

# ETHYLENE OXIDE

Ethylene oxide was considered by previous IARC Working Groups in 1976, 1984, 1987, 1994, and 2007 ([IARC, 1976, 1985, 1987, 1994, 2008](#)). Since that time new data have become available, which have been incorporated in this *Monograph*, and taken into consideration in the present evaluation.

## 1. Exposure Data

### 1.1 Identification of the agent

From [IARC \(2008\)](#), unless indicated otherwise

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

*Chem. Abstr. Serv. Name:* Oxirane

*Synonyms:* 1,2-Epoxyethane



$C_2H_4O$

Relative molecular mass: 44.06

*Description:* Colourless, flammable gas ([O'Neill, 2006](#))

*Boiling-point:* 10.6 °C ([Lide, 2008](#))

*Solubility:* Soluble in water, acetone, benzene, diethyl ether, and ethanol ([Lide, 2008](#))

*Conversion factor:*  $mg/m^3 = 1.80 \times ppm$ ; calculated from:  $mg/m^3 = (\text{relative molecular weight}/24.45) \times ppm$ , assuming standard temperature (25 °C) and pressure (101.3 kPa).

### 1.2 Uses

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. More than half of the ethylene oxide produced worldwide is used in the manufacture of mono-ethylene glycol. Conversion of ethylene oxide to ethylene glycols represents a major use for ethylene oxide in most regions: North America (65%), western Europe (44%), Japan (63%), China (68%), Other Asia (94%), and the Middle East (99%). Important derivatives of ethylene oxide include di-ethylene glycol, tri-ethylene glycol, poly(ethylene) glycols, ethylene glycol ethers, ethanol-amines, and ethoxylation products of fatty alcohols, fatty amines, alkyl phenols, cellulose and poly(propylene) glycol ([Occupational Safety and Health Administration, 2005](#); [Devanney, 2010](#)).

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](#)). It is used 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 Human exposure

### 1.3.1 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 ([IARC, 2008](#)).

CAREX (CARcinogen EXposure) is an international information system on occupational exposure to known and suspected carcinogens, with data collected from 1990 to 1993 in the European Union (EU). The CAREX database provides selected exposure data and documented estimates of the number of exposed workers by country, carcinogen, and industry ([Kauppinen et al., 2000](#)). [Table 1.1](#) presents the results for ethylene oxide for the top-10 industries in the EU ([CAREX, 1999](#)). From the US National Occupational Exposure Survey (1981–1983), it was estimated that approximately 270 000 workers (including approximately 120 000 women) in the USA were potentially exposed to ethylene oxide ([NIOSH, 1990](#)).

More recent data on employment in the industrial sectors that use ethylene oxide have been published by the US [Occupational Safety and Health Administration \(2005\)](#). Estimated employment figures were: 1100 ethylene oxide-production workers, 4000 ethoxylators, who use ethylene oxide to make chemical derivatives, and 40 000 workers using ethylene oxide as a sterilant or fumigant in hospitals. In addition, approximately 2700 workers were employed in commercial sterilization by manufacturers of medical and pharmaceutical products and producers of food spices, as contract sterilizers, and in other

**Table 1.1 Estimated numbers of workers exposed to ethylene oxide in the European Union (top 10 industries)**

Industry, occupational activity	
Medical, dental, other health and veterinary services	22300
Manufacture of other chemical products	5100
Construction	3000
Printing, publishing and allied industries	2400
Manufacture of industrial chemicals	1700
Manufacture of rubber products	1500
Crude petroleum and natural gas production	1100
Manufacture of plastic products, not elsewhere classified	1100
Agriculture and hunting	1000
Manufacture of furniture and fixtures, except primary of	1000
<b>TOTAL</b>	<b>46900</b>

From [CAREX \(1999\)](#)

sterilization and fumigation facilities ([IARC, 2008](#)).

#### (a) Production of ethylene oxide and its derivatives

The *IARC Monographs* Volumes 60 and 97 provide detailed descriptions of studies on historical occupational exposures to ethylene oxide ([IARC, 1994, 2008](#)).

[Table 1.2](#) (available at <http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-23-Table1.2.pdf>) summarizes reported exposure levels in industries where ethylene oxide and its derivatives are manufactured. Exposures vary with job category: workers involved in loading and distribution of ethylene oxide have the highest exposure. Where comparisons over time are possible, exposures appear to have decreased, presumably as control measures have been improved, with the most recent time-weighted average (TWA) values in the range of 1 ppm or less. Exposure to a large variety of chemicals other than ethylene oxide may occur, depending on the types of industrial process and job. These other chemicals include unsaturated aliphatic

hydrocarbons (e.g. ethylene, propylene), other epoxides (e.g. propylene oxide), chlorohydrins (e.g. epichlorohydrin and ethylene chlorohydrin), chlorinated aliphatic hydrocarbons (e.g. dichloromethane, dichloroethane), glycols and ethers (e.g. ethylene glycol, glycol ethers, bis(2-chloroethyl)ether), aldehydes (e.g. formaldehyde), amines (e.g. aniline), aromatic hydrocarbons (e.g. benzene, styrene), 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 items such as medical equipment and products (e.g. surgical instruments, single-use medical devices), disposable health-care products, pharmaceutical and veterinary products, food spices and animal feed (see Table 1.3, available at <http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-23-Table1.3.pdf>). Short-term exposures may be high for some workers. Despite recent reductions in exposure, in some countries and for some job categories high exposures to ethylene oxide may still occur.

Workers involved in the sterilization of medical products may also be exposed to gases that are present with ethylene oxide in the sterilizing mixture, such as chlorofluorocarbons and carbon dioxide (Heiden Associates, 1988), and – in the past – to methyl formate, as reported in a study from Sweden (Hagmar *et al.*, 1991).

(c) *Use of ethylene oxide in hospitals*

Ethylene oxide is widely used in hospitals as a gaseous sterilant for heat-sensitive medical items, surgical instruments and other objects and fluids that come in contact with biological tissues. 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).

The *IARC Monograph Volume 97* (IARC, 2008) summarized levels of exposure to ethylene oxide in hospitals. The more recent studies from Japan and France suggest that the 8-hour TWA concentrations are often below 1 mg/m<sup>3</sup> in hospitals.

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 result in full-shift exposure levels of less than 0.1 ppm [0.18 mg/m<sup>3</sup>] and short-term exposure concentration of less than 2 ppm [3.6 mg/m<sup>3</sup>] (Mortimer & Kercher, 1989). In a survey of 125 hospitals in the USA, however, use of personal protective equipment was found to be limited to wearing gloves while transferring sterilized items, but respirators were not used (Elliott *et al.*, 1988).

As in industrial sterilization facilities, sterilizer operators in hospitals may also be exposed to other gases present in the sterilizing mixture, e.g. chlorofluorocarbons – banned by the Montreal Protocol in 1989 – and carbon dioxide (Wolfs *et al.*, 1983; Deschamps *et al.*, 1989). Some operating-room personnel handling ethylene oxide may also be exposed to anaesthetic gases and X-rays (Sarto *et al.*, 1984a; Chessor *et al.*, 2005), and some may have occasional exposure to low concentrations of formaldehyde (Gardner *et al.*, 1989).

### 1.3.2 Non-occupational exposure

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  $5 \times 10^5$  hydroxyl radicals/cm<sup>3</sup>, was reported to be 211 days. Neither rain nor absorption into aqueous aerosols is capable

of removing ethylene oxide from the atmosphere ([National Library of Medicine, 2005](#)).

Mainstream tobacco smoke contains 7 mg/cigarette ethylene oxide ([IARC, 2004](#)). With the possible exception of cigarette smoke, other non-occupational sources of exposure to ethylene oxide (e.g. residues in spices and other food products ([Jensen, 1988](#); [Fowles et al., 2001](#)) and in skin-care products ([Kreuzer, 1992](#)) are expected to be minor. Ethylene oxide is formed during the combustion of fossil fuel, but the amount is expected to be negligible ([WHO, 2003](#)). Hospital patients may be exposed during dialysis when the equipment has been sterilized with ethylene oxide ([IPCS-CEC, 2001](#)).

## 2. Cancer in Humans

Epidemiological evidence of the risk for human cancer from ethylene oxide derives principally from the follow-up of 14 cohorts of exposed workers, either in chemical plants where ethylene oxide was produced or converted into derivatives, or in facilities where it was used as a sterilant. Many of the workers employed at chemical factories were also exposed to other chemicals. The *IARC Monograph Volume 97* ([IARC, 2008](#)) concluded that there is *limited evidence* in humans for the carcinogenicity of ethylene oxide.

The most informative epidemiological investigation of ethylene oxide and cancer risk was a study by NIOSH of more than 18 000 employees at 14 industrial facilities where ethylene oxide was used to sterilize medical supplies or food spices, or to test the sterilizing equipment ([Steenland et al., 1991](#); [Stayner et al., 1993](#)). This investigation benefited from greater statistical power than did other studies, as a consequence of its large sample size. In addition, there was a lower potential for confounding by concomitant exposure to other chemicals, while detailed quantitative

assessments were made of individual exposures to ethylene oxide. For these reasons, the Working Group gave greatest weight to the findings of this study when assessing the balance of epidemiological evidence on ethylene oxide, although findings from other studies were also taken into account.

### 2.1 Lympho-haematopoietic malignancies

[Steenland et al. \(1991\)](#) reported on the initial mortality results for the NIOSH ethylene-oxide cohort. There were 343 deaths from cancer (380.3 expected; SMR, 0.90; 95%CI: 0.81–1.00). SMRs were not statistically significantly increased for lymphatic and haematopoietic cancers combined (SMR, 1.06; 95%CI: 0.75–1.47), for lymphosarcoma-reticulosarcoma [ICD-9 200] (SMR, 1.52; 95%CI: 0.65–3.00), Hodgkin lymphoma (SMR, 1.14; 95%CI: 0.31–2.92), leukaemia (SMR, 0.97; 95%CI: 0.52–1.67), non-Hodgkin lymphoma [ICD-9 202] (SMR, 1.20; 95%CI: 0.57–2.37) or myeloma (SMR, 0.59; 95%CI: 0.12–1.73). No significant trend in mortality was observed in relation to duration of exposure, but the SMR for leukaemia (1.79, based on five deaths) and non-Hodgkin lymphoma (1.92, based on five deaths) were higher after allowance for a latency of more than 20 years. Among the sterilizer operators, mortality ratios were 2.78 (two deaths observed) for leukaemia and 6.68 (two deaths) for lymphosarcoma/reticulosarcoma. In a further analysis of the same study ([Stayner et al., 1993](#)), an exposure–response analysis was conducted with the use of previously derived quantitative estimates of individual exposure to ethylene oxide ([Greife et al., 1988](#)). Analysis was limited to 13 of the facilities studied, since exposure information at one facility was inadequate. Mortality from lymphatic and haematopoietic cancer was greatest in the group with the highest category of cumulative exposure to ethylene



oxide (> 8500 ppm-days) (13 deaths; SMR, 1.24; 95%CI: 0.66–2.13), but the trend across three categories of cumulative exposure was weak ( $\chi^2$ , 0.97;  $P = 0.32$ ). A similar pattern was observed for non-Hodgkin lymphoma, but not for leukaemia. In addition, a Cox proportional-hazard model was used to examine risk in relation to cumulative exposure (ppm-days), average exposure (ppm), maximal exposure (ppm) and duration of exposure (days) to ethylene oxide. A significant positive trend in risk with increasing cumulative exposure to ethylene oxide was observed for all neoplasms of the lymphatic and haematopoietic tissues [ $P < 0.05$ , two-tailed]. Moreover, this trend was strengthened [ $P < 0.01$ ] when the analysis was restricted to neoplasms of lymphoid-cell origin (lymphocytic leukaemia, ICD-9 204; non-Hodgkin lymphoma, ICD-9 200, 202). The exposure-response relationship between cumulative exposure to ethylene oxide and leukaemia was positive but non-significant [ $P = 0.23$ ]. The regression coefficients for neoplasms of the lymphatic and haematopoietic tissues for duration of exposure, average exposure, and maximal exposure were either weakly positive or negative.

Extending the mortality assessments through 1998, an updated life-table analysis of cancer mortality in the cohort was carried out (Steenland *et al.*, 2004) (see Table 2.1, available at <http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-23-Table2.1.pdf>). There were 860 deaths from cancer overall (SMR, 0.98; 95%CI: 0.92–1.03), and a statistically significant excess was found only for cancer of the bone (SMR, 2.82; 95%CI: 1.23–5.56, based on six observed deaths). In an internal analysis (excluding one small plant for which exposure data were not available), mortality from lymphatic and haematopoietic cancer was associated with log-cumulative exposures to ethylene oxide lagged by 15 years in men ( $p$  for trend = 0.02), but not in women. However, duration of exposure, peak exposure, and average or cumulative exposure did not predict mortality from lymphatic and

haematopoietic cancer. A similar pattern was observed for lymphoid-cell tumours specifically (including non-Hodgkin lymphoma, myeloma and lymphocytic leukaemia), with risks of 3.76 (95%CI: 1.03–13.64;  $p$  for trend = 0.13). [The Working Group noted that the exposure assessment in the Steenland *et al.* (2004) update was limited by the assumption that exposure levels did not change during extended follow-up for about 25% of workers who were exposed at the time of the last actual exposure-data collection. Follow-up taking place long after the period of highest exposure may have attenuated results in the most recent publication.]

A cohort of ethylene oxide-production workers in the Kanawha Valley Union Carbide facility (UC) in West Virginia (USA) was studied by Greenberg *et al.* (1990), Teta *et al.* (1993), and most recently by Swaen *et al.* (2009). The latter report updated the cohort to include 2063 men employed between 1940 and 1988, and updated mortality information through 2003. No indications were found for excess cancer risks from exposure to ethylene oxide, including risks for lympho-haematopoietic malignancies, by SMR analysis. Combining primary data from the NIOSH and UC cohorts Valdez-Flores *et al.* (2010) also reported no excess cancer risks by SMR-based analysis for these cohorts followed respectively to 1998 (Steenland *et al.*, 2004) and 2003 (Swaen *et al.*, 2009). Other cohort studies did not consistently point at an increased risk for specific haematolymphoproliferative malignancies, although moderate elevations of risk were reported in some investigations (see Table 2.1 online).

A meta-analysis on the data available on nearly 33 000 workers from Germany, Italy, Sweden, the United Kingdom and the USA was performed by Teta *et al.* (1999). The meta-SMR for all leukaemia was 1.08 (95%CI: 0.61–1.93, based on 35 deaths); for non-Hodgkin lymphoma it was 1.34 (95%CI: 0.96–1.89, based on 33 deaths).

[The Working Group noted that evaluation of the possible risks for lymphatic and haematopoietic cancer was hampered by inconsistencies in the histopathological classification of diagnoses over time. The interpretation of results for these malignancies was constrained by the diagnostic groupings that had been used by researchers when the studies were conducted.]

## 2.2 Cancer of the breast

Studies from four cohorts of workers exposed to ethylene oxide provided useful information on the association between this exposure and breast cancer (Gardner *et al.*, 1989; Hagmar *et al.*, 1991, 1995; Norman *et al.*, 1995; Steenland *et al.*, 2003, 2004; Coggon *et al.*, 2004; see Table 2.2, available at <http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-23-Table2.2.pdf>). The NIOSH study (Steenland *et al.*, 2004) and a cohort study of hospital-based sterilization workers in the United Kingdom (Gardner *et al.*, 1989; Coggon *et al.*, 2004) examined mortality from breast cancer and found no overall excess risk. Three studies examined the incidence of breast cancer: the NIOSH study (Steenland *et al.*, 2003) and a cohort study from Sweden (Hagmar *et al.*, 1991, 1995) found no overall excess risk, while another cohort study from New York State, USA, found an excess risk of about 60%, which was borderline significant (Norman *et al.*, 1995). Internal analyses with inclusion of questionnaire data were carried out in the NIOSH study (Steenland *et al.*, 2003) showing increased relative risks for breast cancer at the highest level of cumulative exposure to ethylene oxide (> 11620 ppm–days, 15-year lag, OR = 1.87, 95%CI: 1.12–3.10), with a significant exposure–response relationship [*P* for trend = 0.002], after controlling for parity and history of breast cancer in a first-degree relative.

## 2.3 Other cancers

Several cohort studies provided data on exposure to ethylene oxide and mortality from other cancers (stomach, brain, pancreas; see Table 2.2, available at <http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-23-Table2.2.pdf>). There was no consistent evidence of an association of these cancers with exposure to ethylene oxide.

## 2.4 Synthesis

The Working Group found some epidemiological evidence for associations between exposure to ethylene oxide and lymphatic and haematopoietic cancers, and specifically lymphoid tumours (i.e. non-Hodgkin lymphoma, multiple myeloma and chronic lymphocytic leukaemia).

## 3. Cancer in Experimental Animals

Carcinogenicity studies with mice and rats exposed to ethylene oxide by inhalation, oral gavage, and subcutaneous injection were previously reviewed (IARC, 1994, 2008). Results of adequately conducted carcinogenicity studies are summarized in Table 3.1. There have been no additional carcinogenicity studies in animals reported since the previous evaluation in *IARC Monograph Volume 97* (IARC, 2008).

### 3.1 Inhalation exposure

In two inhalation studies in mice, there was an increased incidence of alveolar bronchiolar carcinomas and combined adenomas and carcinomas in male and female B6C3F<sub>1</sub> mice (NTP, 1987) and of lung adenomas in strain A/J female mice (Adkins *et al.*, 1986). Treatment-related increases in lymphomas, Harderian gland

**Table 3.1 Carcinogenicity studies in experimental animals exposed to ethylene oxide by inhalation, oral gavage and subcutaneous injection**

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M) 2 yr <a href="#">Lynch et al. (1984)</a>	Inhalation 0, 50, 100 ppm 7 h/d, 5 d/wk 80/group	Brain <sup>a</sup> : 0/76, 2/77, 5/79 Mononuclear-cell leukaemia 24/77, 38/79, 30/76 Peritoneal mesotheliomas 3/78, 9/79, 21/79	$P < 0.05$ (high dose) $P = 0.03$ (low dose) $P = 0.002$ (high dose)	99.7% purity
Rat, F344 (M) 2 yr <a href="#">Snellings et al. (1984)</a> , <a href="#">Garman et al. (1985, 1986)</a>	Inhalation 0 (control I), 0 (control II), 10, 33, 100 ppm 6 h/d, 5 d/wk 120/group	Brain <sup>b</sup> : 1/181, 0/92, 3/85, 6/87 Mononuclear-cell leukaemia 13/97, 9/51, 12/39, 9/30 Peritoneal mesotheliomas 2/97, 2/51, 4/39, 4/30 Subcutaneous fibromas 3/97, 9/51, 1/39, 11/30	$P < 0.01$ (trend); $P < 0.05$ (high dose) $P < 0.05$ (trend) $P < 0.005$ (trend) $P < 0.001$ (high dose)	> 99.9% purity Two control groups combined. Interim sacrifices at 6 (10 rats), 12 (10 rats), and 18 mo (20 rats). Increased mortality due to viral sialodacryoadenitis at 15 mo. No increases in tumour incidence up to 18 mo. Incidence for all sites other than brain are for rats that died or were sacrificed after 18 mo.
Rat, F344 (F) 2 yr <a href="#">Snellings et al. (1984)</a> , <a href="#">Garman et al. (1985, 1986)</a>	Inhalation 0 (control I), 0 (control II), 10, 33, 100 ppm 6 h/d, 5 d/wk 120/group	Brain <sup>b</sup> 0/187, 1/94, 2/90, 2/78 Mononuclear-cell leukaemia 11/116, 11/54, 14/48, 15/26	$P < 0.05$ (trend) $P < 0.005$ (trend); $P < 0.001$ (high dose)	> 99.9% purity Two control groups combined. Interim sacrifices at 6 (10 rats), 12 (10 rats), and 18 mo (20 rats). Increased mortality due to viral sialodacryoadenitis at 15 mo. No increases in tumour incidence up to 18 mo. Incidence for all sites other than brain are for rats that died or were sacrificed after 18 mo.
Mouse, A/J (F) 6 mo <a href="#">Adkins et al. (1986)</a>	Inhalation 0, 70, 200 ppm 6 h/d, 5d/wk 0, 200 ppm 6 h/d, 5 d/wk 30/group	Lung adenomas 8/30, 16/28, 25/29 Lung adenomas 8/29, 12/28	$[P < 0.001, \text{trend \& high dose}]$ NS	$\geq 99.7\%$ purity Two independent experiments; tumour multiplicities increased for high-dose vs control in both ( $P < 0.05$ ).

Table 3.1 (continued)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F <sub>1</sub> (M) 102 wk <a href="#">NTP (1987)</a>	Inhalation 0, 50, 100 ppm 6 h/d, 5 d/wk 50/group	Lung (alveolar/bronchiolar carcinomas): 6/50, 10/50, 16/50 Lung (alveolar/bronchiolar adenomas and carcinomas combined): 11/50, 19/50, 26/50 Harderian gland cystadenomas 1/43, 9/44, 8/42 <sup>c</sup>	$P = 0.032$ (trend), $P = 0.048$ (high dose) $P = 0.010$ (trend), $P < 0.05$ (high dose) $P < 0.03$ (trend), $P < 0.05$ (low and high dose)	> 99% purity
Mouse, B6C3F <sub>1</sub> (F) 102 wk <a href="#">NTP (1987)</a> , <a href="#">Piccut et al. (2003)</a>	Inhalation 0, 50, 100 ppm 6 h/d, 5 d/wk 50/group	Lung (alveolar/bronchiolar carcinomas): 0/49, 1/48, 7/49 Lung (alveolar/bronchiolar adenomas and carcinomas combined): 2/49, 5/48, 22/49 Harderian gland cystadenomas 1/46, 6/46 <sup>c</sup> , 8/47 Lymphoma: 9/49, 6/48, 22/49 Uterine adenocarcinomas 0/49, 2/47, 5/49 Mammary gland adenocarcinomas or adenosquamous carcinomas 1/49, 8/48, 6/49	$P < 0.05$ (trend), $P < 0.05$ (high dose) $P = 0.023$ (trend), $P < 0.05$ (high dose) $P < 0.03$ (trend) $P \leq 0.02$ (low dose)	> 99% purity
Rat, SD (F) 150 wk <a href="#">Dunkelberg (1982)</a>	Gavage 0 (untreated), 0 (vehicle, salad oil), 7.5, 30.5 mg/kg bw 2x/wk 50/group	Fore-stomach squamous cell carcinomas 0/50, 0/50, 8/50, 29/50	$[P < 0.01, \text{low and high dose}]$	99.7% purity Many of the fore-stomach tumours in the high-dose group metastasized or were locally invasive to other organs.



**Table 3.1 (continued)**

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, NMRI (F) 95 wk <a href="#">Dunkelberg (1981)</a>	Subcutaneous injection 0 (untreated), 0 (vehicle, tricaprylin), 0.1, 0.3, 1.0 mg/injection once/wk 200/group (controls), 100/group	Sarcomas at the injection site: 0/200, 4/200, 5/100, 8/100, 11/100	[ $P < 0.001$ , trend]	99.7% purity

<sup>a</sup> Brain tumours were gliomas; focal proliferation of glial cells (termed 'gliosis') also observed in two low-dose and four high-dose treated rats

<sup>b</sup> Brain tumours included in Table are only gliomas

<sup>c</sup> One cystadenocarcinoma in an animal with cystadenoma  
bw, body weight; d, day or days; F, female; h, hour or hours; M, male; mo, month or months; NS, not significant; wk, week or weeks; yr, year or years

cystadenoma, mammary gland carcinomas and uterine adenocarcinomas were also seen in B6C3F<sub>1</sub> mice (NTP, 1987; Picut *et al.*, 2003).

In two inhalation studies in F344 rats (Lynch *et al.*, 1984; Snellings *et al.*, 1984; Garman, *et al.*, 1985, 1986), there was an increased incidence in gliomas [not further specified], mononuclear cell leukaemia and peritoneal mesotheliomas. A treatment-related increase in subcutaneous fibromas also occurred in male rats (Snellings *et al.*, 1984).

### 3.2 Other routes of exposure

In one study, subcutaneous injection of ethylene oxide in female NMRI mice resulted in a dose-related increase in the incidence of sarcomas at the injection site (Dunkelberg, 1981).

In one study with female Sprague-Dawley rats that received ethylene oxide by gavage, there was a treatment-related increase in fore-stomach squamous-cell carcinomas (Dunkelberg, 1982).

## 4. Other Relevant Data

Experimental studies on ethylene oxide have been evaluated previously in *IARC Monograph* Volumes 60 and 97 (IARC, 1994, 2008). There is an extensive body of data on the mechanism of ethylene oxide-induced carcinogenicity encompassing toxicokinetics, DNA-adduct formation, biomarkers, genotoxicity, and molecular biology. Ethylene oxide is a direct alkylating agent that reacts with nucleophiles without the need for metabolic transformation. It has been shown to have genotoxic and mutagenic activity in numerous assays in both somatic and germ cells, and prokaryotic and eukaryotic organisms (IARC, 1994, 2008). Ethylene oxide is active in a wide range of *in vitro* and *in vivo* systems. Increases in both gene mutations and chromosomal alterations, two general classes

of cancer-related genetic changes, have been observed. The direct reaction of ethylene oxide with DNA is thought to initiate the cascade of genetic and related events that lead to cancer (Svenberg *et al.*, 1990). Thus, formation of DNA adducts and resultant mutations are key steps in the mechanism of carcinogenicity for this agent.

### 4.1 Absorption, distribution, metabolism, and excretion

Ethylene oxide is readily taken up by the lungs and is absorbed relatively efficiently into the blood. A study of workers exposed to ethylene oxide revealed an alveolar retention of 75–80%, calculated from hourly measurements of ethylene oxide in ambient air, which ranged from 0.2 to 24.1 mg/m<sup>3</sup> [0.11–13.2 ppm], and in alveolar air, which ranged from 0.05 to 6 mg/m<sup>3</sup> [0.03–3.3 ppm] (Brugnone *et al.*, 1985, 1986). At steady-state, therefore, 20–25% of inhaled ethylene oxide that reached the alveolar space was exhaled as the unchanged compound and 75–80% was taken up by the body and metabolized. Blood samples taken from workers at four hours after the work-shift gave venous blood/alveolar air coefficients of 12–17 and venous blood/environmental air coefficients of 2.5–3.3.

The mammalian metabolic pathways of ethylene oxide are shown in Fig. 4.1 and can be summarized as follows: Ethylene oxide is converted (*a*) by enzymatic and non-enzymatic hydrolysis to ethylene glycol, which is partly excreted as such and partly metabolized further via glycolaldehyde, glycolic acid and glyoxalic acid to oxalic acid, formic acid and carbon dioxide; and (*b*) by conjugation with glutathione (GSH) followed by further metabolism to *S*-(2-hydroxyethyl)cysteine, *S*-(2-carboxymethyl)cysteine and *N*-acetylated derivatives (*N*-acetyl-*S*-(2-hydroxyethyl)cysteine (also known as *S*-(2-hydroxyethyl)mercapturic acid or HEMA) and *N*-acetyl-*S*-(2-carboxymethyl)cysteine) (Wolfs

[et al., 1983](#); [Popp et al., 1994](#)), which are partly converted to thio-diacetic acid ([Scheick et al., 1997](#)).

Concentrations of ethylene glycol were determined at the end of day 3 of a normal working week in blood samples from sterilization personnel exposed to ethylene oxide. TWA concentrations of ethylene oxide determined over eight hours ranged from 0.3 to 52 ppm [0.55–95.2 mg/m<sup>3</sup>] (overall mean, 4.2 ppm [7.7 mg/m<sup>3</sup>]). The mean concentrations of ethylene glycol in the blood of exposed subjects were twice as high (90 mg/L) as those in controls (45 mg/L) ([Wolfs et al., 1983](#)).

The concentration of thioethers excreted in urine collected at the end of sterilization processes was found to be twice as high in non-smoking personnel (10.2 mmol/mol creatinine) exposed to peak concentrations of 1–200 ppm [1.83–366 mg/m<sup>3</sup>] ethylene oxide as the thioether concentration in unexposed workers (5.46 mmol/mol creatinine). The concentration of ethylene oxide in air was not monitored routinely ([Burgaz et al., 1992](#)).

The glutathione-S-transferase (GST) activity towards ethylene oxide in cytosolic fractions from human livers was low (too low to determine the Michaelis-Menten constant [K<sub>m</sub>] value). The maximum velocity ( $V_{\max}$ ) varied from 7.6 to 10.6 nmol/min/mg protein. Epoxide-hydrolase (EH) activity in the microsomal fraction of human liver averaged 1.8 nmol/min/mg protein. The K<sub>m</sub> for hydrolysis was estimated to be approximately 0.2 mM, but non-enzymatic hydrolysis was considerable and precluded accurate measurement ([Fennell & Brown, 2001](#)).

Metabolism of ethylene oxide to the GSH conjugate and ethylene glycol is generally considered to be the major pathway for the elimination of DNA-reactive ethylene oxide. However, strongly suggestive evidence *in vitro* was presented by [Hengstler et al. \(1994\)](#) that glycolaldehyde is formed by further metabolism of ethylene glycol and that this derivative leads to DNA–protein crosslinks and DNA strand-breaks (as measured

with the alkaline elution assay) after in-vitro incubation with human mononuclear peripheral blood cells.

## 4.2 Genetic and related effects

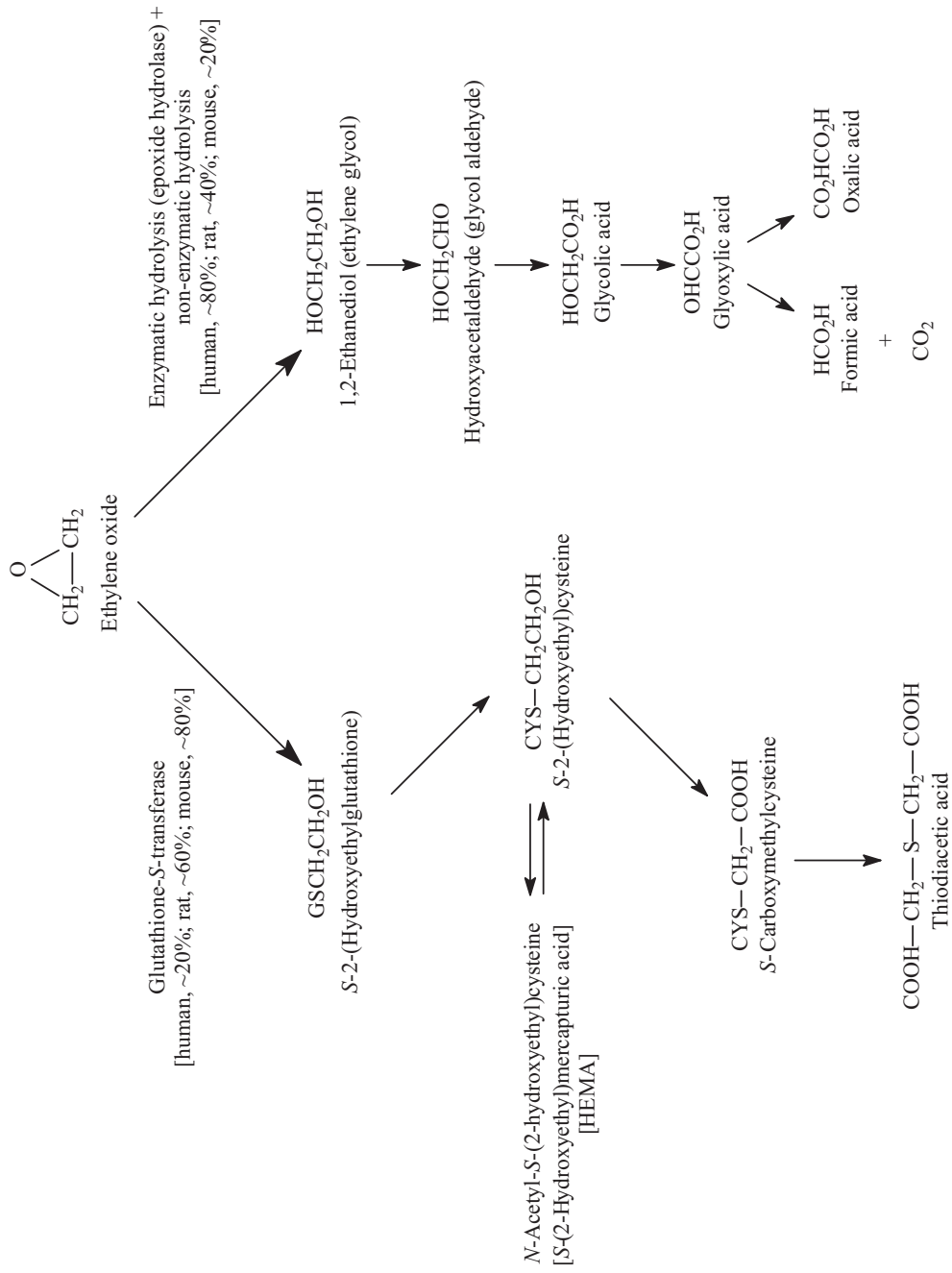
### 4.2.1 GST polymorphisms

Ethylene oxide is a substrate of the GST iso-enzyme T1 ([Hayes et al., 2005](#)). This detoxifying enzyme is polymorphic and a relatively large proportion of the population (about 20% of Caucasians, almost 50% of Asians) has a homozygous deletion (GSTT1-null genotype) ([Bolt & Thier, 2006](#)). As expected, these individuals show a significantly higher amount of hydroxyethyl valine in their haemoglobin due to the presence of endogenous ethylene oxide ([Thier et al., 2001](#)). Nevertheless, the influence of this genetic trait on the formation of this type of adduct as a result of exposure to exogenous ethylene oxide at the workplace is much less clear, as discussed below.

In the cytoplasm of erythrocytes obtained from 36 individuals, ethylene oxide was eliminated three to six times faster in samples from so-called conjugators (defined by a standardized conjugation reaction of methyl bromide and GSH; 75% of the population) than in those from the remaining 25% (who lack this GST-specific activity). In the latter samples, the rate of disappearance did not differ from that of controls. In this experiment, the disappearance of ethylene oxide was investigated in the gas phase, in closed vials that contained GSH and cytoplasm of erythrocytes ([Hallier et al., 1993](#)).

Studies on the genotoxicity of ethylene oxide were reviewed in detail in *IARC Monograph Volume 97* ([IARC, 2008](#)). Studies with peripheral blood of exposed workers have shown that exposure to ethylene oxide is associated with an elevated number of chromosomal aberrations including breaks, gaps, exchanges, and supernumerary chromosomes. An increased frequency

Fig. 4.1 Metabolism of ethylene oxide

Adapted from [Wolfs et al. \(1983\)](#), [Scheick et al. \(1997\)](#)

of sister chromatid exchange (SCE) in the peripheral lymphocytes of workers handling ethylene oxide was also reported.

#### 4.2.2 DNA-adduct formation

In-vitro and in-vivo studies have shown that ethylene oxide can bind to cellular macromolecules, which results in a variety of DNA, RNA and protein adducts. The major DNA adduct recovered *in vivo* is N7-(2-hydroxyethyl) guanine (7-HEG), while some minor adducts such as N3-(2-hydroxyethyl)adenine (3-HEA) and O<sup>6</sup>-(2-hydroxyethyl)guanine (O<sup>6</sup>-HEG), are detected at much lower levels ([Walker et al., 1992](#)). In-vitro studies indicate that other minor adducts can also be formed from the reaction of ethylene oxide with the N1 and N<sup>6</sup> positions of adenine and the N3 position of cytosine, uracil and thymine ([IARC, 1994](#); [Tates et al., 1999](#); [Kolman et al., 2002](#)).

[Tompkins et al. \(2009\)](#) suggested that the mutagenicity and carcinogenicity of ethylene oxide could be attributed to formation of multiple 2-hydroxyethyl (HE) DNA adducts such as 3-HEA and O<sup>6</sup>-HEG. [Boysen et al. \(2009\)](#) argued that there is little evidence that 7-HEG adducts cause mutations since – unlike the N1, N<sup>2</sup>, or O<sup>6</sup> positions of guanine – they do not participate in hydrogen bonding in the DNA double-helix and easily de-purinate. These authors conclude that the formation of N7-guanine adducts cannot be used in isolation as a quantitative biomarker for pro-mutagenic DNA lesions or mutagenic response. [Marsden et al. \(2009\)](#) used a dual-isotope approach to distinguish between endogenously formed background levels of 7-HEG and exogenously formed 7-HEG adducts in rats following exposure to [<sup>14</sup>C]-labelled ethylene oxide. By combining liquid chromatography-tandem mass spectrometry and high-performance liquid chromatography/accelerator mass spectrometry analysis, both the endogenous and exogenous N7-HEG adducts were quantified in

tissues of [<sup>14</sup>C]ethylene oxide-treated rats. Levels of [<sup>14</sup>C]-7-HEG induced in spleen, liver, and stomach DNA were insignificant compared with the measured background levels of N7-HEG naturally present.

The exact mechanism by which the other ethylene oxide-induced DNA adducts such as 3-HEA and O<sup>6</sup>-HEG may lead to mutation is unknown. Several mechanisms could be involved, including the mispairing of altered bases or the formation of apurinic/apyrimidinic sites via DNA repair or chemical depurination/depyrimidination combined with the insertion of another base, which would typically be an adenine opposite an apurinic site ([Tates et al., 1999](#); [Houle et al., 2006](#)). These lesions can also lead to the formation of DNA single-strand breaks and, subsequently, to chromosomal breakage. In addition, the putative ethylene oxide metabolite, glycolaldehyde, has been shown to form DNA–protein crosslinks and DNA single-strand breaks ([Hengstler et al., 1994](#)).

#### 4.2.3 Cytogenetic alterations and mutations

Studies of human exposure to ethylene oxide have focused on individuals employed in the operation of hospital- or factory-based sterilization units, and on workers who were involved in manufacturing or processing of ethylene oxide. The studies show that exposure to ethylene oxide results in chromosomal alterations that are related to both the level and duration of exposure, while a single study suggested that exposure to ethylene oxide causes gene mutations.

##### (a) Sister chromatid exchange

The induction of increased frequencies of sister chromatid exchange (SCE) has been found to be a sensitive indicator of genotoxic exposure to ethylene oxide in humans ([Tates et al., 1991](#)). In several studies, significant differences were found in SCE frequencies in individuals and/or groups exposed to levels of ethylene oxide higher



than the designated low-exposure group from the same or a similar environments ([Yager et al., 1983](#); [Sarto et al., 1984a](#); [Stolley et al., 1984](#); [Tates et al., 1991](#); [Schulte et al., 1992](#)). These findings support the observation that SCE frequencies varied with level and frequency of exposure to ethylene oxide. In two studies SCE frequencies were investigated over time: they remained elevated for at least six months even when exposures diminished or ceased after the first assessment ([Sarto et al., 1984b](#); [Stolley et al., 1984](#)).

#### (b) Chromosomal aberrations

Chromosomal aberration frequencies correlate with exposure concentrations of ethylene oxide and/or duration of the exposure ([Clare et al., 1985](#); [Galloway et al., 1986](#); [Tates et al., 1991](#); [Lerda & Rizzi, 1992](#)). As reported for SCE, the validity of these comparisons is supported by the observation that some investigators found significant increases in chromosomal aberrations in high-dose groups but not in low-dose groups exposed in the same or similar environments ([Sarto et al., 1984b](#); [Galloway et al., 1986](#)). In workers exposed to a range of concentrations of ethylene oxide [0.01–200 ppm; 0.02–366 mg/m<sup>3</sup>] the presence of chromosomal aberrations was evaluated; in most of the workers significant increases in chromosomal aberrations were found ([Pero et al., 1981](#); [Högstedt et al., 1983, 1990](#); [Sarto et al., 1984b](#); [Richmond et al., 1985](#); [Galloway et al., 1986](#); [Karelová et al., 1987](#); [Tates et al., 1991](#); [Lerda & Rizzi, 1992](#); [Ribeiro et al., 1994](#); [Major et al., 1996](#)). In one study, such increases were found in individuals exposed to concentrations of ethylene oxide of approximately 1 ppm [1.83 mg/m<sup>3</sup>] and even lower ([Högstedt et al., 1983](#)). However, in other studies of workers exposed to these low concentrations of ethylene oxide, evidence of increased chromosomal aberrations was not found ([Van Sittert et al., 1985](#); [Mayer et al., 1991](#)).

#### (c) Micronuclei

Few investigators have evaluated the impact of exposure to ethylene oxide on the frequency of micronucleated cells, and the available studies reported positive or no effects. [Högstedt et al. \(1990\)](#) and [Ribeiro et al. \(1994\)](#) found an increased frequency of micronucleated lymphocytes in workers, while [Tates et al. \(1991\)](#) found significant increases in micronucleus frequency in workers exposed to high, but not to low doses. Exposure concentrations in all these studies varied widely, ranging from < 1 ppm to 400 ppm [1.83–732 mg/m<sup>3</sup>] ethylene oxide. Studies that evaluated micronucleus formation in individuals exposed to ethylene oxide at concentrations ≤ 1 ppm were negative ([Högstedt et al., 1983](#); [Sarto et al., 1990, 1991](#); [Tates et al., 1995](#)).

In two studies micronucleus formation was determined in cells other than lymphocytes. [Ribeiro et al. \(1994\)](#) evaluated both peripheral blood lymphocytes and exfoliated buccal cells in individuals exposed to 2–5 ppm [3.66–9.15 mg/m<sup>3</sup>] ethylene oxide (TWA); micronucleus frequencies in buccal cells were not associated with the exposure, while those in lymphocytes showed a significant positive association. [Sarto et al. \(1990\)](#) found a significant increase in micronucleus frequency in nasal mucosal cells, but not in exfoliated buccal cells of workers exposed to ethylene oxide at concentrations below 0.38 ppm [0.7 mg/m<sup>3</sup>] (TWA).

#### (d) Gene mutations

The question whether occupational exposure to ethylene oxide is associated with the induction of gene mutations has been addressed in three reports. In the first study, the T-cell cloning assay was used to measure *HPRT* mutant frequencies in peripheral blood lymphocytes from nine ethylene oxide-exposed hospital workers and 15 ethylene oxide-exposed factory workers ([Tates et al., 1991](#)). Hospital workers included nurses and technicians involved in the sterilization of medical

equipment and exposed to ethylene oxide once or twice a week for about 10 minutes. The concentrations of ethylene oxide ranged from 20 to 25 ppm [36.6–45.8 mg/m<sup>3</sup>] in the sterilization room and from 22 to 72 ppm [40.3–131.8 mg/m<sup>3</sup>] in front of the sterilizer immediately after opening. The hospital workers were matched for age, sex and smoking habits with a control group of eight unexposed administrative workers. The factory workers were employed at a plant that was involved in the production of ethylene oxide-sterilized disposable medical equipment, and were similarly matched with a group of 15 unexposed controls in the same factory. During a four-month monitoring period (equivalent to the lifespan of erythrocytes in humans), five workers were engaged in ‘daily’ sterilization activities, two workers were involved in ‘daily’ sterilization except for leave periods of 7 or 11 days, and the eight remaining workers were ‘occasionally’ exposed to ethylene oxide during exposure control, packing and quality control of sterilized products. Before the collection of samples in early 1990, the mean duration of exposure of factory workers to ethylene oxide had been 12 years (range, 3–27 years), with average ambient exposure levels from 1989 onwards that were estimated at about 17 ppm [~31 mg/m<sup>3</sup>]. Based on measurements of *N*-(2-hydroxyethyl)valine-haemoglobin adducts, which integrate exposure over time, average exposures to ethylene oxide in the four months before blood sampling were estimated at a 40-hour TWA of 0.025 ppm [0.046 mg/m<sup>3</sup>] for hospital workers and 5 ppm [9.15 mg/m<sup>3</sup>] for factory workers ([Tates et al., 1991](#)). The average *HPRT* mutant frequencies in hospital workers ( $12.4 \pm 9.9 \times 10^{-6}$ ) and factory workers ( $13.8 \pm 4.4 \times 10^{-6}$ ) were remarkably similar and showed increases of 55% and 60%, respectively, above the background frequency in their respective control groups ( $8.0 \pm 3.6 \times 10^{-6}$  and  $8.6 \pm 4.4 \times 10^{-6}$ ); however, the mutagenic response was significantly elevated only in the factory workers, which was probably due to the

higher exposure concentrations and tissue doses of ethylene oxide in these workers.

In a follow-up study of workers in an ethylene oxide-production plant, [Tates et al. \(1995\)](#) used the T-cell cloning assay to measure *HPRT* mutant frequencies in three exposed groups and one unexposed group (seven subjects per group). Group-I workers were incidentally exposed to acute high concentrations of ethylene oxide, while workers in Groups II and III had been chronically exposed to low concentrations of ethylene oxide for < 5 years and > 15 years, respectively. No significant differences in mutant frequencies were observed between any combination of worker or control groups, which implies that incidental exposure to high levels of ethylene oxide (28–429 ppm; 52–785 mg/m<sup>3</sup>) or chronic exposure to low concentrations of ethylene oxide (< 0.005–0.02 ppm; < 0.01–0.04 mg/m<sup>3</sup>) did not cause any measurable permanent gene mutation in lymphocytes at this locus.

In-vivo mutation-induction studies with reporter genes such as *Hprt* or the *LacI*-transgene have shown that ethylene oxide can significantly increase the frequency of mutations in both mice and rats ([Walker & Skopek, 1993](#); [Sisk et al., 1997](#); [Walker et al., 1997a, b](#); [Tates et al., 1999](#); [Recio et al., 2004](#)). The type of mutation that is recovered appears to be influenced by the assay system used. In mouse splenic and/or thymic T lymphocytes, mutations in *Hprt* could be detected after shorter exposures (a 4-week inhalation exposure or multiple intra-peritoneal injections over the course of one week) and appeared to consist of larger deletion mutations as well as base-pair substitutions and frame-shift mutations ([Walker & Skopek, 1993](#); [Walker et al., 1997a, b](#)). The latter point mutations appeared to originate primarily from either altered G or A nucleobases ([Walker & Skopek, 1993](#); [IARC, 1994](#)). In the inhalation study, no significant increases in *LacI* mutations were seen in the spleen, bone marrow or germ cells of mice after four weeks of exposure to ethylene oxide ([Sisk](#)

[et al., 1997](#)). A modest but significant increase in *LacI* mutants was seen in the lungs of mice exposed to 200 ppm [366 mg/m<sup>3</sup>] ethylene oxide. In a follow-up study with prolonged exposure (up to 48 weeks), significant increases in *LacI* mutants were seen in the bone marrow and testes of the ethylene oxide-exposed transgenic mice ([Recio et al., 2004](#)). DNA-sequence analysis of mutants obtained from the bone marrow showed that only AT→TA transversions were recovered at a significantly increased frequency in the exposed mice. A unique mutational spectrum was not seen in the testes.

An elevated frequency of mutations or a change in mutational spectra has been seen in the tumours of ethylene oxide-treated mice ([Houle et al., 2006](#); [Hong et al., 2007](#)). In the study by [Hong et al. \(2007\)](#), *K-Ras* mutations were detected in 100% (23/23) of ethylene oxide-induced lung tumours compared with 25% (27/108) of spontaneous tumours. Codon-12 G→T transversions occurred frequently in the ethylene oxide-induced lung neoplasms (21/23) but infrequently in spontaneous lung neoplasms (1/108). Similarly, *K-Ras* mutations were found in 86% (18/21) of Harderian gland tumours from ethylene oxide-treated animals, but were seen in only 7% (2/27) of the spontaneous tumours in this organ. Codon-13 G→C and codon-12 G→T transversions were common in the ethylene oxide-induced Harderian gland tumours, but they were absent in the spontaneous tumours in this organ (0/27). *K-Ras* mutations were also seen in 83% (5/6) of ethylene oxide-induced uterine tumours, all of which showed a G→C transition in codon 13. The incidence in spontaneous uterine tumours was not reported. A similar study by [Houle et al. \(2006\)](#) provided evidence of the involvement of *H-Ras* and *p53* mutations in mammary gland tumours induced by ethylene oxide in mice. The mutation frequency was only slightly elevated for *H-Ras* (33% in treated vs 26% in controls) or *p53* (67% in the ethylene oxide-treated versus 58% in the control animals), but the mutational spectra

in tumours obtained from control and treated animals differed significantly. The mutational spectra were generally consistent with a targeting of G and A bases by ethylene oxide ([Houle et al., 2006](#); [Hong et al., 2007](#)). The high frequency of mutation in these genes, particularly mutations in the critical codons of *K-Ras* and inactivation of *p53*, indicate that mutations are induced in the tumours of ethylene oxide-treated mice and that the changes probably play an important role in ethylene oxide-induced tumour development in these tissues.

Acute myelogenous leukaemia in patients previously treated with alkylating agents frequently shows specific characteristics that allow it to be distinguished from acute myelogenous leukaemia induced by other agents (such as topoisomerase II-inhibitors) or occurring spontaneously ([Pedersen-Bjergaard & Rowley, 1994](#); [Pedersen-Bjergaard et al., 2006](#)). One of the hallmarks of leukaemias induced by alkylating agents is that they frequently show loss of chromosomes 5 or 7 (-5, -7) or loss of part of the long arms of these chromosomes (5q-, 7q-). In addition, mutations in *p53* are frequently seen in leukaemias with the -5/5q- karyotype, and mutations in *p53* and *Ras* are seen in a subset of those that exhibit the -7/7q- karyotype ([Christiansen et al., 2001](#); [Pedersen-Bjergaard et al., 2006](#)). Although ethylene oxide has not been investigated specifically for its ability to induce losses of chromosomes 5 or 7, or deletions of the long arms of these chromosomes (5q- or 7q-), it has been reported to induce similar types of chromosomal alteration and deletions in a variety of experimental models and/or in the lymphocytes of exposed workers ([IARC, 1994](#); [Major et al., 1996, 1999](#)). The detection of elevated levels of chromosomal aberrations and micronuclei in the peripheral blood lymphocytes of ethylene oxide-exposed workers is of particular interest, as individuals with increased levels of chromosomal aberrations or micronuclei in these cells are at an increased risk for cancer ([Hagmar et al.,](#)

**Table 4.1 Comparison of the evidence for key events – cytogenetic, genetic, and related changes – induced by ethylene oxide in humans, human cells, and experimental animals**

End-point	In-vivo exposure		In-vitro exposure
	Animals	Humans	Human cells
Haemoglobin-adduct formation	Strong	Strong	Strong
DNA-adduct formation	Strong	Weak <sup>a</sup>	Strong
Mutations in reporter genes in somatic cells	Strong	Weak <sup>a</sup>	Strong
Mutations in cancer-related genes in tumours	Strong	NR	not applicable
Increased levels of cancer-related proteins in tumours	Strong	NR	not applicable
Cytogenetic alterations in somatic cells			
Sister chromatid exchange	Strong	Strong	Strong
Structural chromosomal aberrations	Strong <sup>b</sup>	Strong	Moderate
Micronucleus formation	Strong <sup>b</sup>	Strong	NR

<sup>a</sup> Possibly due to a lack of adequate studies

<sup>b</sup> Positive responses were seen only at exposure concentrations above those used in the rodent cancer-bioassays

NR, not reported

From [IARC \(2008\)](#)

1998; [Liou et al., 1999](#); [Smerhovsky et al., 2001](#); [Hagmar et al., 2004](#); [Boffetta et al., 2007](#); [Bonassi et al., 2007](#)).

A comparison of the evidence for ethylene oxide-induced genetic and related changes in experimental animals and humans is summarized in [Table 4.1](#).

In conclusion, the numerous studies on ethylene oxide that focused on toxicokinetics, DNA-adduct formation, biomarkers, genotoxicity, and molecular biology provide strong evidence that the carcinogenicity of ethylene oxide, a direct-acting alkylating agent, involves a genotoxic mechanism of action. The direct reaction of ethylene oxide with DNA is thought to initiate the cascade of genetic and related events that lead to cancer. Ethylene oxide induces a dose-related increase in the frequency of ethylene oxide-derived haemoglobin adducts in exposed humans and rodents, induces a dose-related increase in the frequency of ethylene oxide-derived DNA adducts in exposed rodents, consistently acts as a mutagen and clastogen at all phylogenetic levels, induces heritable translocations in the germ cells of exposed rodents, and induces a dose-related increase in the frequency

of sister chromatid exchange, chromosomal aberrations and micronucleus formation in the lymphocytes of exposed workers.

## 5. Evaluation

There is *limited evidence* in humans for a causal association of ethylene oxide with lymphatic and haematopoietic cancers (specifically lymphoid tumours, i.e. non-Hodgkin lymphoma, multiple myeloma and chronic lymphocytic leukaemia), and breast cancer.

There is *sufficient evidence* in experimental animals for the carcinogenicity of ethylene oxide.

There is strong evidence that the carcinogenicity of ethylene oxide, a direct-acting alkylating agent, operates by a genotoxic mechanism. A dose-related increase in the frequency of ethylene oxide-derived haemoglobin adducts has been observed in exposed humans and rodents, and a dose-related increase in the frequency of ethylene oxide-derived DNA adducts has been demonstrated in exposed rodents. Ethylene oxide consistently acts as a mutagen and clastogen at all phylogenetic levels, it induces heritable



translocations in the germ cells of exposed rodents, and a dose-related increase in the frequency of sister chromatid exchange, chromosomal aberrations and micronucleus formation in the lymphocytes of exposed workers.

Ethylene oxide is *carcinogenic to humans* (Group 1).

In making the overall evaluation, the Working Group considered that there is *sufficient evidence* for the carcinogenicity of ethylene oxide in experimental animals, and relied heavily on the compelling data in support of the genotoxic mechanism described above.

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