NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT for ETHYLENE OXIDE

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Prepared by

Integrated Laboratory Systems
Post Office Box 13501
Research Triangle Park, North Carolina 27709
NIEHS Contract No. N01-ES-25346

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NTP Report on Carcinogens Listing for Ethylene Oxide

Carcinogenicity

Ethylene oxide is *known to be a human carcinogen* based on evidence from studies in humans and experimental animals and from supporting mechanistic data. Ethylene oxide is a direct-acting alkylating agent that has been used as an industrial intermediate and as a disinfectant/sterilant. The DNA damaging activity of ethylene oxide provides its effectiveness as a sterilant, and it is this same property that accounts for its potential carcinogenic risk to humans. An IARC (1994) reevaluation of data on ethylene oxide resulted in upgrading its classification from "probably carcinogenic to humans" (Group 2A) to "carcinogenic to humans" (Group 1), though the epidemiology studies alone provided only "limited evidence" for the carcinogenicity of ethylene oxide in humans. In making their overall evaluation of this direct-acting alkylating agent, the IARC panel utilized supporting mechanistic data (see below).

Several epidemiological studies evaluated by IARC (1994) 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, exposure information 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 (Steenland et al., 1991) 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. 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 nonsignificant (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 workers.

Experimental studies in laboratory animals demonstrated that ethylene oxide is carcinogenic at multiple organ sites in rats and mice. Sites of tumor induction in mice included the hematopoietic system, lung, Harderian gland, mammary gland, and uterus (NTP 326, 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). The IARC (1994) evaluation

noted that ethylene oxide is associated with malignancies of the lymphatic and hematopoietic system in both humans and experimental animals. No additional cancer studies of ethylene oxide in experimental animals have been reported since the IARC (1994) review.

Other Information Relating 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 occupational 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 (Törnqvist, 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; Högstedt 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.

Listing Criteria from the Report on Carcinogens, Eighth Edition

Known To Be A Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated To Be A Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded; or

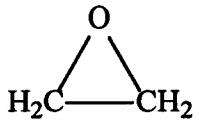
There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either a known to be human carcinogen or reasonably anticipated to be human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

1.0 CHEMICAL PROPERTIES

Ethylene Oxide
[75-21-8]



1.1 Chemical Identification

Ethylene oxide (C_2H_4O, mol. wt. = 44.06) is also called:

Amprolene	Merpol
Anprolene	NCI-C50088
Anproline	Oxacyclopropane
Dihydrooxirene	Oxane (VAN)
Dimethylene oxide	Oxidoethane
ENT-26263	α,β-Oxidoethane
EO	Oxirane
1,2-Epoxyethane	Oxirane (9CI)
Ethane, 1,2-epoxy-	Oxirene, dihydro-
Ethene oxide	Oxyfume
Ethox	Oxyfume 12
ETO	Sterilizing Gas Ethylene Oxide 100%
ETOX	t-Gas
FEMA no. 2433	T-Gas

Ethylene oxide has a UN shipping number of 1040. The RCRA waste number is U115.

1.2 Physical-Chemical Properties

Property	Information	Reference
Color	Colorless	Budavari (1996)
Physical State	Gas	Budavari (1996)
Melting Point, °C	-111	Budavari (1996)
Boiling Point, °C	13.2 @ 746 mm Hg	IARC (1994)
	10.8 @ 760 mm Hg	IARC (1994)
Density		
Liquid	0.882 @ 10 °C/10 °C	IARC (1994)
Odor	sweet etheric odor	Hoechst Celanese Polyester Intermediates et al. (1995)
Solubility	soluble in water, acetone, benzene, ethanol, diethyl ether	IARC (1994)
Partition Coefficients:		
Log octanol/water (log P)	-0.30	IARC (1994)
Vapor pressure	145.6 kPa @ 20 °C	IARC (1994)

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 (Hoechst Celanese Polyester Intermediates et al., 1995). 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 (HSDB, 1998). It has been sold as a mixture with either carbon dioxide or fluorocarbon 12 to reduce its fire hazard.

2.0 HUMAN EXPOSURE

2.1 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 and polyester. By 1995, the demand for ethylene oxide in ethylene glycol and polyester production was approximately half and half (Chem. Mark. Rep., 1995). Ethylene glycol is used primarily in automotive antifreeze and 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., 1987b; cited by NTP, 1998). 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 (NIOSH, 1976; ATSDR, 1990). By the mid-1990s, ethylene oxide use for sterilization in hospitals was being replaced by other systems (Biomed. Mark. Newlett., 1995). The estimated 8 to 9 million lb used for sterilization and fumigation in 1996 represented about 0.1% of the total demand for ethylene oxide (SRIc, 1997).

At one time, it was used in the production of acrylonitrile, but the process ended in 1966 (ATSDR, 1990). Ethylene oxide has also been used to accelerate the maturing of tobacco leaves.

It has been investigated for use as an agent to improve wood durability (CHIP, 1982b; IARC V.11, 1976; both cited by NTP, 1998).

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).

2.2 Production

Ethylene oxide has been ranked among the top 50 largest volume chemicals produced in the United States for the past several years by *Chemical and Engineering News*. The worldwide production capacity exceeds 8 million tons per year (Hoechst Celanese Polyester Intermediates et al., 1995). The 1997 *Directory of Chemical Producers* identified 11 companies producing ethylene oxide at 13 plants (SRIa, 1997).

Year	Production (billions of pounds)
1997	8.2
1996	7.2
1995	7.6
1994	7.2
1993	5.3
1992	5.8
1991	5.2
1990	5.4
1989	5.8
1988	6.0
1987	4.8
1986	5.4
1985	5.4
1984	5.7
1983	> 5.5
1982	~ 5.0
1981	4.9
1980	5.2
1979	5.7

Sources: Data were taken from Chem. Eng. News, 1996-1998 and USITC, 1980-1985 (cited by NTP, 1998).

Year	Imports	Exports
	(millions of pounds)	
1989	33.6	12.1
1988	32	18
1987	> 28	35
1986	3	~ 28
1985	23	> 62.3
1984	12.4	24.7
1983	-	-
1982	9.48	3.3

Sources: Import and export data were taken from ATSDR, 1990-9R068; USDOC Imports, 1990; USDOC Exports, 1986 and 1990; cited by NTP, 1998; and Chem. Prod., 1988.

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 10-30 atm (1-3 MPa) and 200-300 °C to give ethylene oxide (IARC, 1994).

The chlorohydrin process used to be 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).

2.3 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 process equipment containing it generally consists of tightly closed and highly automated systems, which decreases the risk of occupational exposure (NCI DCE, 1985h; cited by NTP, 1998). Workers in the synthetic organic chemicals manufacturing industry using ethylene oxide are required to wear respirators when air concentrations exceed the PEL. Personnel in workplaces up to 50 ppm ethylene oxide in the air should wear full facepiece respirators with an ethylene oxide-approved canister (Ludwig, 1994).

2.3.1 Measurement of Exposure

Ethylene oxide forms DNA and hemoglobin adducts. These adducts have been used to monitor human exposure to ethylene oxide (see Section 6).

2.3.2 Commercial Facility Emission Estimates

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 (U.S. EPA, 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 (Table 2-1). Emissions expected from mobile beehive fumigator units were not included in the estimation.

Table 2-1. Average Ethylene Oxide Emissions from Three Sizes of Commercial Sterilization Facilities (U.S. EPA, 1993)

Chamber vol., m^3 (no.)	Mean EO use, kg/yr	EF[a]	Mean EO emissions, kg/yr
< 11 (87)	580	0.90	520
11-56 (71)	6,500	0.65	4,200
> 56 (38)	37,000	0.54	20,000

[a]emission factor (kilograms emission/kilograms used)

2.3.3 Occupational Exposure

NIOSH collected data on potential exposure to specific substances in the National Occupational Hazard Survey (NOHS) from 1972 to 1974 (NIOSH, 1976) and in the National Occupational Exposure Survey (NOES) from 1981 to 1983 (NIOSH, 1990). The industries most likely to use ethylene oxide for sterilization or chemical synthesis are listed in Tables 2-2 and 2-3.

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 tradename products known to contain the compound (NIOSH, 1976). NIOSH estimated that approximately 75,000 health care workers employed in sterilization areas in the period 1972-1974 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 35, 1981; cited by NTP, 1998). 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, 1982b; cited by NTP, 1998).

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 DCE, 1985h; cited by NTP, 1998; IARC V.36, 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 (Science, 1986). The National Occupational Exposure Survey (1981-1983) estimated that 50,132 workers, including 28,942 women, potentially were exposed to ethylene oxide (NIOSH, 1984). [Presumably, the data have been reevaluated since 1984. Current estimates based on the NOES are given in Table 2-3.] This estimate was derived from observations of the actual use of the compound (98% of total observations) and the use of the tradename 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 DCE, 1985h; cited by NTP, 1998).

TABLE 2-2. POTENTIAL ETHYLENE OXIDE EXPOSURE IN SELECTED INDUSTRIES REPORTED IN THE 1972-1974 NATIONAL OCCUPATIONAL HAZARD SURVEY (NOHS) (NIOSH, 1976)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
0742	VETERINARY SERVICES, SPECIALTIES	230	1,838	1,608
2013	SAUSAGES AND OTHER PREPARED MEATS	17	748	35
2051	BREAD, CAKE, AND RELATED PRODUCTS	47	773	
2082	MALT BEVERAGES	65	1,170	
2261	FINISHING PLANTS, COTTON	10	435	300
2647	SANITARY PAPER PRODUCTS	34	2,041	
2821	PLASTICS MATERIALS AND RESINS	4	413	
2824	ORGANIC FIBERS, NONCELLULOSIC	7	8,524	1,324
2833	MEDICINALS AND BOTANICALS	116	5,718	729
2834	PHARMACEUTICAL PREPARATIONS	112	6,087	5,637
2841	SOAP AND OTHER DETERGENTS	11	2,019	106
2842	POLISHES AND SANITATION GOODS	25	49	
2843	SURFACE ACTIVE AGENTS	45	1,565	
2869	INDUSTRIAL ORGANIC CHEMICALS, NEC	79	4,017	236
2893	PRINTING INK	45	5,124	356
2899	CHEMICAL PREPARATIONS, NEC	94	1,976	
2911	PETROLEUM REFINING	90	2,048	
3011	TIRES AND INNER TUBES	7	2,850	
3021	RUBBER AND PLASTICS FOOTWEAR	72	2,581	
3069	FABRICATED RUBBER PRODUCTS, NEC	211	5,025	2,694
3079	MISCELLANEOUS PLASTICS PRODUCTS	44	173	
3841	SURGICAL AND MEDICAL INSTRUMENTS	28	743	307
7211	POWER LAUNDRIES, FAMILY & COMMERCIAL	48	2,449	1,921
7216	DRY CLEANING PLANTS, EXCEPT RUG	1,821	9,793	6,190
7219	LAUNDRY AND GARMENT SERVICES, NEC	62	246	
7391	RESEARCH & DEVELOPMENT LABORATORIES	43	1,217	309
8062	GENERAL MEDICAL & SURGICAL HOSPITALS	2,594	96,468	81,992
8072	DENTAL LABORATORIES	316	2,529	316
SUBTOTAL, LISTED INDUSTRIES		**6,277**	**168,619**	**104,060**
SUBTOTAL, OTHER INDUSTRIES		4,380	102,064	16,026
TOTAL		10,657	270,683	120,086

TABLE 2-3. POTENTIAL ETHYLENE OXIDE EXPOSURE IN SELECTED INDUSTRIES REPORTED IN THE 1981-1983 NATIONAL OCCUPATIONAL EXPOSURE SURVEY (NOES) (NIOSH, 1990)

SIC CODE	DESCRIPTION	PLANTS	TOTAL EMPLOYEES	FEMALE EMPLOYEES
0722	VETERINARIANS AND ANIMAL HOSPITALS	78	783	
2033	CANNED FRUITS AND VEGETABLES	41	372	
2121	CIGARS	6	6	
2262	FINISHING PLANTS, SYNTHETICS	18	683	
2818	INDUSTRIAL ORGANIC CHEMICALS, NEC	41	1,036	
2819	INDUSTRIAL INORGANIC CHEMICALS, NEC	21	518	
2831	BIOLOGICAL PRODUCTS	33	660	
2834	PHARMACEUTICAL PREPARATIONS	14	280	
2842	POLISHES AND SANITATION GOODS	48	3,625	
2843	SURFACE ACTIVE AGENTS	21	1,078	
2851	PAINTS AND ALLIED PRODUCTS	158	1,059	
2879	AGRICULTURAL CHEMICALS, NEC	43	691	
3069	FABRICATED RUBBER PRODUCTS, NEC	11	33	
3079	MISCELLANEOUS PLASTICS PRODUCTS	98	4,914	
3585	REFRIGERATION MACHINERY	17	545	
3841	SURGICAL AND MEDICAL INSTRUMENTS	14	35	
3842	SURGICAL APPLIANCES AND SUPPLIES	8	17	
5014	TIRES AND TUBES	680	2,720	
7211	POWER LAUNDRIES, FAMILY & COMMERCIAL	352	352	
7391	RESEARCH & DEVELOPMENT LABORATORIES	5	93	
8061	HOSPITALS	1,035	16,328	
8092	SANATORIA, CONVALESCENT & REST HOMES	56	1,064	
SUBTOTAL, LISTED INDUSTRIES		**2,798**	**36,892**	
SUBTOTAL, OTHER INDUSTRIES		4,613	70,558	
TOTAL		7,411	107,450	

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.

Production of ethylene oxide

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 time-weighted average (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 usually entails exposure to a variety of other chemicals, e.g., unsaturated aliphatic hydrocarbons, other epoxides, and chlorinated aliphatic hydrocarbons (IARC, 1994).

Use of ethylene oxide as a chemical intermediate

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 2-5 ppm TWA for an 8-hr 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.

Use of ethylene oxide for industrial sterilization

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 (0-794 ppm), depending on operation, conditions, and duration of sampling.

Use of ethylene oxide in hospitals

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 mostly results from peak emissions during operations such as opening the door of the sterilizer and unloading and transferring sterilized material. Short-term (2-30 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 1977-1990. 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 1990-1992 (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 tertiary-care 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 0-2.8 ppm from use of engineering and administrative controls.

2.3.4 Emissions in Air

In 1985, U.S. emissions of ethylene oxide in air were approximately 5,000 Mg (metric tones) 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 amounted to some 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 EOIC estimated that about 3 million lb of ethylene oxide are released into the air 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 about 3 million lb per year were lost to the air and that about 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 air, while none was lost to water (CHIP, 1982b; cited by NTP, 1998).

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, 1982b; cited by NTP, 1998). The Toxic Chemical Release Inventory (EPA) listed 197 industrial facilities that produced, processed, or otherwise used ethylene oxide in 1988 (TRI88, 1990). In compliance with the Community Right-to-Know Program, the facilities reported releases of ethylene oxide to the environment which were estimated to total 4.7 million lb. By 1995, the total release to air was lower, 839,229 lb (157 facilities releasing at least 10 lb) (TRI95, 1997). The U.S. 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.

2.3.5 Other Occurrences

The risk of potential consumer exposure to ethylene oxide occurs mainly through the use of products which 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 35, 1981; cited by NTP, 1998). 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 (14-580 mg/kg), dairy (0.06-4.2 mg/kg), pickled fish (0.08-2.0 mg/kg), meat products (0.05-20 mg/kg), cocoa products (0.06-0.98 mg/kg), and black and herb teas (3-5 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).

Used as a pesticide, some of the ethylene oxide producers and ethoxylators have measured ethylene oxide residuals in ethoxylated products at their plants. The amount varied, depending on the material, and ranged from nondetectable to a few instances of 200 ppm in an ethoxylated surfactant. Surfactants, however, represent a small percentage of the end uses of ethylene oxide. Spot analyses of several ethoxylates by one producer showed the average ethylene oxide concentration was 20 ppm. Most products made from ethylene oxide are distilled or processed further so that no unreacted ethylene oxide is present. The ethoxylators who reported ethylene oxide residuals stated that the concentrations were found to be < 5 ppm. Unreacted levels in these products should reduce with time due to reaction, storage, further pumping, and other processing (CHIP, 1982b; cited by NTP, 1998).

Exposure of the general population to ethylene oxide may occur via inhalation and food ingestion, although there was no information indicating that ethylene oxide is a common

contaminant in food. Most of the ingested ethylene oxide comes from the use of the food additive polyethylene glycol. Also, the use of ethylene oxide polymer is permitted in beer; however, FDA indicates that the compound is not presently used in this capacity. There are also no data to indicate that ethylene oxide is a common constituent of air or water sources of any type in any geographic location within the United States. The limited data available indicate the presence or absence of ethylene oxide in water (drinking water supplies, groundwater, etc.) on a national scale. In water, the compound reacts to form glycols (ATSDR, 1990). The majority of ethylene oxide used as a fumigant or sterilant evaporates and is hydrolyzed by water vapor and oxidized by hydroxy free radicals (CHIP, 1982b; cited by NTP, 1998). From its chemical and physical properties, it can be inferred that ethylene oxide in soil will either volatilize as water evaporates, will leach down into the soil, or will be removed by runoff if water-saturated conditions persist. It is, therefore, unlikely that ethylene oxide will accumulate in organic sediments. No data on the accumulation and/or fate of ethylene oxide in the soil environment are available; however, due to its high level of reactivity, the formation of glycols may occur (ATSDR, 1990). Other sources of exposure to ethylene oxide for the general population may be the by-products of gasoline combustion and cigarette and tobacco smoke (ATSDR, 1990; IARC, 1994).

2.4 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. A Rebuttable Presumption Against Registration (RPAR) for ethylene oxide has been issued under FIFRA. 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 (U.S. EPA, 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 recordkeeping requirements.

The deadline for compliance with these emission standards was December 8, 1997 (U.S. EPA, 1996). Sources which use one ton, but are not major or located at major sources, may be deferred by the applicable Title V permitting authority from the Title V permitting requirements for five years until December 9, 1999. However, due to explosions of several ethylene oxide commercial sterilization and fumigation facilities, which may be attributable to emission scrubbers, this compliance was deferred for one year, until December 8, 1998 (62 FR 64736, July 1998).

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 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 lowered the permissible exposure limit (PEL) from 50 ppm to 1 ppm as an 8-hr TWA in 1984 and established an STEL of 5 ppm during a 15-minute period in 1988. OSHA regulates ethylene oxide under the Hazard Communication Standard and as a chemical hazard in laboratories.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 60—PART 60—STANDARDS OF PERFORMANCE FOR NEW STATIONARY SOURCES. Promulgated: 36 FR 24877, 12/23/71. U.S. Code: 42 U.S.C. 7401, 7411, 7413, 7414, 7416, 7429, 7601 and 7602.	
	40 CFR 60—Subpart VV—Standards of Performance for Equipment Leaks of VOC in the Synthetic Organic Chemicals Manufacturing Industry. Promulgated: 48 FR 48335, 10/18/83.	The provisions of this subpart apply to affected facilities in the synthetic organic chemicals manufacturing industry that commences construction or modification after January 5, 1981.
	40 CFR 60.489—Sec. 60.489 List of chemicals produced by affected facilities.	Ethylene oxide is produced, as an intermediate or final product, by process units covered under this subpart. Ethylene oxide is designated as a potential human health hazard.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 60—Subpart III—Standards of Performance for Volatile Organic Compound (VOC) Emissions From the Synthetic Organic Chemical Manufacturing Industry (SOCMI) Air Oxidation Unit Processes. Promulgated: 55 FR 26922, 06/29/90.	The provisions of this subpart apply to each affected facility that produces ethylene oxide as a product, co-product, by-product, or intermediate; however, if the facility has a total resource effectiveness (TRE) index value > 4.0, it is exempt from all provisions of this subpart except for 60.612, 60.614(f), 60.615(h), and 60.615(l).
	40 CFR 60—Subpart NNN—Standards of Performance for Volatile Organic Compound (VOC) Emissions From Synthetic Organic Chemical Manufacturing Industry (SOCMI) Distillation Operations. Promulgated: 55 FR 26942, 06/29/90.	The provisions of this subpart apply to each affected facility that produces ethylene oxide as a product, co-product, by-product, or intermediate; exceptions do apply.
	40 CFR 60—Subpart RRR—Standards of Performance for Volatile Organic Compound Emissions From Synthetic Organic Chemical Manufacturing Industry (SOCMI) Reactor Processes. Promulgated: 58 FR 45962, 08/31/93.	The provisions of this subpart apply to each affected facility that produces ethylene oxide as a product, co-product, by-product, or intermediate; exceptions do apply.
	40 CFR 61—PART 61—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS. Promulgated: 38 FR 8826, 04/06/73. U.S. Code: 42 U.S.C. 7401, 7412, 7413, 7414, 7416, 7601 and 7602.	
	40 CFR 61—Subpart A—General Provisions.	
	40 CFR 61.1—Sec. 61.1 Lists of pollutants and applicability of part 61.	Ethylene oxide is a substance for which a Federal Register notice has been published that included consideration of the serious health effects, including cancer, from ambient air exposure to the substance.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 63—PART 63—NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS FOR SOURCE CATEGORIES. Promulgated: 57 FR 61992, 12/29/92. U.S. Code: 42 U.S.C. 7401 et seq.	
	40 CFR 63—Subpart DD—National Emission Standards for Hazardous Air Pollutants from Off-Site Waste and Recovery Operations. Promulgated: 61 FR 34158, 07/01/96.	Ethylene oxide is listed as a hazardous air pollutant (HAP).
	40 CFR 63—Subpart JJ—National Emission Standards for Wood Furniture Manufacturing Operations. Promulgated: 60 FR 62936, 12/07/95.	Ethylene oxide is listed as a volatile HAP (VHAP), a pollutant excluded from use in cleaning and washoff solvents, and a VHAP of potential concern ("nonthreshold" and "high-concern" pollutant).
	40 CFR 63—Subpart D—Regulations Governing Compliance Extensions for Early Reductions of Hazardous Air Pollutants. Promulgated: 57 FR 61992, 12/29/92, as amended at 58 FR 62543, 11/29/93; 59 FR 53110, 10/21/94.	The provisions of this subpart apply to an owner or operator of an existing source who wishes to obtain a compliance extension from a standard issued under section 112(d) of the CAA. Listed as a high-risk pollutant, ethylene oxide has a chemical weighting factor of 10.
	40 CFR 63—Subpart F—National Emission Standards for Organic Hazardous Air Pollutants From the Synthetic Organic Chemical Manufacturing Industry. Promulgated: 59 FR 19454, 04/22/94.	Ethylene oxide is listed as a synthetic organic chemical manufacturing industry chemical, an organic HAP, and an organic HAP subject to cooling tower monitoring requirements in section 63.104.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 63—Subpart G—National Emission Standards for Organic Hazardous Air Pollutants From the Synthetic Organic Chemical Manufacturing Industry for Process Vents, Storage Vessels, Transfer Operations, and Wastewater. Promulgated: 59 FR 19468, 04/22/94.	Ethylene oxide is subject to the wastewater provisions for process units at new and existing sources, with a corresponding fraction removed (Fr) value of 0.98. The fraction measured (Fm) and fraction emitted (Fe) are 1.00 and 0.50, respectively, in wastewater streams. Ethylene oxide is also a compound used for compliance demonstrations for enhanced biological treatment processes.
	40 CFR 63—Subpart O—Ethylene Oxide Emissions Standards for Sterilization Facilities. Promulgated: 59 FR 62589, 12/06/94. [Effective Date Note: At 62 FR 64738, 12/09/97, this subpart is suspended from Dec. 4, 1997, until Dec. 6, 1998.]	All sterilization sources using 1 ton per year in sterilization or fumigation operations are subject to the emissions standards in section 63.362, except as specified in paragraphs (b)-(e) of this section. Standards for ethylene oxide commercial sterilizers and fumigators are summarized in Table 1. This subpart does not apply to ethylene oxide sterilization operations at stationary sources such as hospitals, doctors' offices, clinics, or other facilities whose primary purpose is to provide medical services to humans or animals.
	40 CFR 63—Subpart U—National Emission Standards for Hazardous Air Pollutant Emissions: Group I Polymers and Resins. Promulgated: 62 FR 46925, 09/05/96.	Ethylene oxide is listed as a known organic HAP from elastomer products.
	40 CFR 68—PART 68—CHEMICAL ACCIDENT PREVENTION PROVISIONS. Promulgated: 59 FR 4493, 01/31/94. U.S. Code: 42 U.S.C. 7412(r), 7601(a)(1), and 7661-7661f.	
	40 CFR 68—Subpart F—Regulated Substances for Accidental Release Prevention.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 68.130—Sec. 68.130 List of substances.	Ethylene oxide is a regulated toxic substance. Its threshold quantity for accidental release prevention is 10,000 lb. Its toxic endpoint (for analyses of offsite consequences, toxics) is 0.09 mg/L.
	40 CFR 180—PART 180—TOLERANCES AND EXEMPTION FROM TOLERANCES FOR PESTICIDE CHEMICALS IN FOOD. Promulgated: 41 FR 4537, 01/30/76.	Ethylene oxide is listed as a pesticide chemical.
	40 CFR 180—Subpart C—Specific Tolerances.	
	40 CFR 180.151—Sec. 180.151 Ethylene oxide; tolerances for residues.	A tolerance of 50 ppm is established for residues of the antimicrobial agent and insecticide ethylene oxide, when used as a postharvest fumigant in or on the following raw agricultural commodities: Black walnut meats, copra, whole spices.
	40 CFR 180—Subpart D—Exemptions from Tolerances.	
	40 CFR 180.1001—Sec. 180.1001 Exemptions from the requirement of a tolerance.	Residues of ethylene oxide are exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest.
	40 CFR 185—PART 185—TOLERANCES FOR PESTICIDES IN FOOD. Promulgated: 40 FR 14156, 03/28/75. Redesignated at 41 FR 26568, 06/28/76, and 53 FR 24667, 06/29/88. U.S. Code: 21 U.S.C. 346a and 348.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 185—Subpart B—Food Additives Permitted in Food for Human Consumption.	
	40 CFR 185.2850—Sec. 185.2850 Ethylene oxide.	Ethylene oxide may be safely used as a fumigant for the control of microorganisms and insect infestation in ground spices and other processed natural seasoning materials, except mixtures to which salt has been added, provided that either alone or admixed with carbon dioxide or dichlorodifluoromethane, it shall be used in amounts not to exceed that required to accomplish the intended technical effects, and residues of ethylene oxide in ground spices from both postharvest application to the raw agricultural commodity whole spices and application to the ground spices do not exceed the established tolerance of 50 ppm in whole spices.
	40 CFR 192—PART 192—HEALTH AND ENVIRONMENTAL PROTECTION STANDARDS FOR URANIUM AND THORIUM MILL TAILINGS. Promulgated: 48 FR 602, 01/05/83. U.S. Code: 42 U.S.C. 2022, as added by the Uranium Mill Tailings Radiation Control Act of 1978, as amended.	Ethylene oxide is listed as a constituent of this part.
	40 CFR 261—PART 261—IDENTIFICATION AND LISTING OF HAZARDOUS WASTE. Promulgated: 45 FR 33119, 05/19/80. U.S. Code: 42 U.S.C. 6905, 6912(a), 6921, 6922, 6924(y), and 6938.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 261—Subpart D—Lists of Hazardous Wastes.	Ethylene oxide is listed as a toxic substance and is subject to the small quantity generator exclusion defined in section 261.5 (a) and (g). It is also listed as a hazardous waste; the hazardous waste number is U115.
	40 CFR 266—PART 266—STANDARDS FOR THE MANAGEMENT OF SPECIFIC HAZARDOUS WASTES AND SPECIFIC TYPES OF HAZARDOUS WASTE MANAGEMENT FACILITIES. Promulgated: 50 FR 666, 01/04/85. U.S. Code: 42 U.S.C 1006, 2002(a), 3004, 3014, 6905, 6906, 6912, 6922, 6923, 6924, 6925, 6934, and 6937, effective 07/11/96.	
	40 CFR 266—Subpart M—Military Munitions. Promulgated: 62 FR 6654, 02/12/97.	The regulations in this subpart identify when military munitions become a solid waste, and, if these wastes are also hazardous under this subpart or part, the management standards that apply to these wastes. The risk specific dose of ethylene oxide is 0.1 $\mu g/m^3$. The concentration limit for residues of ethylene oxide is 3×10^{-4} mg/kg.
	40 CFR 261.11, 261.33. Promulgated 5/19/80. RCRA 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1,000 kg to handling and report/recordkeeping requirements. Also designates ethylene oxide as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements.	Based on toxic effects other than acute. The EPA Carcinogen Assessment Group has included this chemical on its list of potential carcinogens. As a result of this listing, ethylene oxide is regulated under the hazardous waste disposal rule of RCRA.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
E P A	40 CFR 302—PART 302—DESIGNATION, REPORTABLE QUANTITIES, AND NOTIFICATION. Promulgated: 50 FR 13474, 04/04/85. U.S. Code: 42 U.S.C. 9602, 9603, and 9604; 33 U.S.C. 1321 and 1361.	
	40 CFR 302.4—Sec. 302.4 Designation of hazardous substances.	The statutory final reportable quantity (RQ) for ethylene oxide is 10 lb (4.54 kg).
	40 CFR 355—PART 355—EMERGENCY PLANNING AND NOTIFICATION. Promulgated: 52 FR 13395, 04/22/87. U.S. Code: 42 U.S.C. 11002, 11004, and 11048.	Ethylene oxide is listed as an extremely hazardous substance, and its threshold planning quantity is 1,000 lb.
	40 CFR 372—PART 372—TOXIC CHEMICAL RELEASE REPORTING: COMMUNITY RIGHT-TO-KNOW. Promulgated: 53 FR 4525, 02/16/88. U.S. Code: 42 U.S.C. 11023 and 11048.	This part sets forth requirements for the submission of information relating to the release of toxic chemicals under section 313 of Title III of SARA of 1986, which is intended to inform the general public and the communities surrounding covered facilities about releases of toxic chemicals, to assist research, to aid in the development of regulations, guidelines, and standards, and for other purposes.
	40 CFR 372—Subpart D—Specific Toxic Chemical Listings.	
	40 CFR 372.65—Sec. 372.65 Chemicals and chemical categories to which this part applies.	The effective date for reporting for ethylene oxide was January 1, 1987.
	40 CFR 721—PART 721—SIGNIFICANT NEW USES OF CHEMICAL SUBSTANCES. Promulgated: . U.S. Code: 15 U.S.C. 2604, 2607, and 2625(c).	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
EPA	40 CFR 721—Subpart E—Significant New Uses for Specific Chemical Substances. [Sections were promulgated in 57 FR in 1992.]	This subpart lists several ethylene oxide adducts and a chemical substance identified generically as a polymer of disodium maleate, allyl ether, and ethylene oxide, which are subject to reporting for significant new uses. Specific requirements, recordkeeping requirements, and limitations or revocation of certain notification requirements are also given.
	40 CFR 721.3680—Sec. 721.3680 Ethylene oxide adduct of fatty acid ester with pentaerythritol. Promulgated: 57 FR 46466, Oct. 8, 1992, as amended at 58 FR 34204, June 23, 1993]	The chemical substance is subject to reporting under this section for the significant new uses of releases to water. Specific requirements, recordkeeping requirements, and limitations
FDA	21 CFR 172—PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION. Promulgated: 42 FR 14491, 03/15/77. U.S. Code: 21 U.S.C. 321, 341, 342, 348, 371, and 379e.	
	21 CFR 172—Subpart H—Other Specific Usage Additives.	
	21 CFR 172.770—Sec. 172.770 Ethylene oxide polymer.	The polymer of ethylene oxide may be safely used as a foam stabilizer in fermented malt beverages provided that it has a minimum viscosity of 1,500 centipoises in a 1% aqueous solution at 25 °C.
	21 CFR 172—Subpart I—Multipurpose Additives.	
	21 CFR 172.808—Sec. 172.808 Copolymer condensates of ethylene oxide and propylene oxide. Promulgated: 42 FR 14491, 03/15/77, as amended at 46 FR 57476, 11/24/81.	Copolymer condensates of ethylene oxide may be safely used in food provided that certain prescribed conditions listed in this section are met.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
F D A	21 CFR 172.820—Sec. 172.820 Polyethylene glycol (mean molecular weight 200-9,500).	Polyethylene glycol may be safely used in food provided that the additive is an addition polymer of ethylene oxide and water with a mean molecular weight of 200 to 9,500.
	21 CFR 175—PART 175—INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS. Promulgated: 42 FR 14534, 03/15/77. U.S. Code: 21 U.S.C. 321, 342, 348, 379e.	This part gives substances containing ethylene oxide permitted for use in adhesives
	21 CFR 176—PART 176—INDIRECT FOOD ADDITIVES: PAPER AND PAPERBOARD COMPONENTS. Promulgated: 42 FR 14554, 03/15/77. U.S. Code: 21 U.S.C. 321, 342, 346, 348, 379e.	This part gives substances containing ethylene oxide that may be safely used as components of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food.
	21 CFR 176.210—Sec. 176.210 Defoaming agents used in the manufacture of paper and paperboard.	Substances permitted to be used in the formulation of defoaming agents include fatty triglycerides, and marine oils, and the fatty acids and alcohols reacted with ethylene oxide, with or without dehydration, to form esters and ethers.
	21 CFR 178—PART 178—INDIRECT FOOD ADDITIVES: ADJUVANTS, PRODUCTION AIDS, AND SANITIZERS. Promulgated: 42 FR 14609, 03/15/77. U.S. Code: 21 U.S.C. 321, 342, 348, 379e.	This part concerns ethylene oxide use with other substances as a sanitizing solution, antistatic and/or antifogging agent in food-packaging materials, food contact surface lubricant, and industrial starch modifier.
	21 CFR 201—PART 201—LABELING. Promulgated: 40 FR 13998, 03/27/75. U.S. Code: 21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg-360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
F D A	21 CFR 201—Subpart A—General Labeling Provisions.	
	21 CFR 201.1—Sec. 201.1 Drugs; name and place of business of manufacture, packer, or distributor.	FDA finds that it is the common practice in the drug industry to contract out the performance of certain manufacturing operations, which include ethylene oxide sterilization.
	21 CFR 872—PART 872—DENTAL DEVICES. Promulgated: 52 FR 30097, 08/12/87. U.S. Code: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.	
	21 CFR 872—Subpart D—Prosthetic Devices.	
	21 CFR 872.3410—Sec. 872.3410 Ethylene oxide homopolymer and/or carboxymethyl cellulose sodium denture adhesive. Promulgated: 52 FR 30097, 08/12/87, as amended at 59 FR 63008, 12/07/94.	An ethylene oxide homopolymer and/or carboxymethyl cellulose sodium denture adhesive is a device intended to be applied to the base of a denture before the denture is inserted in a patient's mouth to improve denture retention and comfort.
	21 CFR 872.3450—Sec. 872.3450 Ethylene oxide homopolymer and/or karaya denture adhesive. Promulgated: 52 FR 30097, 08/12/87, as amended at 59 FR 63008, 12/07/94.	An ethylene oxide homopolymer and/or karaya denture adhesive is a device intended to be applied to the base of a denture before the denture is inserted in a patient's mouth to improve denture retention and comfort.
	21 CFR 880—PART 880—GENERAL HOSPITAL AND PERSONAL USE DEVICES. Promulgated: 45 FR 69682-69737, 10/21/80. U.S. Code: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.	This part sets forth the classification of general hospital and personal use devices intended for human use that are in commercial distribution.
	21 CFR 880—Subpart G—General Hospital and Personal Use Miscellaneous Devices.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
FDA	21 CFR 880.6100—Sec. 880.6100 Ethylene oxide gas aerator cabinet.	An ethylene oxide gas aerator cabinet is a device that is intended for use by a health care provider and consists of a cabinet with a ventilation system designed to circulate and exchange the air in the cabinet to shorten the time required to remove residual ethylene oxide from wrapped medical devices that have undergone ethylene oxide sterilization. (Class II—performance standards)
	21 CFR 880.6860—Sec. 880.6860 Ethylene oxide gas sterilizer.	An ethylene gas sterilizer is a nonportable device intended for use by a health care provider that uses ethylene oxide to sterilize medical products. (Class II—performance standards)
NIOSH	8/77. Special Occupational Hazard Review with Control Recommendations for the Use of Ethylene Oxide as a Sterilant in Medical Facilities. NIOSH Publication 77-200. NTIS No. PB 274795.	Summary of current NIOSH recommendation: exposure limits—Ca, 0.1 ppm (0.18 mg/m^3) 8-hr TWA, 5 ppm (9 mg/m^3) ceiling concentration (10-minute).
	5/81. Recommended that ethylene oxide be treated as a potential human carcinogen, occupational exposure should be decreased, and OSHA should reexamine PEL.	Recommended 5-ppm (9 mg/m^3) ceiling (10 min/day).
	5/22/81. Current Intelligence bulletin #35—Ethylene Oxide (EtO): Evidence of Carcinogenicity.	
	4/2/82. Comments Regarding the OSHA Advanced Notice of Proposed Rulemaking—Occupational Exposure to Ethylene Oxide.	
	6/22/83. Comments on OSHA's Proposed Rule on Occupational Exposure to Ethylene Oxide.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
NIOSH	7/20/83. Testimony on OSHA's Proposed Rule on Occupational Exposure to Ethylene Oxide. 7/18/84. Comments to OSHA on the Evaluation of the OMB Comments on OSHA's Draft STEL for Ethylene Oxide. 3/19/85. Comments to OSHA on Short-Term Exposures to Ethylene Oxide. 4/30/85. Comments to OSHA on Proposed Rule: Occupational Exposure to Ethylene Oxide; Labeling Requirements. 9/26/85. Comments to OSHA on a Short-Term Exposure Limit for Ethylene Oxide. 2/22/88. Comments on OSHA's Proposed Rule on Occupational Exposure to Ethylene Oxide. 7/13/89. Current Intelligence Bulletin #52—Ethylene Oxide Sterilizers in Health Care Facilities; Engineering Controls and Work Practices.	Blood monitoring and medical counseling recommended.
OSHA	29 CFR 1910—PART 1910—OCCUPATIONAL SAFETY AND HEALTH STANDARDS. Promulgated: 39 FR 23502, 06/27/74. U.S. Code: 29 U.S.C. 653, 655, and 657. 29 CFR 1910—Subpart B—Adoption and Extension of Established Federal Standards. U.S. Code: 29 U.S.C. 653, 655, 657; 41 U.S.C. 35 et seq.; 41 U.S.C. 351 et seq.; 40 U.S.C. 333; 33 U.S.C. 941; and 20 U.S.C. 951 et seq.	

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
OSHA	29 CFR 1910.19—Sec. 1910.19 Special provisions for air contaminants.	This section states that section 1910.1047 shall apply to the exposure of every employee to ethylene oxide in every employment and place of employment covered by construction work, shipyard employment, and longshoring and marine terminals, in lieu of any different standard on exposure to ethylene oxide which would otherwise be applicable by virtue of those sections.
	29 CFR 1910—Subpart H—Hazardous Materials.	Ethylene oxide is listed as a toxic and reactive highly hazardous chemical which presents a potential for a catastrophic event at or above the threshold quantity of 5000 lb.
	29 CFR 1910—Subpart Z—Toxic and Hazardous Substances.	
	29 CFR 1910.1047—Sec. 1910.1047 Ethylene Oxide. Promulgated: 49 FR 25796, 06/22/84 through 63 FR 1292, 01/08/98. Establishes PEL of 1 ppm as an 8-hr TWA and an STEL of 5 ppm sampled over 15 min.	This section applies to all occupational exposures to ethylene oxide (EtO), but does not apply to the processing, use, or handling of products containing EtO where objective data are reasonably relied upon that demonstrate that the product is not capable of releasing EtO in airborne concentrations at or above the action level, and may not reasonably be foreseen to release EtO in excess of the excursion limit.
	29 CFR 1910.1200—Sec. 1910.1200 Hazard Communication. Promulgated: 11/25/83. U.S. Code: also includes 5 U.S.C. 553.	Requires chemical manufacturers and importers and all employers to assess chemical hazards and to provide information to employees. Hazard Communication Program to include labels, material safety data sheets, and worker training.

REGULATIONS[a]

	Regulatory Action	Effect of Regulation/Other Comments
O S H A	29 CFR 1910.1450—Sec. 1910.1450 Occupational exposure to hazardous chemicals in laboratories. Promulgated: 55 FR 3327, 01/31/90 through 55 FR 12111, 03/30/90. OSH Act: Final rule.	As a select carcinogen (IARC Group 2A), ethylene oxide is included as a chemical hazard in laboratories. Employers are required to provide employee information and training and a Chemical Hygiene Plan.
	29 CFR 1916—PART 1926—SAFETY AND HEALTH REGULATIONS FOR CONSTRUCTION. Promulgated: 44 FR 8577, 02/09/79; 44 FR 20940, 04/06/79.	
	29 CFR 1926—Subpart Z—Toxic and Hazardous Substances.	
	29 CFR 1926.1147—Sec. 1916.1147 Ethylene oxide. Promulgated: 61 FR 31434, 06/20/96.	The requirements applicable to construction work under this section are identical to those set forth in section 1910.1047.

[a]The regulations in this table have been updated through the 1998 issues of Code of Federal Regulations titles 21, 29, and 40.

3.0 HUMAN STUDIES

3.1 Studies Evaluated by IARC (1994)

The IARC Working Group for consideration of ethylene oxide concluded that there is limited evidence in humans for the carcinogenicity of ethylene oxide (IARC, 1994). The majority of reviewed studies evaluated the risk from occupational ethylene oxide exposure. These studies provided some evidence that the risk of lymphatic and hematopoietic cancer was increased among workers exposed to ethylene oxide.

Lymphatic and hematopoietic cancer were the most frequently reported cancers associated with exposure to ethylene oxide in epidemiological studies (IARC, 1994). Study populations were either workers using ethylene oxide as a sterilant or chemical workers involved in production of the compound or its derivatives. The study with the largest number of sterilization personnel included only workers in the United States (Steenland et al., 1991). Three European studies of sterilization workers found non-significant excesses of lymphatic and hematopoietic cancer.

An increase in these cancers was also shown in a study of chemical workers at two production plants in the United States, but the increase was only seen in a small subgroup with occasional exposure to low levels of ethylene oxide (Benson and Teta, 1993; cited by IARC, 1994). In six other studies of chemical workers involving fewer deaths, four found increases in

lymphatic and hematopoietic cancer (two of which showed statistical significance) and two found no excess deaths compared to the control group (IARC, 1994).

A study of U.S. sterilization workers (Steenland et al., 1991) reported mortality in a cohort of over 18,000 workers from 14 industrial plants that regularly used ethylene oxide to sterilize medical supplies or spices. Vital status through the end of 1987 was determined. The average length of exposure was 4.9 years and the average length of follow-up was 16.1 years. Vital status was determined for 95.5% of the cohort. Overall, there was no association with hematopoietic cancers as a group (Standardized Mortality Ratio [SMR] = 1.06; 95% CI = 0.75-1.47). An elevated, but imprecise SMR was found for lymphosarcoma-reticulosarcoma (SMR = 1.52; 95% CI = 0.65-3.00). The SMR for leukemia was not elevated. An increased risk of death from kidney cancer (SMR = 1.80; 95% CI = 0.96-3.08) was found. Potential exposure to ethylene oxide was determined from job title and department at each plant. Analysis by duration of exposure to ethylene oxide did not show any consistent pattern of increased risk of death (including hematopoietic cancers). The analysis by length of time since first exposure to ethylene oxide, however, did show a trend toward an increased risk of death from several hematopoietic cancers including leukemia, Hodgkin's disease and non-Hodgkin's lymphoma. However, the short follow-up period and the lack of precise estimates for some exposure categories limit the interpretation.

An expanded analysis of this cohort study included the use of an industrial hygiene-based regression model to estimate individual cumulative exposure to ethylene oxide (Stayner et al., 1993). The mean of the individual time-weighted exposure values from the facilities for 1976 through 1985 was calculated for exposure categories based on the aggregation of jobs with similar potential for exposure. A regression model was then derived using a number of predictors such as exposure category, sterilizer volume, product age, and engineering controls. This model was used to estimate individual cumulative ethylene oxide exposure for workers in each facility. Life-table methods and the Cox proportional hazards model were used to evaluate cancer mortality. An elevated SMR was found for all hematopoietic neoplasms in the highest cumulative exposure category, but a dose-response gradient was not apparent. Non-Hodgkin's lymphoma also showed an excess risk in the highest exposure category. The Cox regression analysis showed a significant relationship between cumulative exposure and mortality from the combined group of "lymphoid" cancers (lymphocytic leukemia and Non-Hodgkin's lymphoma). Weaker dose-response effects were found for non-Hodgkin's lymphoma and all hematopoietic cancers. The positive association appeared to be limited to male workers. Other exposure measures (duration, average, and maximum exposure) were not as strongly associated as the cumulative exposure measure. A lagged model estimated a rate ratio of about 1.2 for the lymphatic and hematopoietic neoplasms at the current OSHA standard level for ethylene oxide. This study was large and included a relatively sophisticated exposure estimation model. Nonetheless, a definitive conclusion is limited by some analyses based on a small number of deaths and the apparent specificity by gender. However, the results provide additional support for an association between ethylene oxide and hematopoietic cancers.

Shore et al. (1993) reported the findings of a meta-analysis of 10 cohort mortality studies published from 1979-1993 that included workers potentially exposed to ethylene oxide. A total of 29,800 workers (2,540 deaths) were included. The studies were reviewed and their quality assessed, although quality scores were not incorporated in the meta-analysis. The summary SMR for leukemia was 1.06 (95% CI = 0.73-1.48). Overall, there were no significant trends

based on duration or intensity of exposure. The summary SMR for non-Hodgkin's lymphoma was elevated (SMR = 1.35; 95% CI = 0.93-1.90), but there did not appear to be any trend in risk with frequency or intensity, duration of exposure, or latency. The summary SMR was 1.28 (95% CI = 0.98-1.65) for stomach cancer, but after removal of the one study responsible for the significant test of heterogeneity, the SMR decreased to 1.11. There were no significant gradients in risk accounting for intensity, duration of exposure, or latency. However, studies that evaluated brain cancer (with a total of 19 deaths and SMRs from 0.0 to 12.7) showed a significant heterogeneity. The summary 95% confidence interval, accounting for the heterogeneity, was relatively wide (0.39-2.04). There was no suggestion of a trend in exposure intensity or duration. Pancreatic cancer was not associated with an elevated summary SMR (SMR=0.98; 95% CI = 0.69-1.36).

The authors concluded that there did not appear to be strong evidence for an increased risk of death from selected cancers, although they recommended continued investigation of leukemia and non-Hodgkin's lymphoma. The meta-analysis was limited by the fact that even with the pooling of studies, many of the risk estimates for specific cancers were imprecise and the follow-up period inadequate. In addition, individual exposure estimates were not available in most studies, and confounding exposures could not be ruled out in some studies.

3.2 Studies Post-IARC (1994)

A study reported that the incidence of breast cancer was elevated in a cohort of workers at a plant that used ethylene oxide as a sterilant (Norman et al., 1995). An earlier study found an increased incidence of sister chromatid exchange (SCE) in workers at this plant compared to community controls (Stolley et al., 1984; cited by Norman et al., 1995 and IARC, 1994). The cohort consisted of 1,132 persons employed between 1974 and 1980, the period of potential ethylene oxide exposure at the plant. Cancer incidence was determined through 1987. The 8-h time TWA exposure concentrations for sterilizer operators was 50-200 ppm, based on three 2-h samples obtained in March 1980; samples taken subsequent to corrective action showed exposures ranging from 5-20 ppm.

Cancer incidence was ascertained from a variety of sources, including a health exam or interview. A total of 79% of the workers participated in either one exam or interview. The number of observed cancers was compared with the expected number based on incidence rates reported by the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. Twelve of the 28 cancers observed were breast cancers. The standardized morbidity ratio for breast cancer among regular female employees ranged from 2.55 (95% CI = 1.31-4.98; 8 observed, 3.14 expected; p = 0.02) to 1.70 (95% CI = 0.89-3.23; 9 observed, 5.28 expected; p = 0.09) depending on calendar year of follow-up, assumptions about completeness of follow-up, and the reference rates used. None of the breast cancer cases were discovered from screening observations at the worksite, and there was no unusual distribution of risk factors for breast cancer (e.g., nulliparity, family history of breast cancer) among the cases. Incorporating a 2-yr latency period into the analysis produced similar results. No statistically significant excess of breast cancer was found for temporary employees, and there was no increase in cancer incidence at other sites associated with ethylene oxide in previous studies. Because of the size of the study, the statistical power to detect significant increases at these sites was very low. The latency, length of follow-up, and absence of detailed exposure data are additional study limitations.

An update of the cohort study of Swedish sterilant workers reported by Hagmar et al. in 1991 did not find a significant positive association between ethylene oxide exposure and cancer risk (Hagmar et al., 1995). The cohort (n = 2,170) comprised workers employed at least one year before 1986 in two plants that produced disposable medical equipment sterilized with ethylene oxide. Cancer incidence was assessed for 1972 to 1990 and 1976 to 1990 using a national registry. No worker was lost to follow-up. Only 13% of the cohort had direct exposure to ethylene oxide. Peak exposure concentrations when unloading autoclaves were estimated to be 500-1,000 ppm until 1973. The median estimated cumulative exposure for the cohort was 0.13 ppm-yr. Increased Standardized Incidence Ratios (SIRs) for lymphohematopoietic tumors (SIR = 1.78; 95% CI = 0.65-3.88; 6 observed, 3.37 expected) and leukemia (SIR = 2.44; 95% CI = 0.3-8.81; 2 observed, 0.82 expected) were found but were not statistically significant. Among those workers with exposure greater than the median and with a minimum induction period of 10 years, the SIR for leukemia was increased, but imprecise (SIR = .14; 95% CI = 0.87- 25.8). The study, based on cancer incidence, included individual exposure estimates and complete follow-up. However, the cohort was not large, many workers did not have a high level of exposure, and the follow-up time was relatively short.

Workers in plants that produced ethylene oxide by the ethylene chlorohydrin process were followed-up for mortality and associated cancer incidence (Olsen et al., 1997). The cohort consisted of male workers (n = 1,361) from 1940-1992 in process areas within several U.S. plants. The production work areas were used for synthesis of ethylene chlorohydrin and ethylene oxide, but analyses of work area or personal samples were not reported. In later years, all of these plants were converted for production of propylene chlorohydrin and propylene oxide, and many cohort members were also exposed to these substances. The overall SMR for lymphopoietic and haematopoietic cancer, with a 25-yr induction latency period, was 1.44 (95% CI = 0.52-3.12). The Mantel-Haenszel relative risk increased to 3.56 (95% CI = 1.23-10.29) with 10-20 years employment, but decreased for more than 20 years duration. The analysis of workers only in the ethylene chlorohydrin production process showed elevated risks of lymphopoietic and haematopoietic cancer (SMR = 1.49; 95% CI = 0.60-3.07) overall, and with a 25-yr latency induction period (SMR = 1.94; 95% CI = 0.71-4.23). There were no lymphopoietic and hematopoietic cancer deaths observed among both the propylene and ethylene chlorohydrin production process workers. The overall mortality and mortality associated with other cancers was not significantly increased. The study was limited by the length of the follow-up period (mean of 24.5 years) and the imprecision of the SMR estimates.

The apparent discrepancy between the positive studies identified by IARC (1994) and these later studies may be attributed to the relatively small size of the cohorts and short time of follow-up, as well as limitations of the earlier studies.

Table 3-1. Post-IARC (1994) Ethylene Oxide Human Studies

Design	Population Group	Exposure	Effects	Comments	References
Cohort	1,132 Workers employed from 1974-1980 observed cancers compared to expected cancers based on age- and sex-specific cancer rates in the Surveillance, Epidemiology, End Results (SEER) database	Ethylene oxide only major process chemical used from mid-1970s to 1980; documentation of ethylene oxide leaks on several occasions; elevated SCE in workers compared to controls from community The 8-h TWA exposure concentrations for sterilizer operators was 50-200 ppm, based on three 2-h samples obtained in March 1980. Samples taken subsequent to corrective action showed 5-20 ppm.	Calculated breast cancer standardized morbidity ratios (SMRs) with 95% CI; no. observed/no. expected; p value 2.55 (1.31-4.98; 8/3.14; p=0.02) for regular female employees and follow-up to date of last interview, to death, or to first diagnosis 1.70 (0.89-3.23; 9/5.28; p=0.09) for regular female employees through 1987 with later SEER rates Excess diminished over time. No excess at any time for temporary female employees.	SMRs varied with calendar yr of follow-up, assumptions about completeness of follow-up, and reference rates.	Norman et al. (1995)
Cohort update	2,170 Workers employed at least 1 yr in two plants that produced equipment sterilized with ethylene oxide	Peak exposure concentrations were estimated to be 500-1000 ppm, up to 1973; individual cumulative exposure (ppm-yr) estimated; median value 0.13 ppm-yr; median calendar year start of exposure was 1978; median employment duration from start of exposure was 5.6 yr until 1985	Calculated cause-specific standardized incidence ratios (SIRs) with 95% CI; no. observed/no. expected <u>Lymphohematopoietic tumors:</u> 1.78 (0.65-3.88; 6/3.37) for entire cohort and no latency period <u>Leukemia:</u> 2.44 (0.30-8.81; 2/0.82) for entire cohort and no latency period 7.14 (0.87-25.8; 2/0.28) for cumulative exposure to more than 0.13 ppm-yr and 10-yr latency No SIRs were significant.	Cohort was small, many workers did not have high level of exposure, follow-up time was relatively short.	Hagmar et al. (1995)

Table 3-1. Post-IARC (1994) Ethylene Oxide Human Studies (Continued)

Design	Population Group	Exposure	Effects	Comments	Reference
Cohort	1,361 Workers from 1940-1992 in U.S. plants that produced ethylene oxide by the ethylene chlorohydrin process	Work areas used for synthesis of ethylene chlorohydrin and ethylene oxide; analyses of work area or personal samples n.p.; some workers also later exposed to propylene chlorohydrin and propylene oxide	Calculated SMRs and Mantel-Haenszel relative risks (RRs) with 95% CI Lymphopoietic and haematopoietic cancer: 1.44 (0.52-3.12) SMR overall with 25-yr latency period 3.56 (1.23-10.29) RR with 10-20 yr employment 1.72 (0.24-12.21) RR with > 20 yr employment 1.49 (0.6-3.07) SMR overall for workers only in the ethylene chlorohydrin production areas 1.94 (0.7-4.23) SMR for workers only in the ethylene chlorohydrin production areas and a 25-yr induction no lymphopoietic and haematopoietic cancer deaths among propylene chlorohyrin production workers	Limited by length of follow-up (mean = 24.5 yr) and imprecise estimates	Olsen et al. (1997)

Abbreviations: CI = confidence interval; n.p. = not provided; SCE = sister chromatid exchange

4.0 EXPERIMENTAL CARCINOGENICITY

4.1 Studies Reviewed by IARC (1994)

4.1.1 Mice

In mice, local sarcomas were induced by subcutaneous injection of ethylene oxide (Dunkelberg, 1981; cited by IARC, 1994). Female NMRI mice, aged 6-8 wk, were injected with ethylene oxide (99.7% pure) in tricaprylin at doses of 0.1, 0.3, or 1.0 mg/mouse, once/wk for 95 wk. A significant dose-dependent increase in tumor incidence occurred at the injection site (4/200 vehicle only, 5/100 low-dose, 8/100 mid-dose, 11/100 high-dose), but not at other sites. Survival was reduced in the high-dose group.

When administered by inhalation, ethylene oxide increased the incidences of tumors at several sites in male and female mice (NTP 326, 1987). Groups of male and female B6C3F1 mice, aged 8 wk, were exposed to 0, 50, or 100 ppm (0, 92, or 183 mg/m^3) ethylene oxide (>99% pure) for 6 h/day, 5 days/wk for up to 102 wk. The survival of treated groups was similar to that of the control groups. The combined incidences of lung tumors were increased in males (11/50 control, 19/50 low-dose, 26/50 high-dose) and females (2/49 control, 5/48 low-dose, 22/49 high-dose). Harderian gland papillary cystadenoma incidences were also significantly increased in males (1/43 control, 9/44 low-dose, 8/42 high-dose) and females (1/46 control, 6/46 low-dose, 8/47 high-dose). In females, the incidences of malignant lymphomas (9/49 control, 6/48 low-dose, 22/49 high-dose), uterine adenocarcinomas (0/49 control, 1/47 low-dose, 5/49 high-dose) and mammary gland carcinomas (1/49 control, 8/48 low-dose, 6/49 high-dose) were significantly increased.

No skin tumors were observed in mice treated by skin application (Van Duuren et al., 1965; cited by IARC, 1994). ICR/Ha Swiss female mice were painted with ethylene oxide (99.7% pure) in acetone (~100 mg of a 10% solution), three times/wk from age 8 wk until death (median survival time = 493 days).

4.1.2 Rats

Rats administered ethylene oxide by inhalation showed increased incidences of gliomas of the brain and mononuclear cell leukemia in both sexes, and males showed increased incidences of peritoneal mesotheliomas in the testicular region and subcutaneous fibromas (Snellings et al., 1984; Garman et al., 1986; both cited by IARC, 1994). Groups of male and female Fischer 344 rats, aged 8 wk, were exposed to ethylene oxide (>99.9% pure) at 10, 33, or 100 ppm (18, 59, or 180 mg/m^3) for 6 h/day, five days/wk for two yr. Survival was reduced in groups exposed to the mid- and high dose. Glioma incidences were greater in males (1/181 controls, 0/92 low-dose, 3/86 mid-dose, 6/87 high-dose) and females (0/187 controls, 1/94 low-dose, 2/90 mid-dose, 2/78 high dose). Mononuclear cell leukemia was also seen in males (5/48 control I, 8/49 control II 9/51 low-dose, 12/39 mid-dose, 9/30 high-dose) and females (5/60 control I, 6/56 control II, 11/54 low-dose, 14/48 mid-dose, 15/26 high-dose). In males, peritoneal mesothelioma (1/48 control I, 1/49 control II 2/51 low-dose, 4/39 mid-dose, 4/30 high-dose) and subcutaneous fibromas (1/48 control I, 2/49 control II, 9/51 low-dose, 1/39 mid-dose, 11/30 high-dose).

Mononuclear-cell leukemia, peritoneal mesothelioma, and glioma were also observed in another inhalation study with Fischer 344 rats (Lynch et al., 1984; cited by IARC, 1994). Male weanling rats were exposed to 0, 50, or 100 ppm (92 or 180 mg/m^3) ethylene oxide (99.7% pure),

7 h/day five days/wk for two yr. Mortality was greater in both treated groups compared to controls. The incidence of mononuclear-cell leukemia was significantly increased in the low-dose group (24/77 control, 38/79 low-dose), but excess mortality in the group exposed to 100 ppm prevented the evaluation of leukemia incidence at a high dose. Peritoneal mesothelioma incidence was significantly increased in the high-dose group (3/78 control, 9/79 low-dose, 21/79 high-dose). In addition, the incidence of glioma was significantly increased in rats exposed to the high dose (0/76 control, 2/77 low-dose, 5/79 high-dose).

When administered by gavage, ethylene oxide induced local tumors, mainly squamous-cell carcinomas of the forestomach, in female rats (Dunkelberg, 1982; cited by IARC, 1994). Groups of female Sprague-Dawley rats, aged ~100 days, were given ethylene oxide (99.7% pure) in vegetable oil at 7.5 or 30 mg/kg by gastric intubation twice/wk for 107 wk. Survival was lessened in rats given the high-dose, compared to control groups. Malignant tumors of the stomach were found in a total of 31/50 treated rats, while no tumors were identified in untreated or vehicle controls.

Based on the studies with mice and rats, IARC (1994) concluded that there is sufficient evidence for the carcinogenicity of ethylene oxide in experimental animals.

4.2 Studies Post-IARC (1994)

No post-IARC (1994) studies were identified.

5.0 GENOTOXICITY

Studies on the genotoxic effects of ethylene oxide published prior to 1994 have been reviewed by IARC (1994, pp. 122-136; see Appendix A). More recent studies are summarized below and in Table 5-1. Ethylene oxide has been reported to induce genotoxic damage in prokaryotic, lower eukaryotic, higher plant, and *in vitro* and *in vivo* mammalian systems, including exposed workers. The types of genetic damage induced by ethylene oxide in exposed animals and workers include biomarkers of exposure (e.g., hemoglobin adducts, DNA breaks, SCE) and biomarkers of effect (e.g., chomosomal aberrations, mutations). The former endpoints are indicative of the ability of ethylene oxide to interact with DNA in cells of exposed animals and humans, while the latter endpoints are indicative of the ability of ethylene oxide to induce heritable cellular DNA changes. In human studies, nucleated blood cells have been used most frequently to evaluate ethylene oxide-induced genotoxic damage. These cells are informative in regard to exposure, but not as a direct indicator of future adverse health outcomes. Such information can only be obtained from cells in the tissue(s) at risk for tumor formation. The fact that the level of damage in blood cells of ethylene oxide-exposed animals and humans declines and returns to control levels with increasing time between the cessation of exposure and sampling is consistent with the repair of ethylene oxide-induced DNA damage and/or the dilution of damaged cells due to cell turnover. However, the decline in genetic damage in nonproliferating blood cells does not preclude the potential for heritable tumor-initiating events from occurring in proliferating cells in other tissues during exposure to ethylene oxide.

5.1 Genotoxicity Studies Reviewed by IARC (1994)

In bacterial systems, ethylene oxide induced an increase in *his* gene mutations in *Salmonella typhimurium* strains TA100 and TA1535 (with and without S9 activation) and TA102 (with S9), but not in strains TA1537 and TA1538 (with and without S9) or TA98

(without S9). Similarly, an increase in forward mutations was observed in *Escherichia coli* strains KMBL 3835, WP2 uvr A, WP6 (pol A), and WU36-10-89, as well as *Bacillus subtilis* (strain not provided), all tested only in the absence of metabolic activation. It was listed as negative only for reverse mutations in *Streptomyces griseoflavus* tested in the absence of S9 activation.

In lower eukaryotes, ethylene oxide induced gene conversions and reverse mutations in *Saccharomyces cerevisiae*, forward mutations in *Schizosaccharo-myces pombe* and *Aspergillus nidulans*, and reverse mutations in *Neurospora crassa*. It was negative for genetic crossing over in *A. nidulans*. Somatic and sex-linked recessive mutations as well as heritable translocations were induced in *Drosophila melanogaster*.

In higher plants, ethylene oxide induced chlorophyll and waxy mutations and chomosome aberrations in *Hordeum* (barley) species, gene mutations in *Oryza sativa* (rice) and *Glycine max* (soy beans), and chromosome aberrations in *Trandescantia* species.

Calf thymus DNA exposed to ethylene oxide *in vitro* produces 7-(2-hydroxyethyl)guanine (7-HEG) as the main DNA adduct; smaller amounts of O6-(2-hydroxyethyl)guanine and N3-(2-hydroxyethyl)adenine were also identified. Using cultured mammalian cells, ethylene oxide induced an increase in SCE in human lymphocytes and fibroblasts, both tested in the absence of metabolic activation. Unscheduled DNA synthesis (UDS) was also induced in human lymphocytes without added S9. Gene mutations at the *hprt* locus were caused by ethylene oxide in Chinese hamster ovary (CHO) cells in the presence and absence of S9 activation, and in lung V79 cells tested in the absence of S9 activation. Similarly, tk gene mutations were induced in mouse lymphoma L5178Y cells without S9. Ethylene oxide induced chromosome aberrations in transformed human amniotic cells, both micronuclei and chromosome aberrations in Chinese hamster V79 cells, and cell transformation in mouse C3H10T1/2 and Syrian hamster embryo (SHE) SA7 cells.

IARC (1994) described numerous acute and subchronic inhalation studies conducted *in vivo* with ethylene oxide. DNA adducts (primarily 7-HEG) were found in liver and kidney of mice and the liver, brain, and lung of rats exposed to ethylene oxide. O6-(2-hydroxyethyl)guanine and N3-(2-hydroxyethyl)adenine were also identified in exposed rats. Ethylene oxide was mutagenic at the *hprt* locus in T-lymphocytes of B6C3F1 mice exposed by i.p. injection. Analysis of the *hprt* mutants indicated that ethylene oxide mutagenesis involves modification of guanine and adenine bases. Ethylene oxide induced DNA damage, as measured by alkaline elution, in mouse (strain not provided) spermatids and sperm (administered i.p.). It was found to bind covalently to mouse and rat DNA exposed via i.p. injection or inhalation. Ethylene oxide caused an increase in SCE in the lymphocytes of rats, rabbits, and cynomolgus monkeys, the bone marrow cells of mice and rats, and the spleens of rats. Dominant lethal mutations were induced in both mice and rats, and heritable translocations in mice using both inhalation and i.p. exposures. Chromosome aberrations were induced in the bone marrow of mice and rats exposed via inhalation, p.o. (rats only), or i.p. (mice only), the lymphocytes of cynomolgus monkeys, and the spermatocytes of mice. Similarly, ethylene oxide induced an increase in bone marrow micronuclei in mice and rats treated both i.v. and via inhalation. It was negative for specific locus mutations in mouse postspermatogonia and other stages, for aneuploidy in 10-day-old mouse fetuses, and for chromosome aberrations in rat lymphocytes.

Fourteen studies reported an increase in the frequency of SCE in the peripheral blood lymphocytes of exposed workers, while four studies reported equivocal or negative results. In

three separate papers, ethylene oxide was reported to be negative for DNA strand breaks, positive for DNA crosslinks, and weakly positive for unscheduled DNA synthesis in human lymphocytes. Differing results were obtained for micronuclei induction in several tissues of exposed workers. Three studies reported an increase in micronuclei in bone marrow, peripheral blood lymphocytes, and nasal cells, while four studies found no increase in lymphocytes, buccal cells, or nasal cells of exposed workers. Ethylene oxide induced an increase in chromosome aberrations in the blood lymphocytes of exposed workers in eight studies, a weak positive response in two studies, and a negative result in four.

5.2 Genotoxicity Studies Published Post-IARC (1994)

5.2.1 Prokaryotic Systems

An investigation of factors that may modify ethylene oxide mutagenicity in *S. typhimurium* was reported in a meeting abstract (Oesch and Hengstler, 1997). Factors investigated were human erythrocytes and theophylline, which were added to the preincubation mixture. Erythrocytes enhanced the mutagenic activity of ethylene oxide by two- to fourfold, while theophylline inhibited erythrocyte-induced enhancement. One experiment used erythrocytes from drinkers of black tea, and controls drank water. Erythrocytes from tea drinkers caused a significantly smaller increase in ethylene oxide mutagenicity compared to controls. The specific factor in erythrocytes that stimulated ethylene oxide mutagenicity was not identified.

5.2.2 Lower Eukaryotic Systems

de Serres and Brockman (1995) reported a reproducible increase in specific locus mutations at the adenine-3 region of *N. crassa*. The two-component heterokaryon H-12 was exposed in solution to five ethylene oxide concentrations ranging from 0.1% to 0.35% for 3 h. Ethylene oxide induced a high percentage of point mutations (97%) and a low percentage of multilocus deletions (3%).

Vogel and Nivard (1997) found an increase in the level of sex-linked-recessive-lethal (SLRL) mutations in repair-defective *D. melanogaster*. Wild-type males were exposed via inhalation to ethylene oxide at doses ranging from 31.3 to 500 ppm for 24 h followed by mating to Basc females competent (NER+) or deficient (NER-) in nucleotide excision repair. No increase in SLRL mutations were seen in post meiotic germ cells when matings were to NER+ females; however, a 17-fold increase in SLRL mutations was obtained with NER- females, indicating the ethylene oxide 2-hydroxyethyl adduct is repaired in the wild-type strains.

5.2.3 Mammalian Systems *In Vitro*

Because *in vitro* reaction of ethylene oxide gave rise to the 3-(2-hydroxyethyl)deoxyuridine (3-HE-dU) adduct, Bhanot et al. (1994) constructed a 55-nucleotide DNA template containing this adduct, and analyzed mutagenic bypass (i.e., DNA products synthesized from this template). The lesion could be bypassed only by DNA polymerases Pol I (Klenow fragment) or T7 Pol lacking a 3′-5′ exonuclease proofreading activity. Both dA and dT were incorporated opposite the dC-derived 3-HE-dU adduct, indicating that G:C to A:T or G:C to T:A mutagenesis results from the 3-HE-dU adduct.

A sensitive method of measuring ethylene oxide-DNA adducts using high performance liquid chromatography/mass spectrometry (HPLC/MS) was developed by Leclercq et al. (1997).

Calf thymus DNA or human blood was incubated with ethylene oxide at doses ranging from 0.1 to 100 mM (DNA) or 2.5 to 10 mM (blood) for 3 h at 37 °C. A clear dose-dependent increase in the level of 7HEG adducts was observed in both systems with lower concentrations observed in blood.

Incubation of human mononuclear cells with ethylene oxide (0.5-10 mM) resulted in a dose-dependent increase in DNA single strand breaks (Hengstler et al., 1994). In another study, Hengstler et al. (1997) compared ethylene oxide-induced DNA damage in human blood *in vitro*, using both the standard (isolated leukocytes) and a faster, more sensitive direct (whole blood) method of alkaline elution. Whole blood was exposed to 0.5 and 2.0 mM gaseous ethylene oxide (injected into sealed culture tubes) for one hour followed by either direct processing or isolation of leukocytes. A statistically significant increase in the direct method over the standard method was observed at the top dose tested.

Human diploid fibroblasts were used in an *in vitro* study of specific genetic changes caused by ethylene oxide (Lambert et al., 1994). Various *hprt* gene mutations, including chromosomal, gross structural alterations, and point mutations were examined after exposure of fibroblasts to ethylene oxide. The mutant frequency increased linearly with 2.5-10 mM ethylene oxide. The most significant mutation was large genomic deletions; 48% of mutant clones showed these deletions compared to 10% in the background. Point mutations were also induced by ethylene oxide.

DNA damage, including single and double strand breaks, was induced in human fibroblasts exposed to ethylene oxide for one hour in suspension or in monolayer (Nygren et al., 1994). The induction rates of DNA breaks depended on the analytical method and treatment conditions.

5.2.4 Mammalian Systems *In Vivo*

The frequency of *hprt* gene mutations was significantly increased in both thymus and spleen T-lymphocytes of ethylene oxide-exposed transgenic mice (Walker et al., 1997). Male B6C3F$_1$ Big Blue® lacI transgenic mice were exposed to 50, 100, or 200 ppm (6 h/day, 5 days/week) for four weeks and necropsied two weeks post-exposure for thymus and eight weeks for spleen.

Using the same mice, Sisk et al. (1997) reported an increase in lacI mutants in the lung but not in the spleen, bone marrow, or germ cells. The mutant frequency in the lung was significantly increased at 8 weeks post-exposure to 200 ppm ethylene oxide. Only DNA of spleens from the 200-ppm-exposed mice was sequenced. Single base substitution accounted for 85% of the mutants (76% transitions/24% transversions). The authors hypothesized that since ethylene oxide is known to induce deletion mutations in other systems, the lack of a response in lacI was likely due to the inability to recover large deletion mutants in the lambda-based shuttle vector.

Mutations were induced at the *hprt* locus of thymus and spleen T-cells in rats and mice exposed to ethylene oxide by inhalation (Walker et al., 1997 abstr.). Mutations were a combination of base substitutions, frameshifts, and small deletions. Transitions and transversions were observed at both GC and AT base pairs.

Vergnes and Pritts (1994) found a significant increase in micronuclei in bone marrow cells of rats and mice exposed to ethylene oxide for four weeks.

5.2.5 Human Studies

Workers in a Brazilian industry that used ethylene oxide as an intermediate showed signs of DNA damage (Ribeiro et al., 1994). Exposure to ethylene oxide was indicated by air analyses and measurement of increased levels of ethylene oxide-hemoglobin adducts (HOEtVal). Ambient air measurements made during a three month sampling period indicated that workers were exposed to 2-5 ppm TWA for an eight hour working day. Blood samples were taken from 75 workers and 22 controls (no exposure to ethylene oxide) matched for sex, age, and smoking habits. Exposed workers exhibited a significant increase in chromosomal aberrations and micronuclei (scored in binucleated lymphocytes), but no increase of micronuclei in buccal exfoliated cells.

In humans, a significant increase in DNA damage, as measured by alkaline elution, was found in peripheral mononuclear blood cells of ethylene oxide exposed sterilization workers in Germany (Oesch et al., 1995). A dose-dependent increase in DNA damage was detected in both smokers and nonsmokers exposed to <0.1-2.0 mg/m^3 (0.055-1.1 ppm). The majority of nonsmokers showed a more sensitive response than smokers at doses ranging from 0.5-2.0 mg/m^3 (0.28-1.1 ppm).

A study of ethylene oxide exposed disinfection workers at 15 German hospitals [25 workers (15 female, 10 male), ages 31-57 years] did not show a significantly elevated frequency of SCE in lymphocytes over historical controls (Popp et al., 1994). However, a significant decrease in DNA alkaline elution rates (indicative of DNA-protein crosslinks) was observed in exposed workers. Peak levels of ethylene oxide in air were 417 ppm during the first eight minutes after opening the sterilization units.

Tates et al. (1995) found no increase in lymphocyte *hprt* mutations, SCEs, or micronuclei in ethylene oxide-exposed workers at a chemical manufacturing plant in the Netherlands. Lymphocytes from 28 workers (7 acutely exposed to ethylene oxide, 7 workers employed for <5 years, 7 workers employed for >15 years, and 7 control workers) were analyzed. Blood samples from the acutely exposed workers were collected and analyzed 89-180 days post exposure. For the acutely exposed group, exposures were estimated to be 52-785 mg/m^3 [29-436 ppm], based on hemoglobin adduct levels. Average exposures in the second and third groups were estimated to range from <0.01-0.06 mg/m^3 (<0.1 ppm). No statistically significant difference between any of the groups was detected at any endpoint. The authors cite repair of preclastogenic and premutagenic lesions as well as the small group sizes as possible explanations for the lack of any observable effect.

Schulte et al. (1995) reported an increase in the frequency of SCE and micronuclei in blood lymphocytes from ethylene oxide-exposed female workers. Sixty-eight women (mean age 43.6 years for U.S. women and 29.4 for Mexican women) from one Mexican and nine 9 U.S hospitals were sampled and divided into 0, <32, and >32 ppm-h categories based on a 4-month cumulative exposure estimate from 2-4 day exposure monitoring data. A significant increase in SCE (in both dose groups) and micronuclei (at the high dose group) was observed among the 46 U.S. women, but none at either endpoint in the 22 Mexican workers. The increase in SCEs corresponded with an increase in hydroxyethyl hemoglobin adducts. The authors speculated that the lack of response in the Mexican subjects could be due to various factors including environmental effects, a one-time sampling, the smaller sample size, and the longer time from sampling until processing (up to 20 h).

Fuchs et al. (1994) analyzed single strand breaks in the DNA of peripheral mononuclear blood cells of 97 male and female hospital workers exposed to ethylene oxide. Ethylene oxide was detected in the air of working areas, up to a maximum 4-h TWA concentration of 16 mg/m^3 (9 ppm) or 1-h TWA of 49.5 mg/m^3 (27.5 ppm). DNA single stand breaks were significantly increased in nonsmoking workers.

Occupational exposure of nurses to ethylene oxide in Hungary was associated with increased frequencies of SCE and chromosome aberrations in peripheral blood lymphocytes (Major et al., 1996). Ethylene oxide concentrations in ambient air samples ranged from 5-100 mg/m^3 (2.8-55.6 ppm).

No human studies of ethylene oxide DNA adducts were located.

Table 5-1. Summary of Ethylene Oxide (Eo) Genotoxicity Studies Published Post -IARC (1994)

System	Biological Endpoint	S9/Other Metabolic Activation	Form and Purity	Dose Used	Endpoint Response +/- Activation	Comments	Reference
Prokaryotic Systems							
Salmonella typhimurium TA 1535	reverse mutation	no S9 used	NG	test of factors that may modify EO mutagenicity; human erythrocytes and theophylline added to preincubation mixture; one experiment used erythrocytes from drinkers of black tea while controls drank water	Erythrocytes enhanced the mutagenicity of ethylene oxide by two to fourfold; erythrocytes from tea drinkers caused a significantly smaller increase in EO mutagenicity compared to controls; theophylline inhibited the increase in mutagenicity caused by erythrocytes	Factor in erythrocytes that stimulates EO mutagenicity not identified	Oesch and Hengstler (1997 abstr.)
Lower Eukaryotic Systems							
Neurospora crassa heterokaryon H-12	specific locus mutations in the *adenine-3* region	na	NG	0.1, 0.2, 0.25, 0.3, & 0.35% for 3 h	positive	A high percentage of gene/point mutations (97%) and a low percentage of multilocus deletions (3%) were induced. The authors classified ethylene oxide as a moderate mutagen.	de Serres and Brockman (1995)
Drosophila melanogaster nucleotide excision repair deficient strain	sex-linked recessive lethal (SLRL) mutations	na	NG	31.3, 62.5, 125, 250, & 500 ppm via inhalation for 24 h	positive	No increase in SLRL mutations in post meiotic germ cells when matings were to NER^+ females, however, a 17-fold increase in SLRL mutations was obtained with NER^- females indicating the EO 2-hydroxyethyl adduct is repaired in the wild-type strains.	Vogel and Nivard (1997)

Table 5-1. Summary of Ethylene Oxide (Eo) Genotoxicity Studies Published Post-IARC (1994) (Continued)

System	Biological Endpoint	S9/Other Metabolic Activation	Form and Purity	Doses Used	Endpoint Response as/+ Activation	Comments	Reference
Mammalian Systems *in vitro*							
55-nucleotide DNA template	DNA synthesis across DNA adduct	na	NG	na	positive	A 55-nucleotide DNA template containing the 3-HE-dU adduct at a single site was made and DNA products synthesized from this template were analyzed. The lesion could be bypassed only by DNA polymerases Pol I (Klenow fragment) or T7 Pol lacking a 3′-5′ exonuclease proofreading activity. Both dA and dT were incorporated opposite the dC derived 3-HE-dU adduct, indicating G:C to A:T or G:C to T:A mutagenesis.	Bhanot et al. (1994)
calf thymus DNA and human blood lymphocytes	DNA adducts (detected via HPLC/MS)	na	NG	0.1, 1.0, 10, & 100 mM EO (in calf thymus DNA) or 1.0, 2.0, 5.0, & 10 mM EO (in blood) for 3 h at 37°C	positive in both systems	A clear dose-dependent increase in the level of 7-(2-hydroxyethyl)guanine (7HEG) adducts was observed in both systems with lower amounts observed in blood. Detection levels were on the order of approximately 3 modified bases per 10^8 nucleotides.	LeClercq et al. (1997)
human whole blood and isolated leukocytes	DNA single strand breaks (SSBs) using standard and direct alkaline elution methods	na	99.8%	0.5 and 2.0 mM gaseous ethylene oxide injected into sealed culture tubes for 1 h	positive with both methods	A statistically significant increase in sensitivity with the direct method (using whole blood directly) over the standard method (using isolated leukocytes) was observed at the top dose tested.	Hengstler et al. (1997)

Table 5-1. Summary of Ethylene Oxide (Eo) Genotoxicity Studies Published Post-IARC (1994) (Continued)

System	Biological Endpoint	S9/Other Metabolic Activation	Form and Purity	Doses Used	Endpoint Response and Activation	Comments	Reference
normal human diploid fibroblasts	hypoxanthine phosphoribosyl transferase (*hprt*) gene mutations (chromosomal, gross structural alterations, point mutations)	na	NG	EO exposure levels and duration NG; mutant clones selected after expression time of 8-10 days	positive; 48% showed large genomic deletions of the whole or part of the gene, compared to 10% in background; base substitutions, small deletions and insertions, and splice mutations were also identified, but the frequency was less than background		Lambert et al. (1994)
normal human diploid fibroblasts	DNA SSBs and double strand breaks (DSBs)	na	NG	2.5-30 mM EO; cells exposed for 1 h in suspension or in monolayer	positive	Induction rates of SSBs and DSBs depended on analytical method and treatment conditions (cells in monolayer or suspension)	Nygren et al. (1994)
Mammalian Systems *In Vivo*							
male Fischer 344/CR/BR rats	SCE in spleen and bone marrow	na	99.7%	100 ppm EO for 6 h/day, 300 ppm for 2 h/day, or 600 ppm for 1 h/day for up to 9 months	positive in both tissues	Following 3 months, all treated groups had a significantly higher level of SCE in spleen, but bone marrow SCE were only higher in the low-dose group. After 6 and 9 months, all dose groups were higher than controls for both spleen and bone marrow with the low- and high-dose groups significantly higher then the medium dose group. The authors theorized that the spleen was more sensitive due to cell-cycle kinetics and tissue function.	Ong et al (1993)

Table 5-1. Summary of Ethylene Oxide (Eo) Genotoxicity Studies Published Post-IARC (1994) (Continued)

System	Biological Endpoint	S9/Other Metabolic Activation	Form and Purity	Doses Used	Endpoint Response with Activation	Comments	Reference
male B6C3F1 Big Blue® *lacI* transgenic mice	*hprt* mutations in thymus and spleen	na	99.99%	200 ppm (6 h/day, 5days/wk) for 4 wk - necropsied 2 h and 2 and 8 wk post exposure for time course; for dose response 50, 100, and 200 ppm for 4 wk; necropsied 2 wk post exposure for thymus, 8 wk for spleen.	positive in both tissues	A dose-dependent increase in the frequency of *hprt* gene mutations was observed in the T-lymphocytes of both thymus (at 2 wk) and spleen (at 8 wk).	Walker et al. (1997)
male B6C3F1 Big Blue® *lacI* transgenic mice	*lacI* mutations in lung, spleen, bone marrow, and germ cells	na	99.99%	50, 100, and 200 ppm for 4 wk - necropsied 2 wk and 8 wk post exposure.	positive for lung only	The mutant frequency in the lung was significantly increased at 8 wk post exposure. Only spleens from the 200 ppm exposed mice were sequenced. Single base substitution accounted for 85% of the mutants (76% transitions/24% transversions). The authors hypothesized that since ethylene oxide is known to induce deletion mutations in other systems, the lack of response here was likely due to the inability to recover deletion mutants in the lambda-based shuttle vector.	Sisk et al. (1997)

Table 5-1. Summary of Ethylene Oxide (Eo) Genotoxicity Studies Published Post-IARC (1994) (Continued)

System	Biological Endpoint	S9/Other Metabolic Activation	Form and Purity	Doses Used	Endpoint Response with Activation	Comments	Reference
1) male F344 rats 2) male B6C3F1 mice 3) male B6C3F1 Big Blue® *lacI* transgenic mice	mutations in *hprt* exon 3 of T-cells	na	NG	rats and nontransgenic mice exposed to 0 and 200 ppm EO; transgenic mice exposed to 0, 50, 100, and 200 ppm EO for 4 wk (6 h/day, 5days/wk)	*Hprt* mutant frequencies significantly increased in thymus and spleen of transgenic mice compared to controls, and in nontransgenic rats and mice necropsied 5 and 8 wk post-exposure, respectively. Mutations were a combination of base substitutions, frameshifts, and small deletions.	The authors concluded that this and other data indicate similar mutagenic mechanisms of EO in rats and mice.	Walker et al. (1997 abstr.)
male Fischer 344 rats and male B6C3F1 mice	micronuclei in bone marrow	na	>99.9%	200 ppm EO (target) inhalation exposure 4 wk	positive		Vergnes and Pritts (1994)
Human Studies							
75 workers in a Brazilian industry that used EO as an intermediate; 22 controls from same plant	1) chromosomal aberrations 2) micronuclei in lymphocytes 3) micronuclei in buccal exfoliated cells 4) EO-hemoglobin adducts (HOEtVal)	na	NG	Analyses of air sample pumps showed workers exposed to EO levels of 2-5 ppm TWA for an 8 h working day during 3 mo sampling	significant increase in chromosomal aberrations, micronuclei in binucleated lymphocytes, and hemoglobin adducts in exposed populations compared to controls		Ribeiro et al. (1994)
German sterilization workers (number not provided in source used)	DNA damage (alkaline elution) in mononuclear blood cells	na	NG	<0.1, 0.1-0.5, 0.5-2.0 mg/m^3 in smokers and nonsmokers	positive	A dose-dependent increase in DNA damage was detected in both smokers and nonsmokers. The majority of nonsmokers showed a more sensitive response than smokers at doses ranging from 0.5-2.0 mg/m^3	Oesch et al. (1995)

Table 5-1. Summary of Ethylene Oxide (Eo) Genotoxicity Studies Published Post-IARC (1994) (Continued)

System	Biological Endpoint	S9/Other Metabolic Activation	Form and Purity	Dose Used	Endpoint Response w/o Activation	Comments	Reference
25 disinfection workers (15 female , 10 male, ages 31-57 years) at 15 German hospitals	SCEs and DNA-protein cross-links (alkaline elution) in lymphocytes	na	NG	peak levels up to 417 ppm immediately after opening sterilization units	negative (SCE), positive (cross-links)	Exposed workers did not show a significantly elevated frequency of lymphocyte SCE over historical controls; however, a significant decrease in their DNA alkaline elution rates (indicative of DNA-protein cross-links) was observed.	Popp et al. (1994)
28 workers at a Netherlands chemical manufacturing plant	*hprt* gene mutations, SCE, and micronuclei induction	na	NG	7 workers acutely exposed to 52-785 mg/m^3 (calculated from hemoglobin adducts), 7 workers employed for <5 years, 7 workers employed for >15 years, and 7 control workers	negative	No statistically significant difference between any of the groups was detected at any endpoint. The tests for the acutely exposed workers were performed 89-180 days post exposure. The authors cite lesion repair as well as the small group sizes as possible explanations for the lack of any observable effect.	Tates et al. (1995)
68 female workers in 9 U.S. hospitals and 1 Mexican hospital	SCE and micronuclei in blood lymphocytes	na	NG	0, >0-32, and >32 ppm-h groups based on a 4-month cumulative exposure	positive for both endpoints (U.S.), negative (Mexico)	A significant increase in SCE (in both dose groups) and micronuclei (at the high-dose group) was observed among the 46 U.S. women but none in the 22 Mexican workers. The authors speculated that the lack of response in the Mexican subjects may be due to various factors including environmental effects, a one-time sampling, the smaller sample size, and the longer time until processing (up to 20 h).	Schulte et al. (1995)
hospital worker cohort follow-up	somatic cell mutant frequency	na	na	previously reported (Tomkins et al., 1993)	negative		Tomkins et al. (1996 abstr.)

Table 5-1. Summary of Ethylene Oxide (Eo) Genotoxicity Studies Published Post-IARC (1994) (Continued)

System	Biological Endpoint	S9/Other Metabolic Activation	Form and Purity	Doses Used	Endpoint Response -/+ Activation	Comments	Reference
97 male and female workers in hospitals and plants that used EO to sterilize medical equipment	DNA SSBs in peripheral mononuclear blood cells	na	na	EO detected in air of working areas with a mean of 1.47 $\pm$ 0.52 mg/m^3; max. concn. 16.5 mg/m^3 as 4-h TWA	Significant increase in SSB among nonsmoking workers exposed to 0.1-2 mg/m^3 vs. nonsmoking workers exposed to air with EO below the detection limit (0.1 mg/m^3)	Nonsmoking workers were classified into two subpopulations based on sensitivity to EO.	Fuchs et al. (1994)
exposed hospital nurses in Hungary: Budapest (n=9); Eger (n=27) hospital controls in Hungary: Budapest (n=14); Eger (n=10)	1) SCE 2) chromosome aberrations (CA) in peripheral blood lymphocytes	na	na	ethylene oxide in ambient air samples ranged from 5-100 mg/m^3 (2.8-55.6 ppm)	Significant increase in SCE among Eger nurses Significant increase in CA frequencies in Eger and Budapest nurses	Leukocyte count and mean age showed significant effect on CA in Eger exposed and on SCE in historical controls	Major et al. (1996)

Abbreviations: na = not applicable; NG = not given

6.0 OTHER RELEVANT DATA

6.1 Absorption, Distribution, Metabolism, and Excretion in Humans

Gaseous ethylene oxide in fabric was found to be absorbed by human skin *in vitro*, in a study designed to model skin/fabric exposure to any potentially hazardous gas (Wester et al., 1997). [1,2-^{14}C]Ethylene oxide was introduced into a sealed glass container with fabric discs. After removal, the discs were placed on human skin mounted in glass diffusion cells for measurement of absorption. When the fabric/skin surface was open to surrounding air, the percutaneous absorption was 1.3% of the dose. When the surface was occluded with latex glove material, the percutaneous absorption was 46.0% of the dose. Absorption of intact ethylene oxide occurred within the first 0-4 hours of the assay. Other studies show aqueous ethylene oxide solutions can penetrate human skin *in vivo* (IARC, 1994).

Once inhaled, ethylene oxide is readily absorbed by the lungs. Approximately 20 to 25% of inhaled ethylene oxide reaching the alveolar space is exhaled as unchanged compound and 75-80% is absorbed by the lungs and metabolized (Brugnone et al., 1986; cited by IARC, 1994).

Ethylene oxide is a metabolite of ethene (ethylene), a substance produced endogenously. A study of workers exposed to ethene found that 0.5% of absorbed ethene was metabolized to ethylene oxide (Granath et al., 1996). In a study of sterilization personnel exposed to ethylene oxide (0.3 to 52 ppm [0.55 to 95.2 mg/m^3] [8-hour TWA readings]), the mean concentration of ethylene glycol in the blood of exposed workers (90 mg/L) after three days of exposure was twice that of non-exposed workers (45 mg/L) (Wolfs et al., 1983; cited by IARC, 1994).

Ethylene oxide is eliminated by hydrolysis and by conjugation with glutathione, and excreted in the urine mainly as thioethers (IARC, 1994). When the concentration of thioethers excreted in urine was analyzed in workers at the end of sterilization processes, the concentrations were twice as high in nonsmoking personnel exposed to peak concentrations of 1 to 200 ppm ethylene oxide (1.83-366 mg/m^3) as compared to unexposed workers (Burgaz et al., 1992; cited by IARC, 1994).

The elimination half-life for ethylene oxide in humans has been calculated variously as 14, 39, 42, and 198 minutes (Osterman-Golkar and Bergmark, 1988; Filser et al., 1992; Beliles and Parker, 1987; all cited by IARC, 1994). Using a human data set, Osterman-Golkar and Bergmark (1988; cited by IARC, 1994) calculated the elimination half-life to be 14 minutes and Filser et al. (1992; cited by IARC, 1994) calculated it to be 42 minutes. Using rat data, elimination half-life was calculated for humans on the basis of allometric scaling with body surface factors. Beliles and Parker (1987) and Filser et al. (1992) (both cited by IARC, 1994) calculated the half-life of ethylene oxide in humans to be 3.3 hours and 39 minutes, respectively.

Conjugators (75% of the population), as defined by a standardized conjugation of methyl bromide and glutathione, eliminate ethylene oxide from blood three to six times faster than those who are not conjugators (25% of the population) (Hallier et al., 1993; cited by IARC, 1994).

6.2 Absorption, Distribution, Metabolism, and Excretion in Experimental Systems

Using male Sprague-Dawley rats, Filser and Bolt (1984; cited by IARC, 1994) found that ethylene oxide is absorbed rapidly by the lungs after inhalation. About 50% of the amount inhaled was exhaled without becoming systemically available. Maximal accumulation of ethylene oxide in the body of Sprague-Dawley rats was examined as the thermodynamic partition coefficient whole body:air (Filser et al., 1993; cited by IARC, 1994). Based on the metabolic

elimination rate of ethylene oxide in rats, the whole body:air concentration ratio was estimated to be 1.88, a value that is similar to the coefficient for venous blood:environmental air in exposed workers (Filser, 1992; cited by IARC, 1994). In male Fischer 344 rats, tissue:air partition coefficients are similar for most organs, indicating an almost uniform distribution of ethylene oxide within their bodies (Krishnan et al., 1992; cited by IARC, 1994).

Blood ethylene oxide concentrations in male B6C3F$_1$ mice after a single 4-hr nose-only inhalation exposure increased linearly with concentrations up to 200 ppm but increased more rapidly (sublinear dosimetry) at exposure concentrations greater than 200 ppm (Brown et al., 1998). Tissue measurements of GSH indicated that the deviation from linear dosimetry was due to GSH depletion.

In Sprague-Dawley rats (Filser and Bolt, 1984; cited by IARC, 1994) and Fischer 344 rats (Krishnan et al., 1992; cited by IARC, 1994), elimination of ethylene oxide was described by first-order kinetics. These studies indicated that, at steady state, about 95% of the systemic ethylene oxide was eliminated by metabolism while 5% was exhaled.

To determine metabolites of ethylene oxide, male Sprague-Dawley rats were administered an i.p. injection of ethylene oxide labeled with ^{14}C. The percentages of radioactivity excreted in the urine were 9% *S*-(2-hydroxyethyl)cysteine and 33% *N*-acetyl-*S*-(2-hydroxyethyl)cysteine. In addition, 1.5% of the dose was exhaled as $^{14}CO_2$ and 1% was exhaled as unchanged ethylene oxide (Jones and Wells, 1981; cited by IARC, 1994).

Ethylene glycol, 2-hydroxymercapturic acid, 2-methylthioethanol, and 2-mercaptoethanol were determined as metabolites in the urine of male Wistar rats (Koga et al., 1987; cited by IARC, 1994). Significant levels of thiodiacetic acid were detected in the urine of Sprague-Dawley rats and NMRI mice after inhalation exposure to ethylene oxide, compared to levels in urine collected prior to exposure (Scheick et al., 1997).

Marked species differences were noted in the pattern of excretion of ethylene oxide metabolites in mice, rats, and rabbits. Metabolites resulting from the conjugation of ethylene oxide with glutathione were found in the urine of male Swiss CD-1 mice and male Sprague-Dawley rats, but not in the urine of rabbits. *N*-Acetyl-*S*-(2-hydroxyethyl)cysteine was excreted in mice and rat urine. *S*-(2-Hydroxyethyl)cysteine and *S*-(carboxymethyl)cysteine were found only in mouse urine. Ethylene glycol (reaction product of the hydrolytic pathway of ethylene oxide) was found in the urine of all three species (Tardif et al., 1987; cited by IARC, 1994).

6.3 Glutathione Depletion

After 4-hour exposure to ethylene oxide at concentrations ranging from 100-900 ppm (mice) and 100-1200 ppm (rats), concentration-related decreases in glutathione levels were found in the kidney, heart, lung, brain, stomach, spleen, testis, and liver of male Swiss-Webster mice and male Fischer 344 rats (McKelvey and Zemaitis, 1986; cited by IARC, 1994). Additionally, there were decreases in the glutathione levels in the blood of mice, but not of rats, and in bone marrow examined in rats only. The reduction in glutathione levels in both species was more marked in the liver, lung, and stomach than in other organs. A study with male B6C3F1 mice also demonstrated tissue glutathione depletion that was dependent on ethylene oxide exposure concentration (Brown et al., 1998).

6.4 Binding to DNA and Hemoglobin

Studies analyzing adduct formation caused by ethylene oxide were reviewed and summarized by IARC (1994). Ethylene oxide forms adducts with proteins in both humans and experimental animals and with DNA in experimental animals.

The formation of a DNA adduct (7-hydroxyethylguanine; 7-HEG) was shown in rats exposed to 3 and 10 ppm ethylene oxide (Swenberg et al., 1995). Other DNA adducts of ethylene oxide found in tissues from exposed rats are O6-(2-hydroxyethyl) guanine (in brain, kidney, lung, and spleen) and N3-(2-hydroxyethyl) adenine (in spleen) (IARC, 1994).

Ethylene oxide also forms hemoglobin adducts, as do other alkylating agents (Farmer et al., 1993). Blood levels of the hemoglobin adduct *N*-(2-hydroxyethyl)valine (HOEtVal) were higher in an urban population than in a rural control population (Cordero et al., 1995).

When hemoglobin adducts were used for biomonitoring of workers exposed to ethylene oxide, a significant correlation was found between cumulative exposure over four months and levels of *N*-terminal hydroxyethylvaline in hemoglobin of exposed workers (Schulte et al., 1995). Hydroxyethylvaline was formed at an increment of 12-16 pmol/g hemoglobin per ppm-h ethylene oxide (Ehrenberg and Törnqvist, 1995).

Notably, hydroxyethyl adducts of DNA and hemoglobin (7-HEG) were found in humans and animals even in the absence of known exposure to ethylene oxide (Swenberg et al., 1995; La and Swenberg, 1996). Most of the background hemoglobin adducts of ethylene oxide are believed to arise from the endogenous metabolism of ethene (Törnqvist, 1996).

An analysis of experimentally determined data sets on hemoglobin adducts and DNA adducts of ethylene oxide in lymphocytes from humans and animals indicated that normal background (endogenous) levels are similar across species. Background DNA adduct levels also appeared to be consistent among tissues (Bolt, 1996).

6.5 Structure-Activity Relationships (SAR)

6.5.1 1,2-Propylene oxide

Propylene oxide is a structural analog of ethylene oxide that also displays alkylating activity (DFG, 1993). It was mutagenic and clastogenic in several *in vitro* assays, but only showed mutagenic activity *in vivo* after injection of high doses. Recessive lethal mutations were observed in *D. melanogaster* (Hardin et al., 1983; cited by DFG, 1993), and positive results were reported in Ames assays (Pfeiffer and Dunkelberg, 1980; cited by DFG, 1993). Human lymphocytes treated *in vitro* showed chromosome damage (Bootman et al., 1979; cited by DFG, 1993), as did cultured rat hepatocytes (Dean and Hodson-Walker, 1979; cited by DFG, 1993). Mice showed no effects in a dominant lethal test after oral administration of moderate and high doses (50 mg/kg; 250 mg/kg), or in a micronucleus assay following oral administration of twice 500 mg/kg (Bootman et al., 1979; cited by DFG, 1993). A similar dose (300 mg/kg) administered to mice by i.p. injection produced positive results in a micronucleus test, but lower doses (75 mg/kg; 150 mg/kg) gave negative results (Bootman et al., 1979; cited by DFG, 1993).

Propylene oxide also exhibited carcinogenic activity in experimental animals. Forestomach carcinoma developed in female Sprague-Dawley rats given propylene oxide by gavage for almost three years; at study termination, the tumor incidence was 40% and 4% in the treated and control groups respectively (Dunkelberg, 1982; cited by DFG, 1993). B6C3F_1 mice chronically exposed to 400 ppm propylene oxide by inhalation (6 h/day, 5 days/wk for 103

weeks) had a significant increase in hemangioma and hemangiosarcoma of the nasal cavity (NTP, 1983; cited by DFG, 1993).

6.5.2 1,3-Butadiene

1,3-Butadiene is metabolized to butadiene monoepoxide or monoxide (BMO), also known as epoxybutene, with human isoforms 2E1 and 2A6 exhibiting the highest oxidation rates of all active cytochrome P450 isoforms (Elfarra et al., 1996). The metabolism of butadiene to BMO and oxidation of BMO to diepoxybutane (BDE) was demonstrated in human liver microsomes (Csanády et al., 1996; Seaton et al., 1995).

1,3-Butadiene, its epoxide metabolites, and ethylene oxide have similar mutational spectra at the *hprt* locus in mouse lymphocytes (Walker and Skopek, 1993; Cochrane and Skopek 1994). All these compounds form N7-alkylguanine adducts and are associated with a high percentage of frameshift mutations. Occupational exposure to 1,3-butadiene has been consistently associated with excess mortality from lymphatic and hematopoietic cancers. 1,3-Butadiene is carcinogenic at multiple organ sites in rats and mice.

6.5.3 Styrene oxide

In vitro studies showed binding of styrene oxide to all nucleic acid bases and nucleotides except uracil (Hemminki et al., 1980; cited by Segerback, 1994). However, the primary adduct was from alkylation at N7 of guanine (Vodicka and Hemminki, 1988; cited by Segerback, 1994). N7-Alkylguanine adducts were detected in mice after treatment with radiolabeled styrene oxide (Byfalt Nordqvist et al., 1985; cited by Segerback, 1994).

Styrene oxide also produced tumors in experimental animals. The incidence of squamous-cell carcinoma of the forestomach was significantly increased in B6C3F_1 mice and Fischer 344/N rats chronically (> 100 wk) administered styrene-7,8-oxide in corn oil by gastric intubation (Lijinsky, 1986; cited by IARC, 1994). A shorter term (52-wk) administration of styrene-7,8- oxide in olive oil by gastric intubation also resulted in a significant increase in squamous-cell carcinoma of the forestomach in Sprague-Dawley rats (Maltoni et al., 1979; Conti et al., 1988; both cited by IARC, 1994).

6.6 IARC (1994) Evaluation

In making an overall evaluation of the carcinogenicity of ethylene oxide, the Working Group took into consideration that ethylene oxide is a directly acting alkylating agent that induces a sensitive, persistent dose-related increase in the frequency of chromosomal aberrations and sister chromatid exchange in peripheral lymphocytes and micronuclei in bone marrow cells of exposed workers; has been associated with malignancies of the lymphatic and hematopoietic system in both humans and experimental animals; induces a dose-related increase in the frequency of hemoglobin adducts in exposed humans and dose-related increases in the numbers of adducts in both DNA and hemoglobin in exposed rodents; induces gene mutations and heritable translocations in germ cells of exposed rodents; and is a powerful mutagen and clastogen at all phylogenetic levels. Based on the overall evaluation, IARC (1994) concluded that ethylene oxide is carcinogenic to humans (Group 1).

7.0 MECHANISMS OF CARCINOGENESIS

Ethylene oxide is an electrophile and a direct-acting mutagen in plants, microorganisms, insects, and mammals (IARC, 1994). In their overall evaluation, IARC (1994) considered genetic changes in exposed workers to be important supporting evidence of the carcinogenicity of ethylene oxide in humans. Ethylene oxide induces a dose-related increase in the frequency of chromosomal aberrations and SCE in peripheral lymphocytes and micronuclei in bone marrow cells of exposed humans. In addition, ethylene oxide is associated with a dose-related increase in the frequency of hemoglobin adducts in exposed humans and dose-related increases in numbers of adducts in both DNA and hemoglobin of exposed rodents. More recently published studies on the genetic activity of ethylene oxide are consistent with the IARC (1994) report. The proposed cancer mechanisms for 1,3-butadiene, invoking the alkylating potential of the epoxide metabolites, can be compared to ethylene oxide. This comparison is valuable because epidemiology studies have consistently found an association between occupational exposure to 1,3-butadiene and excess mortality from lymphatic and hematopoietic cancers, and because there are several common sites of tumor induction by ethylene oxide and 1,3-butadiene in experimental animals.

Ethylene oxide is eliminated by hydrolysis and by conjugation with glutathione, but the untransformed epoxide is reactive with DNA and proteins. 1,3-Butadiene, a chemical considered to be a probable human carcinogen (IARC, 1992) or a known human carcinogen (NTP, 1999), is metabolized by liver microsomal cytochrome P-450 enzymes to monoepoxide and diepoxide intermediates. There are striking similarities between the genotoxic activity of ethylene oxide and 1,3-butadiene. The most likely mechanism for the carcinogenicity of 1,3-butadiene is related to DNA damage by one or more reactive metabolites (Melnick and Kohn, 1995). Exposure to 1,3-butadiene resulted in increased levels of DNA damage and mutations in experimentally exposed animals and occupationally exposed workers.

In mice, exposure by inhalation to 1,3-butadiene resulted in increased levels of DNA-DNA and DNA-protein cross-links in liver and lung, N7-alkylguanine adducts in liver DNA, SCE and chromosomal aberrations in bone marrow cells, micronucleated erythrocytes detected in peripheral blood, *hprt* mutations in lymphocytes, dominant lethal mutations, and sperm abnormalities. At the *hprt* locus in mouse lymphocytes, the mutational spectra of 1,3-butadiene, its metabolite epoxybutene, and ethylene oxide are similar, suggesting a common mechanism of mutagenesis (Walker and Skopek, 1993; Cochran and Skopek, 1994).

In workers, occupational exposure to 1,3-butadiene induced a significant increase in hemoglobin adducts, and (in some but not all studies) sister chromatid exchange, *hprt* mutations, and chromosomal aberrations in lymphocytes (Au et al., 1996; IARC, 1992; Sorsa et al., 1996; Ward et al., 1996).

The mutagenic and carcinogenic effects of ethylene oxide appear to mimic those of the epoxide intermediates of 1,3-butadiene metabolism. The carcinogenic effects of these compounds most likely result from their mutagenic and clastogenic effects that have been observed at all phylogenetic levels.

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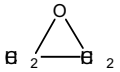
APPENDIX A

Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Volume 60 (Some Industrial Chemicals) Ethylene Oxide pp. 73-159, 1994

ETHYLENE OXIDE
CAS No. 75-21-8

First Listed in the *Fourth Annual Report on Carcinogens* as *Reasonably Anticipated to be a Human Carcinogen* updated 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, involving 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 as a reasonably anticipated human carcinogen, 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 about 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 (Steenland et al., 1991) 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. 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 nonsignificant (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 326, 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 (V.60, 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 (V.60, 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 (V.60, 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; ; Schulte et al., 1995; Major et al., 1996), of micronuclei in erythrocytes (Tates et al., 1991; Högstedt 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 (molecular weight, 44.06) is a colorless gas at room temperature and normal pressure, but is a liquid at or below 12 ^{o}C (Budavari, 1996). The liquid has a characteristic ether-like odor (Hoechst Celanese Polyester Intermediates et al., 1995). 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 V.60, 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, 1998). Because of the potential hazards of shipping bulk quantities of ethylene oxide, some producers have reportedly limited shipments to areas immediately proximate or within 50 miles of the producing point (Chem. Prod., 1988).

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 approximately half and half (Chem. Mark. Rep., 1995). Ethylene glycol is used primarily in automotive antifreeze and 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., 1987b). 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 (NIOSH, 1976; ATSDR, 1990-H005). 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 about 0.1% of the total demand for ethylene oxide (SRIc, 1997c).

At one time, it was used in the production of acrylonitrile, but the process ended in 1966 (ATSDR, 1990-H005). 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, 1982b; IARC V.11, 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 V.60, 1994).

PRODUCTION

Ethylene oxide has been ranked among the top 50 largest volume chemicals produced in the United States for the past several years 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). U.S. production from 1977 to 1984 ranged from 4.4 to 5.7 billion lb (USITC, 1978-1985). In the period 1985 to 1989, imports ranged from 12 to 33.6 million lb (average 26 million lb) and exports ranged from 12.1 to 62.5 million lb (average 31 million lb) (USDOC Imports, 1986, 1990; USDOC Exports, 1988, 1990; Chem. Prod., 1988). Compared to annual U.S. production, imports and exports are negligible (< 1%) (HSDB, 1997).

The 1979 TSCA Inventory identified 18 manufacturers producing 3.4 billion lb of ethylene oxide in 1977. The 1997 Directory of Chemical Producers identified 11 companies producing ethylene oxide at 13 plants (SRIa, 1997).

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 10-30 atm (1-3 MPa) and 200-300 EC to give ethylene oxide (IARC V.60, 1994).

The chlorohydrin process used to be 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 V.60, 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-H005). Because ethylene oxide is highly explosive and reactive, the process equipment containing it generally consists of tightly closed and highly automated systems, which decreases the risk of occupational exposure (NCI DCE, 1985h). Workers in the synthetic organic chemicals manufacturing industry using ethylene oxide are required to wear respirators when air concentrations exceed the 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).

Ethylene oxide forms DNA and hemoglobin adducts. These adducts have been used to monitor human exposure to ethylene oxide.

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 tradename products known to contain the compound (NIOSH, 1976). NIOSH estimated that approximately 75,000 health care workers employed in sterilization areas in the period 1972-1974 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 35, 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, 1982b).

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 DCE, 1985h; IARC V.36, 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 (Science, 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 tradename 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 DCE, 1985h).

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 V.60, 1994). Measurements of worker exposure levels in U.S. hospitals, summarized below, showed a range of exposure concentrations (0-794 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 V.60, 1994).

Exposure mostly results from peak emissions during operations such as opening the door of the sterilizer and unloading and transferring sterilized material. Short-term (2-30 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 1977-1990. 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 V.60, 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 1990-1992 (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 tertiary-care 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 0-2.8 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 (V.60, 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 usually entails exposure to a variety of other chemicals, e.g., unsaturated aliphatic hydrocarbons, other epoxides, and chlorinated aliphatic hydrocarbons (IARC V.60, 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 2-5 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 V.60, 1994).

One entry route into the environment for ethylene oxide is as fugitive emissions lost during production, or as vented gases (ATSDR, 1990-H005). Fugitive emissions amounted to some 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 EOIC estimated that about 3 million lb of ethylene oxide are released into the air 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 about 3 million lb per year were lost to the air and that about 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 air, while none was lost to water (CHIP, 1982b).

Significant gaseous releases of ethylene oxide to the environment are the result of uncontrolled industrial emissions (ATSDR, 1990-H005). These occur during the loading or unloading of transport tanks, product sampling procedures, and equipment maintenance and repair (CHIP, 1982b). 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. The Toxic Chemical Release Inventory (EPA) listed 197 industrial facilities that produced, processed, or otherwise used ethylene oxide in 1988 (TRI88, 1990). In compliance with the Community Right-to-Know Program, the facilities reported releases of ethylene oxide to the environment which were estimated to total 4.7 million lb. By 1995, the total release to air was lower, 839,229 lb (157 facilities releasing at least 10 lb) (TRI95, 1997). The USEPA (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 mainly through the use of products which 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 35, 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-H005). Ethylene oxide residues were detected in the following food products sampled from Danish retail shops: herbs and spices (14-580 mg/kg), dairy (0.06-4.2 mg/kg), pickled fish (0.08-2.0 mg/kg), meat products (0.05-20 mg/kg), cocoa products (0.06-0.98 mg/kg), and black and herb teas (3-5 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, V.60, 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. A Rebuttable Presumption Against Registration (RPAR) for ethylene oxide has been issued under FIFRA. 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 (USEPA, 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 recordkeeping requirements.

The deadline for compliance with these emission standards was December 8, 1997 (USEPA, 1996). Sources which use one ton, but are not major or located at major sources, may be deferred by the applicable Title V permitting authority from the Title V permitting requirements for five years until December 9, 1999. However, due to explosions of several ethylene oxide commercial sterilization and fumigation facilities, which may be attributable to emission scrubbers, this compliance was deferred for one year, until December 8, 1998 (62 FR 64736, July 1998).

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 lowered the permissible exposure limit (PEL) from 50 ppm to 1 ppm as an 8-hr TWA in 1984 and established an STEL of 5 ppm during a 15-minute period in 1988. OSHA regulates ethylene oxide under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations summarized in Volume II, Table A-18.