE OXIDE
CAS No. 75-21-8

First Listed in the *Fourth Annual Report on Carcinogens* as *Reasonably Anticipated to be a Human Carcinogen* -- changed to *Known to be a Human Carcinogen* in the *Ninth Report on Carcinogens*



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 is a direct-acting alkylating agent that has been used as a starting material in the production of other chemicals, and as a disinfectant and sterilant. 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. 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.

In 1985, ethylene oxide was first listed in the Fourth Report on Carcinogens as "reasonably anticipated to be a human carcinogen" based on limited evidence of its carcinogenicity in humans and sufficient evidence in experimental animals. 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 leukemia and stomach cancer risk (Hogstedt *et al*. 1979, 1986, Hogstedt 1988); however, other studies found no significant excesses in cancer risk (Morgan *et al*. 1981, Kiesselbach *et al*. 1990; Teta *et al*. 1993, Steenland *et al*. 1991, Hagmar *et al*. 1991, Bisanti *et al*. 1993). 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. 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. 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 the study by Steenland *et al*. (1991) 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. A more recent study found 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 experimental 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 included the hematopoietic system, lung, harderian gland, mammary gland, and uterus (NTP 1987). Sites of tumor induction in rats included the hematopoietic system, brain, and mesothelium (Snellings *et al*. 1984, Garman *et al*. 1985, Lynch *et al*. 1984). An IARC (1994) evaluation noted that ethylene oxide is associated with malignancies of the lymphatic and hematopoietic system in both humans and experimental animals, and concluded that ethylene oxide was carcinogenic to humans. No additional cancer studies of ethylene oxide in experimental animals have been reported since the IARC (1994) review.

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

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. IARC (1994) noted that ethylene oxide induces a dose-related increase in the frequency of hemoglobin adducts in exposed humans and rodents.

The major DNA adduct of ethylene oxide is N7-(2-hydroxyethyl)guanine. Dose-related increases in this adduct, as well as smaller amounts of O6-(2-hydroxyethyl)guanine and N3-(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 ethene (ethylene) by gut flora or metabolism of unsaturated dietary lipids (Tornqvist 1996).

Ethylene oxide is genotoxic at all phylogenetic levels, including prokaryotic and lower eukaryotic organisms, as well as *in vitro* and *in vivo* mammalian systems. Ethylene oxide induces 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 (Galloway *et al*. 1986, Lerda and Rizzi 1992, Tates *et al*. 1991, Yager *et al*. 1983, Sarto *et al*. 1984, Stolley *et al*. 1984, Mayer *et al*. 1991, Schulte *et al*. 1992, 1995, Major *et al*. 1996), of micronuclei in erythrocytes (Tates *et al*. 1991, Hogstedt *et al*. 1983, Schulte *et al*. 1995), of DNA single-strand breaks in peripheral mononuclear blood cells (Fuchs *et al*. 1994, Oesch *et al*. 1995), and of *hprt* mutations in peripheral lymphocytes (Tates *et al*. 1991) have been observed in workers occupationally exposed to ethylene oxide. Similar genotoxic effects have been observed in rodents exposed to ethylene oxide. 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 is a colorless gas at room temperature and normal pressure, but is a liquid at or below 12°C (Budavari 1996). The liquid has a characteristic ether-like odor (HSDB 2001). Ethylene oxide is completely miscible with 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. Incomplete combustion releases carbon monoxide. It reacts readily with acids resulting in ring opening. Vapors may be flammable or explosive if there is inadequate heat dissipation (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 2001).

USE

The primary use of ethylene oxide is as an intermediate in the production of several industrial chemicals, most notably ethylene glycol. In 1986, 59% of the ethylene oxide produced was used to manufacture ethylene glycol. By 1995, the demand for ethylene oxide in ethylene glycol and polyester production was comparable (Chem. Mark. Rep. 1995). Ethylene glycol is used primarily in automotive antifreeze, while polyester is used in fibers, films, and bottles. Ethylene oxide was also used to produce nonionic surfactants (14%) in household and industrial detergents, ethanolamines (8%), glycol ethers (6%) used as solvents, intermediates, and for other purposes, diethylene glycol (6%), and triethylene glycol (2%) (Chem. Mark. Rep. 1987). Less than 1 to 2% of the industrial production of ethylene oxide is used as a fumigant and sterilizing agent for a variety of purposes and materials, including hospital equipment and foods (ATSDR 1990). By the mid 1990s, ethylene oxide use for sterilization in hospitals was being replaced by other systems (Biomed. Mark. Newslett. 1995). The estimated 8 to 9 million lb used for sterilization and fumigation in 1996 represented approximately 0.1% of the total demand for ethylene oxide (SRI 1997a).

Previously, it was used in the production of acrylonitrile, but the process ended in 1966 (ATSDR 1990). Ethylene oxide has also been to accelerate the maturing of tobacco leaves. It has been investigated for use as an agent to improve wood durability (CHIP 1982, IARC 1976).

Other uses include ethoxylation products of long-chain alcohols and amines, alkyl phenols, cellulose, starch, poly(propylene glycol), and ethylene carbonate. Used directly in the gaseous form or in nonexplosive gaseous mixtures with nitrogen, carbon dioxide, or dichlorofluoromethane, ethylene oxide can serve as a disinfectant, fumigant, sterilizing agent, and insecticide. As a fumigant, ethylene oxide kills pests and microorganisms in spices and seasonings, furs, furniture, nuts, tobacco, books, drugs, leather, motor oil, paper, soil, animal bedding, clothing, and transport vehicles. As a sterilizing agent, it purifies cocoa, flour, dried egg powder, coconut, fruits, dehydrated vegetables, cosmetics, and dental, medical, and scientific supplies (IARC 1994).

PRODUCTION

Ethylene oxide has previously been ranked among the top 50 largest volume chemicals produced in the United States by Chemical and Engineering News; U.S. production from 1985 to 1997 ranged between 5.4 and 8.2 billion lb (Chem. Eng. News 1996, 1998, USITC 1985-1987, 1989, 1990). The 1997 Directory of Chemical Producers identified 11 companies producing ethylene oxide at 13 facilities (SRI 1997b). In 2001, Chem Sources identified 11 domestic suppliers of ethylene oxide (Chem Sources 2001). Eleven U.S. manufacturers were identified in 2001 (HSDB 2001). U.S. domestic exports through December 2000 totaled 10,992,834 kg (24.18 million lb), while U.S. imports for consumption in 2000 totaled 14,148,185 kg (31.13 million lb) (ITA 2002).

The current process for production of ethylene oxide is the direct vapor phase oxidation process (Hoechst Celanese Polyester Intermediates *et al*. 1995). The process oxidizes ethylene with air or oxygen in the presence of a silver catalyst at 10 to 30 atmospheres and 200 to 300°C to give ethylene oxide (IARC 1994).

The chlorohydrin process was once the primary process for ethylene oxide production. In this process, ethylene chlorohydrin is prepared by treating ethylene with hypochlorous acid (chlorine in water), which is then converted to ethylene oxide by reaction with calcium oxide. The chlorohydrin process has been phased out since 1931 and is not used on an industrial scale in the United States because of its inefficiency (IARC 1994).

EXPOSURE

The primary routes of potential human exposure to ethylene oxide are inhalation, ingestion, and dermal contact. A risk of potential occupational exposure exists for workers involved in ethylene oxide production, in the manufacture of its end products, or in the use of these compounds in occupational settings (ATSDR 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). Workers in the synthetic organic chemicals manufacturing industry using ethylene oxide are required to wear respirators when air concentrations exceed the permissible exposure limit (PEL). Personnel in workplaces with up to 50 ppm ethylene oxide in the air should wear full facepiece respirators with an ethylene oxide-approved canister (Ludwig 1994).

Industries that may use only a small portion of the total ethylene oxide produced are responsible for high occupational exposures to many workers. The National Occupational Hazard Survey, conducted by NIOSH from 1972 to 1974, estimated that 107,450 workers in 74 job categories were potentially exposed to ethylene oxide in the workplace. This estimate was based on observations of the actual use of the compound and trade name products known to contain the compound (NIOSH 1976). NIOSH estimated that approximately 75,000 health care workers employed in sterilization areas from 1972 to 1974 were potentially exposed to ethylene oxide, and that an additional 25,000 health care workers may have been exposed due to improper engineering and administrative controls (NIOSH 1981). NIOSH conducted a limited field survey of hospitals and found that ethylene oxide concentrations near malfunctioning or improperly designed equipment may reach transitory levels of hundreds or even a few thousand parts per million, but time-weighted average (TWA) ambient and breathing zone concentrations were generally below the OSHA standard of 50 ppm (CHIP 1982).

In a separate survey, OSHA estimated that in 1983, 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 (NCI 1985, IARC 1985). More recently, OSHA estimated that as many as 100,000 health care technicians may be exposed to ethylene oxide in the workplace. Health care technicians are typically exposed to quick, concentrated bursts of the gas when the door of a sterilizing machine is opened (Sun 1986). The National Occupational Exposure Survey (1981-1983) estimated that 107,450 workers, including 1,990 women, potentially were exposed to ethylene oxide (NIOSH 1990). This estimate was derived from observations of the actual use of the compound (98% of total observations) and the use of the trade name products known to contain the compound (2% of total observations). A small population of workers may potentially be exposed to ethylene oxide during the fumigation of spices. OSHA estimated that 160 workers were directly exposed to the gas during spice manufacture (NCI 1985).

Industrial 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. Although much smaller amounts of ethylene oxide are used in sterilizing medical instruments and supplies in hospitals and for the fumigation of spices, it is during these uses that the highest occupational exposure levels have been measured (IARC 1994). Measurements of worker exposure levels in U.S. hospitals, summarized below, showed a range of exposure concentrations (0 to 794 ppm), depending on operation, conditions, and duration of sampling.

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. Large sterilizers can be found in central supply areas of most hospitals and small sterilizers are used in clinics, operating rooms, tissue banks, and research facilities. Worker exposure may occur during the following operations and conditions: changing pressurized ethylene oxide gas cylinders; leaking valves, fittings, and piping; leaking sterilizer door gaskets; opening of the sterilizer door at the end of a cycle; improper ventilation at the sterilizer door; improperly or unventilated air gap between the discharge line and the sewer drain; removal of items from the sterilizer and transfer of the sterilized load to an aerator; improper ventilation of aerators and aeration areas; incomplete aeration of items; inadequate general room ventilation; and passing near sterilizers and aerators during operation (IARC 1994).

Exposure primarily results from peak emissions during operations such as opening the door of the sterilizer and unloading and transferring sterilized material. Short-term (2 to 30 min) exposure concentrations from below the level of detection to 186 mg/m^3 (103 ppm) were measured in personal samples from hospital sterilizer operators in studies conducted by NIOSH during 1977 to 1990. With the proper use of engineering controls and work practices, exposure levels can be very low (full shift exposure, <0.1 ppm; short-term exposure, <2 ppm). However, the use of personal protective equipment in U.S. hospitals was generally limited to wearing gloves, with no use of respirators, when workers were transferring sterilized items (IARC 1994).

A recent study of hazardous materials incidents in Massachusetts found that most accidental releases at hospitals involved ethylene oxide (Kales *et al*. 1997). Detailed exposure data, including personal and area monitoring, were obtained for employees of Massachusetts hospitals during 1990 to 1992 (LaMontagne and Kelsey 1997). During this period, 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.

A study in a large hospital demonstrated that standard industrial hygiene practices can result in nearly "zero exposure" without personal protective equipment or prohibitive costs (Elias *et al*. 1993). Instantaneous measurements showed a reduction of peak levels from 500 ppm to 0 to 2.8 ppm from use of engineering and administrative controls.

Ethylene oxide was used as a reaction chemical to modify starch in the starch processing area of an industrial U.S. wastewater treatment plant. Exposures (personal breathing zone concentrations) for full shift operators ranged from undetectable to 0.43 mg/m^3 (0.24 ppm) and from undetectable to 2.5 mg/m^3 (1.4 ppm) for full shift mechanics. IARC (1994) reviewed a number of studies of exposure at production facilities. Exposure data were collected in 1987 from 11 ethylene oxide production units in the United States. The highest mean 8-hr TWA was 2.9 mg/m^3 (1.6 ppm) with a range of 0.36 to 6.8 mg/m^3 (0.20 to 3,8 ppm); short-term mean exposure levels for maintenance workers were as high as 19.6 mg/m^3 (10.9 ppm). Respirators were used in operations where engineering controls were not feasible. The manufacture of ethylene oxide typically entails exposure to a variety of other chemicals (e.g., unsaturated aliphatic hydrocarbons, other epoxides, and chlorinated aliphatic hydrocarbons) (IARC 1994).

Workers employed in a Brazilian industry using ethylene oxide as an intermediate were biologically monitored for exposure to ethylene oxide (Ribeiro *et al*. 1994). Ambient air measurements in the general area, made during a 3-month sampling period, indicated that workers were exposed to 2 to 5 ppm TWA for an 8-hour working day. Blood samples were taken from 75 workers and 22 controls (no occupational exposure to ethylene oxide) matched for sex, age, and smoking habits. Cytogenetic methods and analyses showed significant increases in chromosomal aberrations, micronuclei in binucleated lymphocytes, and hemoglobin adducts (HOEtVal) in the exposed group; however, the frequencies of micronucleated cells in buccal mucosa were not significantly different between the exposed and control groups.

In 1985, U.S. emissions of ethylene oxide in air were approximately 5,000 Mg (metric tons) per year. The following lists percentages of total air emissions by use: sterilization and fumigation sites, 57%; production and captive use, 31%; medical facilities, 8%; and ethoxylation, 4% (IARC 1994).

One entry route into the environment for ethylene oxide is as fugitive emissions lost during production, or as vented gases (ATSDR 1990). Fugitive emissions were approximately 1.28 million lb in 1978. No information was available to indicate loss with solid waste. There is an estimated emission of 142,600 lb during storage. All ethylene oxide used as a fumigant (up to 10 million lb) is released into the environment. The Ethylene Oxide Industrial Council (EOIC) estimated that approximately 3 million lb of ethylene oxide are released into the atmosphere each year. Additional sources of ethylene oxide in the environment include inadvertent production from combustion of hydrocarbon fuels (estimated to be millions of pounds annually), cigarette smoke (from ethylene oxide-fumigated tobacco), ethylene oxide degradation products of certain bacteria, photochemical smog, and water disinfection (the latter source only minimal). It has been estimated that approximately 3 million lb per year were lost to the atmosphere and that approximately 800,000 lb per year were lost to water, representing 0.07% of the 1980 production. Most producers reported that water containing ethylene oxide is treated at a biopond before being discharged from the plant. Several producers stated that steps are underway to reduce the water-ethylene oxide discharges from the ethylene oxide plants to the waste treatment areas, so this number should decrease significantly in the near future. Those producers who have monitored ethylene oxide at the fence line reported nondetectable amounts in the water analyzed. Five ethoxylation companies reported that a total of 4,000 lb per year was lost to the atmosphere, while none was lost to water (CHIP 1982).

Significant gaseous releases of ethylene oxide to the environment are the result of uncontrolled industrial emissions (ATSDR 1990). These occur during the loading or unloading of transport tanks, product sampling procedures, and equipment maintenance and repair (CHIP 1982). Ethylene oxide emissions from commercial sterilization facilities in the United States were estimated from data in a 1985 survey of medical equipment suppliers, information provided to EPA (1986, 1988, 1989), and engineering judgment (USEPA 1993). Emissions ranged from 520 to 20,000 kg per year per unit, depending upon chamber volume, number of facilities, and amount of ethylene oxide used. Emissions expected from mobile beehive fumigator units were not included in the estimation. EPA's Toxic Chemical Release Inventory (TRI) listed 148 industrial facilities that produced, processed, or otherwise used ethylene oxide in 1999 (TRI99 2001). The facilities reported releases of ethylene oxide to the environment that were estimated to total 521,423 lb. Releases to the environment have significantly decreased since 1988 (4.7 million lb reported releases). The EPA (1994) estimated that its final air toxics rule for controlling ethylene oxide emissions from commercial sterilization and fumigation operations would reduce ethylene oxide atmospheric emissions by 2 million lb annually from an estimated 114 sources.

The risk of potential consumer exposure to ethylene oxide occurs primarily through the use of products that have been sterilized with the compound. These include medical products; articles in libraries, museums, and research laboratories; beekeeping equipment; certain foods and dairy products; cosmetics; transportation vehicles; and articles of clothing (NIOSH 1981). EPA reported that small amounts of ethylene oxide, used as a fumigant, were found in some food commodities, such as cocoa, flour, dried fruits and vegetables, and fish. Other sources, however, list ethylene oxide as a fumigant for only three foods: spices, black walnuts, and copra. Residual ethylene oxide may also be found in foods temporarily following fumigation. It may react with water and inorganic halides (Cl^- and Br^-) from foods, producing glycols and halohydrins. Researchers concluded that the persistence or disappearance of ethylene oxide and its by-products in fumigated commodities depends on the grain size, type of food aeration procedures, temperature, and storage and cooking conditions. Most fumigated commodities had levels of ethylene oxide below 1 ppm after 14 days in normal storage conditions (ATSDR 1990). Ethylene oxide residues were detected in the following food products sampled from Danish retail shops: herbs and spices (14 to 580 mg/kg), dairy (0.06 to 4.2 mg/kg), pickled fish (0.08 to 2.0 mg/kg), meat products (0.05 to 20 mg/kg), cocoa products (0.06 to 0.98 mg/kg), and black and herb teas (3 to 5 mg/kg; one sample contained 1,800 mg/kg). No ethylene oxide residue was detected in a follow-up study of 59 honey samples (IARC 1994).

REGULATIONS

EPA regulates ethylene oxide under the Clean Air Act (CAA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Resource Conservation and Recovery Act (RCRA), Superfund Amendments and Reauthorization Act (SARA), and Toxic Substances Control Act (TSCA). Under CAA, ethylene oxide has been designated a hazardous air pollutant and potential human health hazard. Under CERCLA, a reportable quantity (RQ) of 10 lb has been established. It is regulated as a hazardous constituent of waste under RCRA. EPA subjects the compound to reporting requirements under SARA and TSCA. Under FIFRA, a Rebuttable Presumption Against Registration (RPAR) for ethylene oxide has been issued. Ethylene oxide is registered under FIFRA as a pesticide for use as a sterilant for medical or veterinary devices, pharmaceuticals and aseptic packaging and as a fumigant for cosmetic, herbs and spices. EPA has changed labeling requirements for pesticide products containing ethylene oxide that are used

for sterilization purposes. These changes will require modifications in workplace design and practice in hospitals and health care facilities.

Emission standards for ethylene oxide from commercial sterilizers/fumigators were implemented in 1994. Existing and new sources that use one to 10 tons must achieve a 99% emission reduction in the sterilization chamber vent, but no controls are required for the aeration room vent or chamber exhaust vent. Operations that use over 10 tons must reduce emissions in the sterilization chamber vent, the aeration room vent, and the chamber exhaust vent. Facilities that use less than one ton have no controls, but must meet record-keeping requirements.

FDA regulates ethylene oxide as a food additive under the Food, Drug, and Cosmetic Act (FD&CA), and finds that it is the common practice in the drug industry to contract out the performance of ethylene oxide sterilization. FDA allows denture adhesives to be composed of an ethylene oxide homopolymer, alone or with carboxymethyl cellulose sodium or karaya. Tolerances for residues of ethylene oxide on agricultural commodities have also been established under FD&CA; however, FDA is re-evaluating its established regulations governing ethylene oxide residues, in light of recent toxicity data and information concerning the formation of 1,4-dioxane.

Ethylene oxide was the subject of a Special Hazard Review performed by NIOSH, which has recommended an exposure limit of <0.1 ppm (<0.18 mg/m^3) as an 8-hr TWA and 5 ppm (9 mg/m^3) ceiling concentration (10-minute). OSHA has set a permissible exposure limit (PEL) of 1 ppm as an 8-hr TWA in 1984 and established an STEL of 5 ppm averaged over a 15-minute period. OSHA also regulates ethylene oxide under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 85.

REFERENCES

ATSDR. Agency for Toxic Substances and Disease Registry. Toxicological Profile for Ethylene Oxide. (Final Report). Atlanta, GA: ATSDR, Public Health Service, U.S. Department of Health and Human Services. 1990. 109 pp. NTIS Accession No. PB91-180554.

Biomedical Market Newsletter. Sterilization Systems Lead Infection Control Market. Biomed. Mark. Newslett. July 1995. pp. N.A.

Bisanti, L., M. Maggini, R. Raschetti, S. Spila Alegiani, F. Menniti Ippolito, B. Caffari, N. Segnan, and A. Ponti. Cancer Mortality in Ethylene Oxide Workers. Br. J. Ind. Med. Vol. 50, 1993, pp. 317-324.

Budavari, S., Ed. The Merck Index, Twelfth Edition. Merck & Co., Inc., Whitehall, NJ, 1996.

Chemical and Engineering News. Organic chemicals. Vol. 74, No. 26, 1996, p. 42.

Chemical and Engineering News. Production Profiles. Vol. 76, No. 26, 1998, p. 43.

Chemical Marketing Reporter. Ethylene Derivatives: The Big Question. Chem. Mark. Rep. March 20, 1995. p. S5. Full text from PROMT 95:141183.

Chemical Marketing Reporter. Vol. 231, No. 10, 1987, p. 54.

Chem Sources. Chemical Sources International, Inc. http://www.chemsources.com, 2001.

CHIP. Chemical Hazard Information Profile. Ethylene Oxide. Office of Pesticide Programs and Toxic Substances, U.S. EPA, Washington, DC, 1982.

Elias, J., N. Wylie, A. Yassi, and N. Tran. Eliminating Worker Exposure to Ethylene Oxide from Hospital Sterilizers—An Evaluation of Cost and Effectiveness of an Isolation System. Appl. Occup. Environ. Hyg. Vol. 8, No. 8, 1993, pp. 687-692.

EPA. U.S. Environmental Protection Agency. Technical Report: Ethylene Oxide Emissions from the Use of Ethylene Oxide as a Sterilant at Commercial Sterilization Facilities. Research Triangle Park, NC. 1986.

EPA Superfund Record of Decision (EPA, Region 3): Tyson's Dump Site, PA (Second Remedial Action), September 1988. EPA/ROD/R03-88/068, PB89-225536, NTIS, 1988. 81 pp.

EPA. U.S. Environmental Protection Agency. Ethylene Oxide Commercial Sterilization Database. Research Triangle Park, NC. 1987, updated 1989.

EPA. U.S. Environmental Protection Agency. Ethylene Oxide Emissions from Commercial Sterilization/Fumigation Operations—Background Information for Proposed Standards. U.S. EPA Office of Air and Radiation, Office of Air Quality Planning and Standards, Research Triangle Park, NC, 1993.

EPA. U.S. Environmental Protection Agency. Final Air Toxics Rule for Controlling Ethylene Oxide Emissions from Commercial Sterilization and Fumigation Operations. Office of Air Quality Planning and Standards, Research Triangle Park, NC. Available at URL http://www.epa.gov/ttnuatw1/eo/fseo.html, 1994.

Fuchs, J., U. Wullenweber, J. Hengstler, H. Bienfait, G. Hiltl, and F. Oesch. Genotoxic Risks for Humans due to Work Place Exposure to Ethylene Oxide: Remarkable Individual Differences in Susceptibility. Arch. Toxicol. Vol. 68, No. 6, 1994, pp. 343-348.

Garman, R., W. Snellings, and R. Maronpot. Brain Tumors in F-344 Rats Associated with Chronic Inhalation Exposure to Ethylene Oxide. Neurotoxicology Vol. 6, 1985, pp. 117-138.

Galloway, S., P. Berry, W. Nichols, S. Wolman, K. Soper, P. Stolley, and P. Archer. Chromosome Aberrations in Individuals Occupationally Exposed to Ethylene Oxide, and in a Large Control Population. Mutat. Res. Vol. 170, 1986, pp. 55-75.

Hagmar, L., H. Welinder, K. Linden, R. Attewell, S. Osterman-Golkar, and M. Tornqvist. An Epidemiological Study of Cancer Risk among Workers Exposed to Ethylene Oxide Using Hemoglobin Adducts to Validate Environmental Exposure Assessments. Int. Arch. Environ. Health Vol. 63, 1991, pp. 271-277.

Hoechst Celanese Polyester Intermediates, Occidental Chemical Corporation, Shell Chemical Company, and Sun Company, Inc. Ethylene Oxide User's Guide. 1995. 66 pp.

Hogstedt, C., N. Malmqvist, and B. Wadman. Leukemia in Workers Exposed to Ethylene Oxide. J. Am. Med. Assoc. Vol. 242, 1979, pp. 1132-1133.

Hogstedt, B., B. Gullberg, K. Hedner, A.-M. Kolnig, F. Mitelman, S. Skerfving, and B. Widegren. Chromosome Aberrations and Micronuclei in Bone Marrow Cells and Peripheral

Blood Lymphocytes in Humans Exposed to Ethylene Oxide. Hereditas Vol. 98, 1983, pp. 105-113.

Hogstedt, C., L. Aromger, and A. Gustavsson. Epidemiologic Support for Ethylene Oxide as a Cancer-Causing Agent. J. Am. Med. Assoc. Vol. 255, 1986, pp. 1575-1578.

Hogstedt, C. Epidemiological Studies on Ethylene Oxide and Cancer: An Updating. In: Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention. IARC Scientific Publications, No. 89. 518 pp. Lyon, France: IARC, 1988, pp. 265-270.

HSDB. Hazardous Substances Data Bank. Online database produced by the National Library of Medicine. Ethylene Oxide. Profile last updated May 21, 2001. Last review date, November 1, 1994.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics. Vol. 11. 306 pp. Lyon, France: IARC, 1976.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Allyl Compounds, Aldehydes, Epoxides, and Peroxides. Vol. 36. 369 pp. Lyon, France: IARC, 1985.

IARC. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans. Some Industrial Chemicals. Vol. 60. 560 pp. Lyon, France: IARC, 1994.

ITA. International Trade Administration. U.S. Department of Commerce. Subheading 291010: Oxirane (Ethylene Oxide). http://www.ita.doc.gov/td/industry/otea/Trade-Detail/Latest-December/, 2001.

Kales, S., G. Polyhronopoulos, M. Castro, R. Goldman, and D. Christiani. Mechanisms of and Facility Types Involved in Hazardous Materials Incidents. Environ. Health Perspect. Vol. 105, No. 9, 1997, pp. 998-1000.

Kiesselbach, N., K. Ulm, H.-J. Lange, and U. Korallus. A Multicentre Mortality Study of Workers Exposed to Ethylene Oxide. Br. J. Ind. Med. Vol. 47, 1990, pp. 182-188.

LaMontagne, A., and K. Kelsey. Evaluating OSHA's Ethylene Oxide Standard: Employer Exposure-Monitoring Activities in Massachusetts Hospitals from 1985 through 1993. Am. J. Public Health Vol. 87, No. 7, 1997, pp. 1119-1125.

Lerda, D., and R. Rizzi. Cytogenetic Study of Persons Occupationally Exposed to Ethylene Oxide. Mutat. Res. Vol. 281, 1992, pp. 31-37.

Ludwig, H. NIOSH Pocket Guide to Chemical Hazards. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Cincinnati, OH. DHHS (NIOSH) Publication No. 94-116. 1994. 398 pp.

Lynch, D., T. Lewis, W. Moorman, J. Burg, D. Groth, D, A. Khan, L. Ackerman, and B.

Cockrell. Carcinogenic and Toxicological Effects of Inhaled Ethylene Oxide and Propylene Oxide in F344 Rats. Toxicol. Appl. Pharmacol. Vol. 76, 1984, pp. 69-84.

Major, J., M. Jakab, and A. Tompa. Genotoxicological Investigation of Hospital Nurses Occupationally Exposed to Ethylene Oxide: I. Chromosome Aberrations, Sister-Chromatid Exchanges, Cell Cycle Kinetics, and UV-Induced DNA Synthesis in Peripheral Blood Lymphocytes. Environ. Mol. Mutagen. Vol. 27, 1996, pp. 84-92.

Mayer, J., D. Warburton, A. Jeffrey, R. Pero, S. Walles, L. Andrews, M. Toor, L. Latriano, L. Wazneh, D. Tang, W.-Y Tsai, M. Kuroda, and F. Perera. Biologic Markers in Ethylene Oxide-Exposed Workers and Controls. Mutat. Res. Vol. 248, 1991, pp. 163-176.

Morgan, R., K. Claxton, B. Divine, S. Kaplan, and V. Harris. Mortality Among Ethylene Oxide Workers. J. Occup. Med. Vol. 23, 1981, pp. 767-770.

NCI. National Cancer Institute, Division of Cancer Etiology. Monograph on Human Exposure to Chemicals in the Workplace: Ethylene Oxide. Technical Report No. 84-668. Bethesda, MD: Department of Health and Human Services, 1985.

NIOSH. National Institute for Occupational Safety and Health. National Occupational Hazard Survey (1972-74). Cincinnati, OH: Department of Health, Education, and Welfare, 1976.

NIOSH. National Institute for Occupational Safety and Health. NIOSH Current Intelligence Bulletin 35: Ethylene Oxide (EtO). DHHS (NIOSH) Publication No. 81-130. 22 pp. Cincinnati, OH: Department of Health and Human Services, 1981.

NIOSH. National Institute for Occupational Safety and Health. National Occupational Exposure Survey (1981-83). Unpublished provisional data as of 7/1/90. Cincinnati, OH: Department of Health and Human Services, 1990.

Norman, S., J. Berlin, K. Soper, B. Middendorf, and P. Stolley. Cancer Incidence in a Group of Workers Potentially Exposed to Ethylene Oxide. Int. J. Epidemiol. Vol. 24, No. 2, 1995, pp. 276-284.

NTP. National Toxicology Program. Technical Report Series No. 326. Toxicology and Carcinogenesis Studies of Ethylene Oxide (CAS No. 75-21-8) in B6C3F_1 Mice (Inhalation Studies). NIH Publication No. 88-2582. 60 pp. National Toxicology Program, Research Triangle Park, NC, and Bethesda, MD, 1987.

Oesch, F., J. Hengstler, M. Arand, and J. Fuchs. Detection of Primary DNA Damage: Applicability to Biomonitoring of Genotoxic Occupational Exposure and in Clinical Therapy. Pharmacogenetics Vol. 5, 1995, pp. S118-S122.

Ribeiro, L., D. Salvadori, A. Rios, S. Costa, A. Tates, M. Törnqvist, and A. Natarajan. Biological Monitoring of Workers Occupationally Exposed to Ethylene Oxide. Mutat. Res. Vol. 313, 1994, pp. 81-87.

Sarto, F., I. Cominato, A. Pinton, P. Brovedani, C. Faccioli, V. Bianchi, and A. Levis. Workers Exposed to Ethylene Oxide Have Increased Incidence of Sister Chromatid Exchange. In: Monitoring Human Exposure to Carcinogenic and Mutagenic Agents. IARC Scientific Publications, No. 59. 457 pp. Lyon, France: IARC, 1984, pp. 413-419.

Schulte, P., M. Boeniger, J. Walker, S. Schober, M. Pereira, D. Gulati, J. Wojciechowski, A. Garza, R. Froelich, G. Strauss, W. Halperin, R. Herrick, and J. Griffith. Biologic Markers in Hospital Workers Exposed to Low Levels of Ethylene Oxide. Mutat. Res. Vol. 278, 1992, pp. 237-251.

Schulte, P., J. Walker, M. Boeniger, Y. Tsuchiya, and W. Halperin. Molecular, Cytogenetic, and Hematologic Effects of Ethylene Oxide on Female Hospital Workers. J. Occup. Environ. Med. Vol. 37, No. 3, 1995, pp. 313-320.

Shore, R.E., M.J. Gaardner, and B. Pannett. Ethylene Oxide: an Assessment of the Epidemiological Evidence on Carcinogenicity. Br. J. Ind. Med. Vol. 50, 1993, pp. 971-997.

Snellings, W., C. Weil, and R. Maronpot. A Two-Year Inhalation Study of the Carcinogenic Potential of Ethylene Oxide in Fischer 344 Rats. Toxicol. Appl. Pharmacol. Vol. 75, 1984, pp. 105-117.

SRI. Ethylene Oxide. Supply and Demand by Region—United States—Consumption—Other. In: Chemical Economics Handbook. Stanford Research Institute, Menlo Park, CA: SRI International, 1997a.

SRI. Directory of Chemical Producers, United States, 1997. Stanford Research Institute, Menlo Park, CA: SRI International, 1997b.

Stayner, L., K. Steenland, A. Greife, R. Horning, R.B. Hayes, S. Nowlin, J. Morawetz, V. Ringenburg, L. Elliot, and W. Halperin. Exposure-Response Analysis of Cancer Mortality in a Cohort of Workers Exposed to Ethylene Oxide. Am. J. Epidemiol. Vol. 138, 1993, pp. 787-798.

Steenland, K., L. Stayner, A. Greife, W. Halperin, R.B. Hayes, R. Hornung, and S. Nowlin. Mortality Among Workers Exposed to Ethylene Oxide. N. Engl. J. Med. Vol. 324, 1991, pp. 1402-1407.

Stolley, P., K. Soper, S. Galloway, W. Nichols, S. Norman, and S. Wolman. Sister Chromatid Exchanges in Association with Occupational Exposure to Ethylene Oxide. Mutat. Res. Vol. 129, 1984, pp. 89-102.

Sun, M. Study Estimates Higher Risk From Ethylene Oxide Exposure. Science. Vol. 231 (4737), 1986, p. 448.

Tates, A., T. Grummt, M. Tornqvist, P. Farmer, F. van Dam, H. van Mossel, H. Shoemaker, S. Osterman-Golkar, C. Uebel, Y. Tang, A. Zwinderman, A. Natarajan, and L. Ehrenberg. Biological and Chemical Monitoring of Occupational Exposure to Ethylene Oxide. Mutat. Res. Vol. 250, 1991, pp. 483-497.

Teta, M., L. Benson, and J. Vitale. Mortality Study of Ethylene Oxide Workers in Chemical Manufacturing: A 10-Year Update. Br. J. Ind. Med. Vol. 50, 1993, pp. 704-709.

Tornqvist, M. Ethylene Oxide as a Biological Reactive Intermediate of Endogenous Origin. Adv. Exp. Med. Biol. Vol. 387, 1996, pp. 275-283.

TRI99. Toxic Chemical Release Inventory 1999. Data contained in the Toxic Chemical Release Inventory (TRI). Available from the U.S. Environmental Protection Agency Office of Environmental Information, http://www.epa.gov/triexplorer/reports.htm, 2001.

USITC. U.S. International Trade Commission. Synthetic Organic Chemicals, United States Production and Sales, 1984. USITC Publication No. 1745. Washington, DC: U.S. Government Printing Office, 1985.

USITC. U.S. International Trade Commission. Synthetic Organic Chemicals, United States Production and Sales, 1985. USITC Publication No. 1892. Washington, DC: U.S. Government Printing Office, 1986.

USITC. U.S. International Trade Commission. Synthetic Organic Chemicals, United States Production and Sales, 1986. USITC Publication No. 2009. Washington, DC: U.S. Government Printing Office, 1987.

USITC. U.S. International Trade Commission. Synthetic Organic Chemicals, United States Production and Sales, 1988. USITC Publication No. 2219. Washington, DC: U.S. Government Printing Office, 1989.

USITC. U.S. International Trade Commission. Synthetic Organic Chemicals, United States Production and Sales, 1989. USITC Publication No. 2338. Washington, DC: U.S. Government Printing Office, 1990.

Yager, J., C. Hines, and R. Spear. Exposure to Ethylene Oxide at Work Increases Sister Chromatid Exchanges in Human Peripheral Lymphocytes. Science Vol. 219, 1983, pp. 1221-1223.