

ETHYLENE OXIDE

This substance was considered by previous Working Groups in February 1976 (IARC, 1976), June 1984 (IARC, 1985), March 1987 (IARC, 1987) and February 1994 (IARC, 1994). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

From IARC (1994) and IPCS-CEC (2001)

Chem. Abstr. Serv. Reg. No.: 75-21-8

Replaced CAS Reg. No.: 19034-08-3; 99932-75-9

Chem. Abstr. Name: Oxirane

IUPAC Systematic Name: Oxirane

RTECS No.: KX2450000

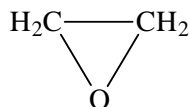
UN TDG No.: 1040

EC Index No.: 603-023-00-X

EINECS No.: 200-849-9

Synonyms: Dihydrooxirene; dimethylene oxide; EO ; 1,2-epoxyethane; epoxyethane; ethene oxide; EtO; ETO; oxacyclopropane; oxane; oxidoethane

1.1.2 Structural and molecular formulae and relative molecular mass



C₂H₄O

Relative molecular mass: 44.06

1.1.3 *Chemical and physical properties of the pure substance*

From IARC (1994), Dever *et al.* (2004), Lide (2005), Rebsdatt and Mayer (2005) and O'Neil (2006), unless otherwise specified

- (a) *Description*: Colourless gas
- (b) *Boiling-point*: 13.2 °C at 746 mm Hg [99.4 kPa]; 10.4–10.8 °C at 760 mm Hg [101.3 kPa]
- (c) *Freezing-point*: –111 °C
- (d) *Density (liquid)*: 0.8824 at 10 °C/10 °C
- (e) *Spectroscopy data*: Infrared [prism, 1109] and mass spectral data have been reported (Weast & Astle, 1985; Sadtler Research Laboratories, 1991).
- (f) *Solubility*: Soluble in water, acetone, benzene, ethanol and diethyl ether
- (g) *Vapour pressure*: 145.6 kPa at 20 °C (Hoechst Celanese Corp., 1992)
- (h) *Relative vapour density (air = 1)*: 1.5 at 20 °C (IPCS-CEC, 2001)
- (i) *Stability*: Reacts readily with acids; reactions proceed mainly via ring opening and are highly exothermic; explosive decomposition of vapour may occur at higher temperatures if dissipation of heat is inadequate.
- (j) *Lower explosive limit*: 2.6–3.0% by volume in air
- (k) *Octanol-water partition coefficient*: $\log P_{ow}$, –0.30 (Sangster, 1989)
- (l) *Flash-point*: Flammable gas (IPCS-CEC, 2001)
- (m) *Inflammability limits in air*: 2.6–99.99% (V) (Shell Chemicals, 2005)
- (n) *Autoignition temperature*: 428 °C (Shell Chemicals, 2005)
- (o) *Dynamic viscosity*: 0.41 mPa at 0 °C (Shell Chemicals, 2005)
- (p) *Conversion factor*: $\text{mg/m}^3 = 1.80 \times \text{ppm}^1$

1.1.4 *Technical products and impurities*

Ethylene oxide for use as a fumigant and sterilizing agent used to be available in mixtures with nitrogen, carbon dioxide or dichlorodifluoromethane. Mixtures of 8.5–80% ethylene oxide/91.5–20% carbon dioxide (Allied Signal Chemicals, 1993) and 12% ethylene oxide in dichlorodifluoromethane were commonly used. As a result of concern about the role of chlorofluorocarbons in the depletion of stratospheric ozone and the phase-out of dichlorofluoromethane under the Montreal Protocol, the fluorocarbon materials now used to make blends of non-flammable ethylene oxide sterilants are hydrochlorofluorocarbons, hydrofluorocarbons and other flame-retardant diluent gases (Dever *et al.*, 2004).

¹ Calculated from: $\text{mg/m}^3 = (\text{relative molecular mass}/24.45) \times \text{ppm}$, assuming normal temperature (25 °C) and pressure (101.3 kPa)

1.1.5 Analysis

Ethylene oxide in air can be determined by packed column gas chromatography (GC) with an electron capture detector (ECD) (NIOSH Method 1614), with an estimated limit of detection of 1 µg ethylene oxide per sample (National Institute for Occupational Safety and Health, 1987). A similar method is reported by the Occupational Safety and Health Administration in the USA (Tucker & Arnold, 1984; Cummins *et al.*, 1987). In a similar method reported by the Canadian Research Institute for Health and Safety at Work (IRSST Method 81-2), the sample is absorbed on an active charcoal tube (SKC ST-226-36), desorbed by benzylic alcohol and analysed by GC/flame ionization detection (FID) (IRSST, 2005).

In another technique (NIOSH Method 3702), a portable gas chromatograph is used with a photoionization detector or photoacoustic detector (IRSST 39-A). The sample is either drawn directly into a syringe or collected as a bag sample; it is then injected directly into the gas chromatograph for analysis. The estimated limit of detection of this method is 2.5 pg/mL injection (0.001 ppm [0.002 mg/m³]) (National Institute for Occupational Safety and Health, 1998).

Passive methods use derivatization techniques that convert ethylene oxide to 2-bromoethanol followed by GC/ECD analysis or collect ethylene oxide in acidic solution (in which it is converted to ethylene glycol) or on a selective membrane followed by colorimetric analysis (Kring *et al.*, 1984; Puskar & Hecker, 1989; Puskar *et al.*, 1990, 1991; Szopinski *et al.*, 1991).

Methods for the analysis and quantification of ethylene oxide in emissions from production plants and commercial sterilizers by GC/FID have been reviewed (Steger, 1989; Margeson *et al.*, 1990).

Ethylene oxide has been measured in alveolar air and blood (Brugnone *et al.*, 1986). Several methods have been reported for the determination of *N*-(2-hydroxyethyl) adducts with cysteine, valine and histidine in haemoglobin: a radioimmunological technique, a modified Edman degradation procedure with GC/mass spectrometry (MS), a GC method with selective ion monitoring MS and a GC/ECD method (Farmer *et al.*, 1986; Bailey *et al.*, 1987; Bolt *et al.*, 1988; Föst *et al.*, 1991; Hagmar *et al.*, 1991; Kautiainen & Törnqvist, 1991; Sarto *et al.*, 1991; van Sittert *et al.*, 1993; Schettgen *et al.*, 2002).

Methods have been reported for the detection of residues of ethylene oxide used as a sterilant: headspace GC (Marlowe *et al.*, 1987) and GC (Wojcik-O'Neill & Ello, 1991) for the analysis of medical devices; capillary GC for the analysis of drugs and plastics (Danielson *et al.*, 1990); and headspace GC for the analysis of packaging materials and ethylene oxide in ethoxylated surfactants and demulsifiers (Dahlgran & Shingleton, 1987). Methods have also been developed for the determination of ethylene oxide residues in processed food products. In one such method, ethylene oxide is converted to ethylene iodohydrin and analysed by GC/ECD (Jensen, 1988).

1.2 Production and use

1.2.1 Production

Production of ethylene oxide began in 1914 by the chlorohydrin process, the main method used until 1937, in which ethylene chlorohydrin is converted to ethylene oxide by reaction with calcium oxide. The production of ethylene chlorohydrin resulted in the formation of two main organochlorine by-products, 1,2-dichloroethane and bis(2-chloroethyl)ether (see IARC, 1999a). Ethylene chlorohydrin was produced in either the same or a separate unit and was pumped over to the ethylene oxide production sector. The chlorohydrin process for the production of ethylene oxide was inefficient, because most of the chlorine that was used was lost as calcium chloride. Since 1931, that process has gradually been replaced by the direct vapour-phase oxidation process, in which ethylene is oxidized to ethylene oxide with air or oxygen and a silver catalyst at 10–30 atm (1–3 MPa) and 200–300 °C (Dever *et al.*, 2004; Anon., 2005).

In 2002, ethylene oxide was produced in more than 30 countries in Asia, Australia, Europe, the Middle East, North America and South America with a production capacity per year of 16.3 million tonnes (Lacson, 2003). Worldwide consumption of ethylene oxide was 14.7 million tonnes in 2002 (Dever *et al.*, 2004) and 18 million tonnes in 2006 (Devanney, 2007). Table 1 shows the number of producers by region as well as the production levels of ethylene oxide in 2004; approximately 17 million tonnes of ethylene oxide were produced worldwide. Production in Canada increased from 625 000 tonnes in 1996 (WHO, 2003) to 1 084 000 tonnes in 2004.

1.2.2 Use

Ethylene oxide is an important raw material used in the manufacture of chemical derivatives that are the basis for major consumer goods in virtually all industrialized countries. Figure 1 gives an overview of global industry demand for ethylene oxide by application. More than half of the ethylene oxide produced worldwide is used in the manufacture of monoethylene glycol (Occupational Safety and Health Administration, 2005; Devanney, 2007). The percentage of total ethylene oxide that is used domestically to manufacture ethylene glycols varies widely between regions: North America (66%), western Europe (43%), Japan (68%) and the Middle East (99%) (Lacson, 2003).

Other derivatives of ethylene oxide include: diethylene glycol, which is used in the production of polyurethanes, polyesters, softeners (cork, glue, casein and paper), plasticizers and solvents and in gas drying; triethylene glycol, which is used in the manufacture of lacquers, solvents, plasticizers and humectants (moisture-retaining agents) and in gas drying; poly(ethylene) glycols, which are reacted with other materials and used in cosmetics, ointments, pharmaceutical preparations, lubricants (finishing of textiles, ceramics), solvents (paints and drugs) and plasticizers (adhesives and printing inks); ethylene glycol ethers, which are frequently a component of brake fluids, detergents and solvents (paints and lacquers) and are used to treat natural and refinery gas; ethanalamines,

which are used in textile finishing, cosmetics, soaps, detergents and natural gas purification; and ethoxylation products of fatty alcohols, fatty amines, alkyl phenols, cellulose and poly(propylene) glycol, which are used in the production of detergents and surfactants (non-ionic), biodegradable detergents, emulsifiers and dispersants (Occupational Safety and Health Administration, 2005; Devanney, 2007).

A very small proportion (0.05%) of the annual production of ethylene oxide is used directly in the gaseous form as a sterilizing agent, fumigant and insecticide, either alone or in non-explosive mixtures with nitrogen, carbon dioxide or dichlorofluoromethane (Dever *et al.*, 2004).

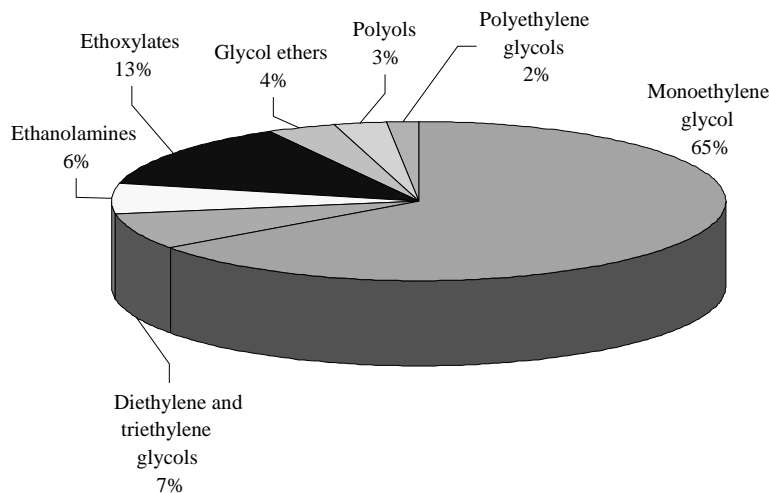
Table 1. Production of ethylene oxide by region in 2004

Region	No. of producers	Production (thousand tonnes)
North America		
USA	10	4009
Canada	3	1084
Mexico	3	350
South America		
Brazil	2	312
Venezuela	1	82
Europe		
Belgium	2	770
France	1	215
Germany	4	995
Netherlands	2	460
Spain	1	100
Turkey	1	115
United Kingdom	1	300
Eastern Europe	NR	950
Middle East		
Iran	2	201
Kuwait	1	350
Saudi Arabia	2	1781
Asia/Pacific	>15	
China, mainland	NR	1354
China (Province of Taiwan)	4	820
India	> 2	488
Indonesia	1	175
Japan	4	949
Malaysia	1	385
Republic of Korea	3	740
Singapore	1	80

From Anon. (2004)

NR, not reported

**Figure 1. Industrial products made from ethylene oxide
(globally, 17 million tonnes per annum)**



From Devanney (2007)

Ethylene oxide is also used as a fumigant and sterilant for microbial organisms in a variety of applications. An estimated 9–10 million pounds [4–5 million tonnes] of ethylene oxide were used in 2002 to sterilize drugs, hospital equipment, disposable and reusable medical items, packaging materials, foods, books, museum artefacts, scientific equipment, clothing, furs, railcars, aircraft, beehives and other items (Lacson, 2003).

1.3 Occurrence

1.3.1 *Natural occurrence*

Ethylene oxide occurs endogenously as a metabolite of ethylene in certain plants and micro-organisms (see Section 4.1). Ethylene oxide can be generated from water-logged soil, manure and sewage sludge, but emissions are expected to be negligible (WHO, 2003).

1.3.2 Occupational exposure

Most of the data on occupational exposure are related to the production of ethylene oxide and its use in industrial and hospital sterilization.

Data were not available on exposures that are incurred outside North America and Europe, where almost half of the global amount of ethylene oxide is produced (Table 1).

The National Occupational Exposure Survey conducted by the National Institute for Occupational Safety and Health in the USA between 1981 and 1983 indicated that 270 000 employees in the USA were potentially exposed to ethylene oxide at work (NOES, 1993). This implies that, with an estimated labour force (aged 16 years and over) of 106 million (US Census, 1980), fewer than 0.3% of employees was exposed. Of this number, 22% was estimated to be exposed to ethylene oxide and 78% to materials that contain ethylene oxide. Workers in hospitals and in the chemical and allied products industry (manufacture of plastics, synthetic materials and drugs) accounted for half of that number.

More recent data on employment in the industrial sectors that use ethylene oxide have been reported by the Occupational Safety and Health Administration (2005). Approximated employment figures were: ethylene oxide production workers, 1100; ethoxylators (use of ethylene oxide to make derivatives), 4000; and sterilant or fumigant use in hospitals, 40 000. In addition, approximately 2700 workers were employed in commercial sterilization by medical and pharmaceutical product manufacturers, in commercial sterilization by spice manufacturers, as contract sterilizers and in other sterilization and fumigation facilities.

The CAREX exposure information system (see General Remarks) includes estimates of the numbers of exposed workers in the 15 member states of the European Union in 1990–93. The estimates were based on expert judgments and did not involve exposure measurements. According to CAREX, 47 000 workers were exposed to ethylene oxide, which is under 0.1% of the 139 million employed who are covered by CAREX (Kauppinen *et al.*, 2000). The major industries in which exposure occurred were medical, dental and other health and veterinary services (22 000 exposed) and the manufacture of industrial chemicals and other chemical products (7000 exposed).

The Finnish Register of occupational exposure to carcinogens reported that 126 workers were notified as having been exposed to ethylene oxide in 2004. This is below 0.01% of the 2.4 million people employed in Finland. Most of the workers exposed were employed in medical occupations. The Register does not include any information on exposure levels, and is based on annual notifications of employers; its completeness is unknown (Saalo *et al.*, 2006).

(a) Production of ethylene oxide and its derivatives

Area samples taken in the 1960s throughout a plant in the USA where ethylene oxide was produced by direct oxidation of ethylene showed concentrations of 0–55 ppm [0–

100 mg/m³]. On the basis of these results, the general long-term exposure of operators to ethylene oxide was estimated to be 5–10 ppm [9–18 mg/m³] (Joyner, 1964).

Area and personal samples were taken by the National Institute for Occupational Safety and Health during 1977 and 1978 in five plants in the USA where ethylene oxide and its derivatives were produced. In most of the 95 personal samples taken, which were representative of whole shifts, the concentration of ethylene oxide was below the detection limit (which varied from 0.1 to 8 mg/m³); a few samples contained between 1 and 148 mg/m³. Similarly, in most area samples, the concentration was below the detection limit or was in the range < 1–1.5 ppm [2–3 mg/m³], apart from exceptional situations such as leaks (Lovegren & Koketsu, 1977a,b,c; Oser *et al.*, 1978a,b, 1979). The fact that full-shift concentrations in these plants were usually well below the standards at that time (50 ppm [90 mg/m³]) has been attributed to three main factors: the use of completely closed systems for the storage, transfer and production of ethylene oxide; the implementation of measures to prevent fire; and operation outdoors which resulted in dilution by natural air (Morgan *et al.*, 1981).

Estimates of exposure to ethylene oxide were made for a Swedish company where ethylene oxide and its derivatives were produced by the chlorohydrin process. Average exposure was estimated to be less than 25 mg/m³ during the period 1941–47 and 10–50 mg/m³ during the 1950s and early 1960s, with occasional peaks above the odour threshold of 1300 mg/m³. After manufacture of ethylene oxide was stopped in this company in 1963, exposure to 1–10 mg/m³ (with occasional higher values) continued to occur because of its use in the manufacture of other compounds (Högstedt *et al.*, 1979a).

At a plant in Germany where ethylene oxide was manufactured, 2-h area samples taken in 1978–79 contained less than 5 ppm [9 mg/m³] under normal working conditions. Concentrations rose to 1900 ppm [3400 mg/m³] for several minutes in exceptional cases during plant breakdown (Thiess *et al.*, 1981).

The typical average daily exposures of workers in a 1979 survey of plants in the USA where ethylene oxide was manufactured and used were 0.3–4 ppm [0.5–7.3 mg/m³]; worst-case peak exposures of maintenance workers were up to 9600 ppm [17 300 mg/m³] for less than 1 min (Flores, 1983).

In one chemical manufacturing complex in the USA, yearly time-weighted average (TWA) exposures to ethylene oxide in 1977–80 were reported to have been below 1 ppm [1.8 mg/m³] in all jobs except loading, during which technicians were exposed to up to 1.7 ppm [3 mg/m³] yearly and 5.7 ppm [10 mg/m³] individually. Peak exposures were usually < 20 ppm [< 36 mg/m³], except in loading, during which concentrations of up to 235 ppm [420 mg/m³] were reported (Currier *et al.*, 1984).

In an ethylene oxide manufacturing plant in the Netherlands, geometric mean concentrations in 8-h personal samples were calculated to be < 0.01 ppm [< 0.02 mg/m³] in 1974, 1978 and 1980 and 0.12 ppm [0.2 mg/m³] in 1981; individual values ranged from not detected (< 0.05 ppm [< 0.1 mg/m³]) to 8 ppm [14 mg/m³] (van Sittert *et al.*, 1985).

At another plant in Sweden where ethylene oxide was produced by oxygenation of ethylene, the 8-h TWA exposure to ethylene oxide was 9–15 mg/m³ [5–8 ppm] in 1963–

76 and 2–4 mg/m³ [1–2 ppm] in 1977–82 during the production of ethylene oxide and ethylene glycol, 6 mg/m³ [3 ppm] in 1963–76 and 2 mg/m³ [1 ppm] in 1977–82 during the processing of ethylene oxide and 2–6 mg/m³ [1–3 ppm] in 1963–76 and 1–3 mg/m³ [0.6–1.7 ppm] in 1977–82 during maintenance and technical service work. Certain workers in each category were reported to have had higher exposures (up to 600–1800 mg/m³ [333–1000 ppm]) during periods of minutes (Högstedt *et al.*, 1986).

In former Czechoslovakia, the 8-h TWA concentrations of ethylene oxide measured in 1982–84 in the working environment of an ethylene oxide production plant were 0–8.25 mg/m³ [4.6 ppm] (Karelová *et al.*, 1987).

Under the sponsorship of the Chemical Manufacturers' Association, company data were collected on current exposures to ethylene oxide of workers in 11 ethylene oxide production units and 24 ethoxylation units in the USA in 1987 (Table 2). Respirators were reported to be used in specific operations, such as rail car loading and unloading, maintenance and product sampling, during which engineering controls are not feasible (Heiden Associates, 1988a).

Table 2. Exposure of workers to ethylene oxide by type of unit and job category in the chemical manufacturing industry in the USA, 1987

Unit and job category	No. of samples	8-h TWA (mg/m ³)		No. of samples	Short-term (10–150 min) exposure (mg/m ³)	
		Mean ^a	Range		Mean ^a	Range
Ethylene oxide production						
Production workers	402	0.7	0.11–3.2	171	7.7	1.62–19.8
Maintenance workers	439	1.3	0.14–5.6	59	19.6	0.20–35.3
Supervisors	123	0.2	0.04–0.18	3	1.3	1.3–1.4
Distribution workers	218	2.9	0.36–6.8	111	11.7	3.6–17.6
Laboratory workers	189	0.7	0.12–4.3	39	1.4	0.4–2.2
Other workers	97	0.2	0.05–0.72			
Ethoxylation						
Production workers	640	0.4	0.12–1.26	172	2.0	0.02–9.9
Maintenance workers	191	1.1	0.02–4.7	56	13.3	0.11–54.9
Supervisors	54	0.4	0.05–0.72	5	8.6	0.9–23.8
Distribution workers	105	0.7	0.20–2.7	100	3.4	0.9–21.6
Laboratory workers	52	0.4	0.02–0.9	19	5.0	0.4–11.0
Other workers	24	0.4	0.18–0.54			

Adapted from Heiden Associates (1988a)

TWA, time-weighted average

^a Weighted by number of workers exposed

Gardner *et al.* (1989) reported that monitoring since 1977 in four British plants where ethylene oxide and derivatives were produced indicated average exposures to less than

5 ppm [9 mg/m³] in almost all jobs and to < 1 ppm [1.8 mg/m³] in many jobs; occasional peaks up to several hundred parts per million occurred as a result of operating difficulties. In earlier years, peak exposures above the odour threshold of 700 ppm [1260 mg/m³] were reported.

In industries in which ethylene oxide and its derivatives are manufactured, exposure to a large variety of chemicals other than ethylene oxide may occur, depending on the types of process and job. These include unsaturated aliphatic hydrocarbons (e.g. ethylene, propylene; see IARC, 1994), other epoxides (e.g. propylene oxide; see IARC, 1994), chlorohydrins (e.g. epichlorohydrin; see IARC, 1999a; and ethylene chlorohydrin), chlorinated aliphatic hydrocarbons (e.g. dichloromethane, dichloroethane; see IARC, 1999a), glycols and ethers (e.g. ethylene glycol, glycol ethers, bis(2-chloroethyl)ether; see IARC, 1999a, 2006), aldehydes (e.g. formaldehyde; see IARC, 2006), amines (e.g. aniline; see IARC, 1987), aromatic hydrocarbons (e.g. benzene, styrene; see IARC, 1987), alkyl sulfates and other compounds (Shore *et al.*, 1993).

(b) *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 (e.g. surgical products, single-use medical devices), disposable health care products, pharmaceutical and veterinary products, spices and animal feed.

In an extensive survey of the industry in the USA conducted by the National Institute for Occupational Safety and Health, exposure to ethylene oxide was estimated on the basis of data collected in 1976–85 by 21 of 36 companies, most of which were involved in the sterilization of medical supplies and spices. Individual 8-h TWA concentrations of samples collected by active sampling on charcoal tubes in the personal breathing zones of workers were included in a model in which regression analysis was used to link exposure concentrations to seven significant variables: year of operation, volume of sterilizer or treatment vessel, period since the product was sterilized, product type, aeration procedure, presence of a rear exhaust valve in the sterilizer and exposure category (sterilizer, chamber area, maintenance, production, warehouse, clean room, quarantine and laboratory) (Greife *et al.*, 1988; Stayner *et al.*, 1993; Hornung *et al.*, 1994). When the model was applied in a cohort study to the job histories of exposed workers in 13 of the companies surveyed, the estimated historical average concentrations ranged from 0.05 to 77.2 ppm [0.1–139 mg/m³], with a mean of 5.5 ppm [9.9 mg/m³] and a median of 3.2 ppm [5.8 mg/m³] (Stayner *et al.*, 1993). Wong and Trent (1993) used the industrial hygiene data from the same companies and estimated that sterilizer operators were exposed to an 8-h TWA concentration of 16 ppm [29 mg/m³] before 1978 and of 4–5 ppm [7–9 mg/m³] after 1978, while production workers were exposed to about 5 ppm [9 mg/m³] before 1978 and 2 ppm [3.6 mg/m³] after that year.

In a Swedish factory where hospital equipment was sterilized, area samples taken in 1977 in the storage area showed concentrations of ethylene oxide that ranged from 2 to 70 ppm [3.6–126 mg/m³]; the 8-h TWA concentration in the breathing zone of workers in

the same area was 20 ppm [36 mg/m³] (Högstedt *et al.*, 1979b). In 1978, full-shift personal sampling indicated that sterilizing room operators had an exposure concentration of 2.4 ppm [4.3 mg/m³]; area sampling indicated an exposure of 1.3 ppm [2.3 mg/m³]. Personal sampling showed a concentration of 0.1 ppm [0.2 mg/m³] in the packing room, and area sampling showed a concentration of 0.8 ppm [1.4 mg/m³] in the stockroom (Högstedt *et al.*, 1983). In another Swedish study, sterilization workers and a laboratory technician in the production of disposable medical equipment were reported to have been exposed to bursts of ethylene oxide at concentrations of 5–10 ppm [9–18 mg/m³] for a total of 1 h per working day, while packers were exposed at an average of 0.5–1 ppm [1–2 mg/m³] for the entire week (Pero *et al.*, 1981). Sterilization workers, packers and truck drivers at another Swedish factory, where single-use medical equipment was produced, were reported to be exposed to an 8-h TWA concentration of 0.5–1 ppm [1–2 mg/m³] (Pero *et al.*, 1982). In two Swedish disposable medical equipment plants, sterilizers and packers were the most heavily exposed, but levels decreased steadily from 35–40 ppm [about 70 mg/m³] in 1970 to < 0.2–0.75 ppm [< 1.5 mg/m³] in 1985; the average levels of exposure of store workers and development engineers decreased from 5–20 ppm [9–36 mg/m³] to < 0.2 ppm [< 0.4 mg/m³] in the same period, while those of people in other job categories (repairmen, laboratory technicians, controllers and foremen) decreased from 1–4 ppm [2–7 mg/m³] to < 0.2 ppm [< 0.4 mg/m³] (Hagmar *et al.*, 1991).

Engineering controls and new work practices designed to lower the exposure of workers to ethylene oxide were generally adopted in the USA in 1978 and 1979 (Steenland *et al.*, 1991). Stolley *et al.* (1984) estimated that the 8-h TWA concentrations of sterilizer operators in three facilities in the USA before 1980 had been 0.5, 5–10 and 5–20 ppm [1, 9–18 and 9–36 mg/m³], while data collected in the two plants that were still operating in 1980–82 indicated concentrations of less than 1 ppm [2 mg/m³].

In Belgium, 12 workers involved in industrial sterilization in three plants were exposed to 8-h TWA concentrations of 0.1–9.3 ppm [0.2–16.7 mg/m³], with averages in each plant of 1.7, 3.7 and 4.5 ppm [3.1, 6.7 and 8.1 mg/m³] (Wolfs *et al.*, 1983).

In a plant in eastern Germany where disposable medical equipment was sterilized, workers were found to have been exposed to an average concentration of about 60 mg/m³ [27.1 ppm] in 1985 and about 30 mg/m³ [13.6 ppm] from 1989 onwards (Tates *et al.*, 1991).

Under the sponsorship of the Health Industry Manufacturers' Association, company data were collected in 1987 on current exposures to ethylene oxide of workers in 71 facilities in the USA where medical devices and diagnostic products were sterilized. The workers included sterilizer operators, maintenance workers, supervisors, warehouse workers, laboratory workers and quality control personnel. Respirators were reported to be used in specific operations, such as unloading the sterilizer, maintenance, quality control sampling, emergencies, loading aeration, and changing ethylene oxide bottles, cylinders and tanks. Concentrations were measured outside the respirators. The routine 8-h TWA concentration that occurred 2 or more days per week was > 1 ppm [> 1.8 mg/m³] for 12.6% of workers, 0.5–1 ppm [0.9–1.8 mg/m³] for 13.9%, 0.3–0.5 ppm

[0.5–0.9 mg/m³] for 26.7% and < 0.3 ppm [$< 0.5 \text{ mg/m}^3$] for 46.8%. Short-term sampling (for 5–120 min; average, 28 min; except in one factory where sampling was for 210 min for workers in other jobs) showed routine short-term exposures of > 10 ppm [$> 18 \text{ mg/m}^3$] for 10.7% of workers, 5–10 ppm [9–18 mg/m³] for 17.1% and < 5 ppm [$< 9 \text{ mg/m}^3$] for 72.2%. Non-routine short-term exposure that occurred 1 day per week or near areas where there was exposure was > 10 ppm [$> 18 \text{ mg/m}^3$] for 5.1% of workers, 5–10 ppm [9–18 mg/m³] for 2.6% and < 5 ppm [$< 9 \text{ mg/m}^3$] for 92.3% (Heiden Associates, 1988b).

At a commercial sterilization operation in the USA, workers were exposed to 8-h TWA concentrations of 1–10 ppm [1.8–18 mg/m³] in 1993–2001 and to 1.3–2.4 ppm [2.3–4.3 mg/m³] in 2002, according to measurements carried out by the employer. The Occupational Safety and Health Administration monitored personal exposures in the same workplace and found 8-h TWA concentrations of 0.6–9.3 ppm [1.1–17 mg/m³]. After improvement of working conditions, 8-h TWA concentrations of 0.2–1.2 ppm [0.4–2.2 mg/m³] were found during follow-ups (Daniel *et al.*, 2004).

Exposures in 10 factories in Taiwan (China) that used ethylene oxide as a sterilant in the manufacture of medical supplies were measured in 2005 (Chien *et al.*, 2007). Sterilizer operators had an average short-term exposure level of 27.6 ppm [50 mg/m³] during unloading of the sterilizer, and the mean 8-h TWA exposure was 7.4 ppm [13 mg/m³]. High concentrations were measured particularly in the aeration area, near the sterilizer and in the warehouse. Increasing the number of post-sterilization purge cycles and improvements to ventilation in the aeration area and warehouse decreased the average short-term exposures to 55% of the earlier values.

Other substances to which workers involved in the sterilization of medical products may be exposed include gases that are present with ethylene oxide in the sterilizing mixture, such as chlorofluorocarbons and carbon dioxide (Heiden Associates, 1988b), and methyl formate in Sweden (Hagmar *et al.*, 1991).

(c) *Use of ethylene oxide in hospitals*

Ethylene oxide is used widely in hospitals as a gaseous sterilant for heat-sensitive medical items, surgical instruments and other objects and fluids that come into contact with biological tissues. The National Institute for Occupational Safety and Health estimated that there were more than 10 000 sterilizers in use in health care facilities in the USA in 1977. Large sterilizers are found in central supply areas of most hospitals, and smaller sterilizers are found in clinics, operating rooms, tissue banks and research facilities (Glaser, 1979).

Exposure to ethylene oxide may result during any of the following operations and conditions: changing pressurized ethylene oxide gas cylinders; leaking valves, fittings and piping; leaking sterilizer door gaskets; opening the sterilizer door at the end of a cycle; improper ventilation at the sterilizer door; improperly ventilated 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

or working in the same room as sterilizers and aerators during operation (Mortimer & Kercher, 1989).

Levels of exposure to ethylene oxide in hospitals are summarized in Table 3.

The National Institute for Occupational Safety and Health conducted a series of studies between 1977 and 1990 to document the exposure to ethylene oxide of hospital sterilization staff in the USA. The main results are summarized in Table 4. The more recent studies from Japan and France (see Table 3) suggest that 8-h TWA concentrations are often $< 1 \text{ mg/m}^3$ [0.6 ppm] in hospitals.

From 1984 to 2001, a total of 256 666 ethylene oxide samples were analysed by a major vendor of passive ethylene oxide monitoring devices in the USA. Most of the measurements (86%) were taken in hospitals. Workshift measurements were taken from 28 373 hospital workers in 2265 hospitals and short-term measurements from 18 894 workers in 1735 hospitals. The percentage of hospitals in which the 8-h TWA exposure limit of 1 ppm [1.8 mg/m^3] was exceeded once or more times in a year decreased from 21% in 1988 to 0.9% in 2001 (La Montagne *et al.*, 2004).

In most studies, exposure to ethylene oxide appears to result mainly from peak emissions during operations such as opening the door of the sterilizer and unloading and transferring sterilized material. Proper engineering controls and work practices have been reported to result in full-shift exposure levels of less than 0.1 ppm [0.18 mg/m^3] and short-term exposure levels of less than 2 ppm [3.6 mg/m^3] (Mortimer & Kercher, 1989). In a survey of 125 hospitals in the USA, however, use of personal protective equipment was found to be limited to the wearing of various types of gloves while transferring sterilized items. No respirators were used (Elliott *et al.*, 1988).

In a unit in Argentina that was equipped with old gas sterilizers with no mechanical ventilation, the 8-h TWA concentration of ethylene oxide was 60–69 ppm [$108\text{--}124 \text{ mg/m}^3$] (Lerda & Rizzi, 1992).

Other substances to which sterilizer operators in hospitals may be exposed include other gases present in the sterilizing mixture such as chlorofluorocarbons (see IARC, 1999a; banned by the Montreal Protocol in 1989) and carbon dioxide (Wolfs *et al.*, 1983; Deschamps *et al.*, 1989). Some operating room personnel exposed to ethylene oxide may also be exposed to anaesthetic gases and X-rays (Sarto *et al.*, 1984a; see IARC, 2000; Chessor *et al.*, 2005), and some may have occasional exposure to low concentrations of formaldehyde (Gardner *et al.*, 1989; see IARC, 2006).

(d) Other uses

In a wastewater treatment plant in the USA, ethylene oxide was used as a reaction chemical to modify starch in the starch processing area; in this area, full-shift personal breathing zone concentrations ranged from undetectable to 0.43 mg/m^3 [0.24 ppm] for operators and from undetectable to 2.5 mg/m^3 [1.4 ppm] for mechanics (McCammon *et al.*, 1990).

Table 3. Concentrations of ethylene oxide observed in hospitals in various countries

Reference	Country	Year of sampling	No. of sites	Job or operation	Duration of sampling	No. of samples	Concentration (mg/m ³)					
							Range	Mean				
Hemminki <i>et al.</i> (1982)	Finland	1981	24	Sterilizer operators	8-h TWA	NR	0.2–0.0					
					Peaks	NR	≤ 450					
					Sterilizing chamber open	20 min	NR	9–18				
Mouilleseaux <i>et al.</i> (1983)	France	NR	4 ^a	Loading, sterilizing, unloading, aerating; area sampling	Few minutes 6–8-h TWA	270 14	0.9–414 0.1–9					
Wolfs <i>et al.</i> (1983)	Belgium	NR	3 1 1	Sterilizer operators	8-h TWA	28	0.4–4.5	0.5–2.9				
				Sterilizer operators; leaking equipment	8-h TWA	16	0.5–32.9	14.0				
				Sterilizer operators; box sterilizer with capsules	8-h TWA	5	16.2–95.2	27.0				
Hansen <i>et al.</i> (1984)	USA	NR	1			14 17 13	< 0.13–7.7 < 4.3–81 4–1430					
				Sarto <i>et al.</i> (1984a,b)	Italy	NR	6	Old sterilizers				
								Opening sterilizer; area sampling	5 min	NR	23–288	113
One sterilization cycle; personal sampling	Variable	NR	6.7–63.9					28.4				
Standard working day; personal sampling	8-h TWA	19 subjects	6.7–36					19.3				
Second-generation sterilizers												
Opening sterilizer; area sampling	5 min	NR	9–47					15.5				
One sterilization cycle; personal sampling	Variable	NR	0.5–4.7	2.0								
Standard working day; personal sampling	8-h TWA	NR	0.4–0.9	0.63								

Table 3 (contd)

Reference	Country	Year of sampling	No. of sites	Job or operation	Duration of sampling	No. of samples	Concentration (mg/m ³)	
							Range	Mean
Brugnone <i>et al.</i> (1985)	Italy	NR	1	Sterilization workers	8-h TWA	10 subjects	1.90–4.71	
Karelová <i>et al.</i> (1987)	Former Czechoslovakia	1984		Sterilization workers; area sampling	8-h TWA	NR	0–4.8	
Sarto <i>et al.</i> (1987)	Italy	NR	1	Sterilizer workers Helpers	7–8-h TWA 7–8-h TWA	4 subjects 4 subjects	11.5–16.7 6.8–9.0	14.3 7.7
Deschamps <i>et al.</i> (1989)	France	1983–86	5	Opening sterilizer and handling sterilized material; personal samples	2.5–102 min	10	0.4–70	
Mayer <i>et al.</i> (1991)	USA	1985–86 1987 1988	1	Sterilizer operators; personal samples	8-h TWA	34 subjects NR 31	≤ 4.3 < 1.8 < 0.18	
Sarto <i>et al.</i> (1991)	Italy	NR	1	Sterilization workers Preparation workers	6.5-h TWA 6.5-h TWA	5 subjects 5 subjects	0.68 ^b 0.045	
Schulte <i>et al.</i> (1992)	Mexico	NR	1	Sterilizer operators	8-h TWA	22 subjects	0–2.4	
Koda <i>et al.</i> (1999)	Japan	NR	2	Central supply division Working area (hospital A) Near sterilizer (hospital A) Working area (hospital B) Near sterilizer (hospital B)		322 322 298 35	0.2–1.1 0.2–1.1 0.5–1.4 2.0–2.3	0.7 0.5 0.9 2.2

Table 3 (contd)

Reference	Country	Year of sampling	No. of sites	Job or operation	Duration of sampling	No. of samples	Concentration (mg/m ³)	
							Range	Mean
Sobaszek <i>et al.</i> (1999)	France	1988–95	2	Sterilization sites				
				Unloading; area samples	8-h TWA	5	0.05–0.72	
				Unloading; personal samples	14–34 min	5	0.09–11.1	
				Bottle changing; personal samples	7–9 min	5	0.18–162	
Hori <i>et al.</i> (2002)	Japan	NR	6	Sterilization, one laundry				
				Area samples	8-h TWA	37	< 0.05–10.3	
					Personal samples	NR	37	< 0.05–0.49
	USA	NR	9	Sterilizer operators	8-h TWA	51 subjects	0–0.54	

NR, not reported; TWA, time-weighted average

^a One was a municipal sterilization and disinfection facility.

^b All samples had the same concentration.

Table 4. Exposure of hospital sterilizer operators to ethylene oxide (personal samples) in studies conducted by the National Institute for Occupational Safety and Health, in the USA, 1977–90

Reference	Period of measurements	No. of hospitals	Operation or conditions	Duration of sampling	No. of samples	Concentration (mg/m ³)
Kercher & Mortimer (1987)	NR	1	Before installation of controls (1984)	Full-shift TWA	NR	[0.43] (average)
				Short-term (15–20 min)	NR	[3.4] (average)
				Short-term (1–2 min)	NR	[4.3] (average)
			After installation of controls (1985)	Full-shift TWA	NR	[< 0.1] (average)
				Short-term (15–20 min)	NR	[< 0.4] (average)
				Short-term (1–2 min)	NR	[1]
Boeniger (1988a)	1987	1	Decontamination room	8-h TWA	2	[0.58–0.77]
			Sterile room	8-h TWA	6	[0.02–1.37]
Boeniger (1988b)	1987	1	Full shift	4–7 h TWA	8	[0.04–0.40]
			Cracking sterilizer door open	30 sec	6	[< 0.05–7.7]
			Transferring load to aerator	30 sec	15	[0.23–18.9]
Elliott <i>et al.</i> (1988)	[1984–85]	12	Good engineering controls and good work practice	8-h TWA	4	ND
				Short-term (2–30 min)	3	ND
			Good engineering controls and poor work practice	8-h TWA	15	[ND–0.29]
				Short-term (2–30 min)	19	[ND–5.4]
			No engineering controls and good work practices	8-h TWA	14	[ND–0.83]
				Short-term (2–30 min)	4	[0.43–7.2]
No engineering controls and poor work practices	8-h TWA	24	[ND–8.3]			
	Short-term (2–30 min)	8	[0.43–186]			
Mortimer & Kercher (1989)	1984–86	8		Full-shift TWA (6–8 h)	50	[ND–0.5]
				Short-term (1–30 min)	59	[ND–10.4]
Newman & Freund (1989)	1988	1		8-h TWA	8	[< 0.02]
Shults & Seitz (1992)	1991	1		6–8-h TWA	3	[< 0.02]

ND, not detected; NR, not reported; TWA, time-weighted average

1.3.3 *Environmental occurrence*

Most ethylene oxide is released into the atmosphere (WHO, 2003). Ethylene oxide degrades in the atmosphere by reaction with photochemically produced hydroxyl radicals. The half-life of ethylene oxide in the atmosphere, assuming ambient concentrations of 5×10^5 hydroxy radicals/cm³, is 211 days. Data suggest that neither rain nor absorption into aqueous aerosols remove ethylene oxide from the atmosphere (National Library of Medicine, 2005).

Releases of ethylene oxide (excluding sterilization) into the environment in Canada totalled 23 tonnes in 1996. The industry sectors that reported data were plastics and synthetics (0.24 tonnes), inorganic chemicals (6.1 tonnes), industrial organic chemicals (8.7 tonnes) and soap and cleaning compounds (8.0 tonnes) (WHO, 2003). An additional 3.0 tonnes per year are estimated to be released from the servicing of medical facilities that use ethylene oxide in sterilization processes and commercial sterilization operations (WHO, 2003). By 1997, the emissions had been reduced by 82% from the 1993 levels.

Emissions of ethylene oxide reported to the Environmental Protection Agency by industrial facilities in the USA declined from approximately 2900 tonnes in 1987 to 835 tonnes in 1991 and 135.3 tonnes in 2005 (National Library of Medicine, 2006). Ethylene oxide is one of the 33 hazardous urban air pollutants identified as those that pose the greatest threat to human health in the largest number of urban areas (Environmental Protection Agency, 2000).

In California, USA, concentrations of ethylene oxide in outdoor air were < 0.001–0.96 mg/m³ (128 samples) in Los Angeles, 0.032–0.40 µg/m³ [0.018–0.22 ppb] (36 samples) in northern California and 0.03–0.36 µg/m³ [0.017–0.20 ppb] in a remote coastal location (Havlicek *et al.*, 1992).

Three of 50 24-h air samples collected outside randomly selected residences in Alberta, Ontario and Nova Scotia in Canada contained 3.7–4.9 µg/m³ ethylene oxide. Ethylene oxide was detected in only one sample (4 µg/m³) taken inside these 50 residences. The limit of detection was 0.19 µg/m³ (WHO, 2003).

1.3.4 *Other occurrence*

Food products, including herbs, spices, nuts, cocoa beans, cocoa, cocoa cake, raisins, dried vegetables and gums, were often treated with ethylene oxide in the 1980s. Of 204 food products from retail shops in Denmark that were examined for ethylene oxide residues in 1985, 96 samples were found to have concentrations of ethylene oxide that ranged from 0.05 to 1800 mg/kg. The food products surveyed included herbs and spices (14–580 mg/kg), dairy products (0.06–4.2 mg/kg), pickled fish (0.08–2.0 mg/kg), meat (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 1800 mg/kg). In a follow-up survey of 59 honey samples, no ethylene oxide residue was detected (Jensen, 1988).

A total of 200 samples of spices that are known to be consumed commonly without cooking (e.g. pepper, cinnamon/cassia, chilli, curry powder and paprika) were taken from

wholesalers and retailers in New Zealand in 1999. Only two samples of cinnamon contained detectable amounts (limit of detection, 2 mg/kg) of ethylene oxide (6 and 15 mg/kg). Ethylene oxide intake, based on average spice consumption in New Zealand, was estimated to be 0.21 µg per person per day (conservative estimate) (Fowles *et al.*, 2001).

Ethylene oxide occurs as a contaminant of skin care products because current commercial preparations of polyglycol ethers may contain ethylene oxide monomer residues of up to 1 ppm (Filser *et al.*, 1994). This is in line with a study in which skin care products were reported to contain 0.08–1.5 mg/L ethylene oxide (Kreuzer, 1992).

Ethylene oxide is formed during the combustion of fossil fuel, but the amount is expected to be negligible (WHO, 2003).

Mainstream tobacco smoke contains 7 µg/cigarette ethylene oxide (IARC, 2004).

Patients may be exposed during dialysis when the equipment has been sterilized with ethylene oxide (IPCS-CEC, 2001).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for ethylene oxide in a number of countries, regions or organizations are presented in Table 5.

A tolerance of 50 ppm (mg/kg) has been established in the USA for residues of ethylene oxide when used as a post-harvest fumigant in or on raw black walnut meats, copra and whole spices (Environmental Protection Agency, 1992a). Ethylene oxide, either alone or with carbon dioxide or dichlorodifluoromethane, is permitted in the USA as a fumigant for the control of micro-organisms and insect infestation in ground spices and other processed natural seasoning materials, except mixtures to which salt has been added. Residues of ethylene oxide in ground spices must not exceed the established tolerance of 50 ppm (mg/kg) in whole spices (Environmental Protection Agency, 1992b).

Table 5. Occupational exposure limits and guidelines for ethylene oxide

Country/region or organization	TWA (ppm) ^a	STEL (ppm) ^a	Carcinogenicity ^b	Notes
Australia	1		2	
Belgium	1		Ca	
Brazil	39			
Canada,				
British Columbia	0.1	1	1	ALARA; skin Recirculation prohibited
Quebec	1		A2	
China (mg/m ³)	2	5		STEL based on ultra limit coefficient
China, Hong Kong SAR	1		A2	

Table 5 (contd)

Country/region or organization	TWA (ppm) ^a	STEL (ppm) ^a	Carcinogenicity ^b	Notes
China (Province of Taiwan)	1	2		
Czech Republic (mg/m ³)	1	3		Skin
Finland	1			
France	1.8			
Germany	1 (TRK)		2 (MAK)	Skin
Ireland	5		Ca2	
Japan-JSOH	1		1	Skin sensitizer-2
Malaysia	1			
Mexico	1		A2	
Netherlands (mg/m ³)	0.84		Ca	
New Zealand	1		A2	
Norway	1		Ca	
Poland (mg/m ³)	1	3	Ca	
Romania	1			
South Africa-DOL CL	5			
Spain	1		Ca2	
Sweden	1	5	Ca	Skin
United Kingdom	5		R45	
USA				
ACGIH	1		A2	
NIOSH REL	0.1	5	Ca	Per day
OSHA PEL	1	5 (ceiling)	Ca	

From ACGIH[®] Worldwide (2005); SZW (2006); Chien *et al.* (2007)

ACGIH, American Conference of Governmental Industrial Hygienists; ALARA, as low as reasonably achievable; DOL CL, Department of Labour ceiling limits; JSOH, Japanese Society of Occupational Health; MAK, maximum allowed concentration; NIOSH, National Institute of Occupational Safety and Health; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; STEL, short-term exposure limit; TRK, technical guidance concentration; TWA, time-weighted average

^a Unless otherwise specified

^b 2 (Australia), probable human carcinogen; 2 (Germany), considered to be carcinogenic to humans; Ca (except Norway), carcinogen/substance is carcinogenic; Ca (Norway), potential cancer-causing agent; 1, substance which causes cancer in humans/carcinogenic to humans; A2, suspected human carcinogen/carcinogenicity suspected in humans; Ca2, suspected human carcinogen; R45, may cause cancer