ETHYLENE

This substance was considered by a previous Working Group, in February 1978 (IARC, 1979). 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*

Chem. Abstr. Serv. Reg. No.: 74-85-1
Replaced CAS Reg. No.: 33060-30-9; 87701-64-2; 87701-65-3
Chem. Abstr. Name: Ethene
IUPAC Systematic Name: Ethylene
Synonyms: Acetene; bicarburetted hydrogen; elayl; olefiant gas

1.1.2 *Structural and molecular formulae and relative molecular mass*

$H_2C{=}CH_2$

C_2H_4 Relative molecular mass: 28.05

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless gas (Lide, 1991)
(*b*) *Boiling-point*: -103.7 °C (Lide, 1991)
(*c*) *Melting-point*: -169 °C (Lide, 1991)
(*d*) *Spectroscopy data*: Infrared [prism, 1131], ultraviolet and mass spectral data have been reported (Weast & Astle, 1985; Sadtler Research Laboratories, 1991).
(*e*) *Solubility*: Very slightly soluble in water (0.26% vol/vol); slightly soluble in acetone, benzene and ethanol; soluble in diethyl ether (American Conference of Governmental Industrial Hygienists, 1991; Lide, 1991)
(*f*) *Volatility*: Vapour pressure, 4270 kPa at 0 °C; relative vapour density (air = 1), 0.9686 (Grantom & Royer, 1987)
(*g*) *Stability*: Lower explosive limit (in air), 2.75 vol% or 34.6 g/m^3 at 100 kPa and 20 °C (Grantom & Royer, 1987)
(*h*) *Octanol–water partition coefficient (P)*: log P, 1.13 (Hansch & Leo, 1979)

(*i*) *Conversion factor*: $mg/m^3 = 1.15 \times ppm$[a]

1.1.4 *Technical products and impurities*

The purity of ethylene is normally greater than 99.9 wt%; quality is adjusted to meet specific requirements. Sulfur, oxygen and acetylene are the most troublesome but carefully controlled impurities, especially when ethylene from multiple sources is mixed for transportation. Specification ranges (mg/kg) for maximal levels of key contaminants in ethylene are: methane + ethane, 50–2000; propylene and heavier, 7–200; acetylene, 1.4–10; hydrogen, 0.1–10; carbon monoxide, 0.15–10; carbon dioxide, 2.2–50; oxygen, 0.6–10; sulfur, 1–10; and water, 0.6–20 (Grantom & Royer, 1987 [results of a survey of 10 US producers]; Dow Chemical Co., 1989; Amoco Chemical Co., 1993). Specifications for the quality of ethylene in Europe, Japan and the USA are similar (Grantom & Royer, 1987).

1.1.5 *Analysis*

Atmospheric hydrocarbons, including ethylene, can be determined by capillary column gas chromatography with flame ionization detection (Locke *et al.*, 1989; Khalil & Rasmussen, 1992). The lower limit of detection with this method is 10 ppb (10 µl/L) by volume (Locke *et al.*, 1989). A variation on this method consists of preconcentration with a two-stage cryotrap system and an aluminium oxide-coated column; the limit of detection is 2.5 ppt (Schmidbauer & Oehme, 1985) or 2 pg (Matuška *et al.*, 1986). A similar method is based on sample enrichment with a solid sorbent, a zeolite, at room temperature, followed by heat desorption for gas chromatographic separation and flame ionization detection (Persson & Berg, 1989). Use of solid sorbent tubes in series (Tenax TA + Carbosphere S) has been suggested, with analysis by gas chromatography and an electron capture detection system parallel to a tandem photoionization and flame ionization system; the limit of detection for ethylene was 24 ppt (Reineke & Bächmann, 1985).

Methods have been developed for the biological monitoring of occupational exposure to ethylene, which are based on determination of a haemoglobin adduct [*N*-(2-hydroxyethyl)valine] of the metabolite, ethylene oxide, using gas chromatography/mass spectrometry (Törnqvist *et al.*, 1986a) and gas chromatography/electron capture detection (Kautiainen & Törnqvist, 1991).

1.2 Production and use

1.2.1 *Production*

Ethylene is the petrochemical produced in largest quantities worldwide. Recovered from coke-oven gas and other sources in Europe since 1930, ethylene emerged as a large-volume intermediate in the 1940s when US oil and chemical companies began separating it from refinery waste gas and producing it from ethane obtained from refinery by-product streams and from natural gas. After that time, the industry rapidly switched its raw material base from coal to hydrocarbons (Grantom & Royer, 1987).

---

[a]Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (101.3 kPa)

Over 95% of the worldwide annual commercial production of ethylene is currently based on steam cracking of petroleum hydrocarbons. Various feedstocks, including ethane, propane, butanes, naphthas and gas oils, are used to produce ethylene. Naphthas are the principal raw material used in western Europe and Japan, accounting for over 80% of the ethylene produced. Ethane is the primary feedstock in the USA, followed by propane, naphthas, gas oils and butane. Small amounts of ethylene are recovered from other feedstocks, such as retrograde-field condensates and refinery waste gases. Dehydration of ethanol is the third commercial route to ethylene (Grantom & Royer, 1987). Production of ethylene in 19 countries and regions is presented in Table 1. Total European Union production in 1990 was 12 820 thousand tonnes (European Commission, 1993).

Table 1. Worldwide production of ethylene (thousand tonnes)

Country or region	1982	1984	1986	1988	1990	1992
Argentina	NR	255	258	NR	NR	NR
Belarus[a]	–	–	–	–	145	NA
Canada	1 013	1 464	1 909	2 346	2 434	2 521
China	565	648	642	1 231	1 572	1 982[b]
Former Czechoslovakia	NR	NR	NR	683	619	NA
France	1 865	2 078	2 259	2 432	2 244	2 650
Germany[c]	2 634	3 217	2 662	3 125	3 072	3 393
Hungary	NR	265	269	264	234	281
Italy	872	1 136	NR	NR	NR	NR
Japan	3 590	4 384	4 291	5 057	5 810	6 104
Mexico	396	643	767	916	NR	NR
Poland	175	256	279	328	308	NA
Republic of Korea	374	526	534	609	1 054	2 769
Romania	NR	317	312	335	243	132[d]
Russia[a]	2 000	2 543	2 799	3 175	2 318	NA
Taiwan	452	660	868	852	776	734
Ukraine[a]	–	–	–	–	446	NA
United Kingdom	1 113	1 153	1 736	2 025	1 495	1 934
USA	11 113	14 235	14 905	16 875	16 541	18 327[b]

From Scientific & Technical Information Research Institute of the Ministry of Chemical Industry of China (1984); Anon. (1985, 1987, 1988, 1989, 1990); Giménez *et al.* (1990); Anon. (1991a, 1992, 1993); NA, not available; NR, not reported

[a]Reported as part of USSR from 1981 through 1988

[b]Preliminary

[c]Western

[d]Estimate

Information available in 1991 indicated that ethylene was produced by 17 companies in the USA, 13 in Japan, nine in Germany, five in France, four each in Brazil and the United Kingdom, three each in Canada and the Netherlands, two each in Argentina, Australia, Belgium, China, the Republic of Korea, Saudi Arabia and the former Yugoslavia, and one each in Austria, the former Czechoslovakia, Finland, India, Italy, Mexico, Norway,

Singapore, South Africa, Spain, Thailand, Turkey and Venezuela (Chemical Information Services Ltd, 1991).

1.2.2 *Use*

About 80% of the ethylene used in western Europe, Japan and the USA is for producing polyethylene (high density, low density and linear low density), ethylene oxide/ethylene glycols and ethylene dichloride/vinyl chloride. Significant amounts are also used to make ethylbenzene/styrene, oligomer products (e.g. alcohols and α-olefins), acetaldehyde/acetic acid and vinyl acetate (Grantom & Royer, 1987). Typical patterns for use of ethylene in western Europe, Japan and the USA are presented in Table 2.

Table 2. Use patterns (%) for ethylene in western Europe, Japan and the USA

Use	Western Europe[a] (1983)	Japan		USA	
		1983	1991	1983	1991
LD-LLD polyethylene[b]	35	30	29	28.5	27
HD polyethylene[c]	15	20	19	20	24
Ethylene oxide	12	11	11	17	14
Ethylene dichloride	19	18	14	14	13
Ethylbenzene	8	9	10	7	7
Ethanol + acetaldehyde	6	5	4	4	2
Vinyl acetate monomer	–[d]	3	–	2.5	3
Miscellaneous	5	4	13	7	10

From Grantom and Royer (1987), Anon. (1991b) and Japan Petrochemical Industry Association (1993)
[a]Belgium, Germany, France, Italy, Luxembourg, the Netherlands and the United Kingdom
[b]LD, low density; LLD, linear low density
[c]HD, high density
[d]Included in 'miscellaneous'

While most commercially produced ethylene is used as a feedstock in the production of polymers and industrial chemicals, a relatively small amount is used for the controlled ripening of citrus fruits, tomatoes, bananas and many other fruits, vegetables and flowers. Endogenous production of ethylene in plant tissue generally increases rapidly during ripening. Application of ethylene to plants before the time of this natural increase not only initiates the ripening process but also increases endogenous ethylene production. Ethylene has commonly been used in this way since the early part of this century (Nickell, 1982; Kader & Kasmire, 1984; Bridgen, 1985; Reid, 1985; Kader, 1986; Watada, 1986).

1.3 Occurrence

Ethylene is ubiquitous in the environment, arising from both natural and man-made sources. Major sources are as a natural product from vegetation of all types (Sawada &

Totsuka, 1986; Rudolph *et al.*, 1989); as a product of burning vegetation, agricultural wastes and refuse, and the incomplete combustion of fossil fuels; and releases during the production and use of ethylene (Sawada & Totsuka, 1986).

Total annual emission of ethylene from the global surface has been estimated to be 18–45 million tonnes per year, of which approximately 74% is released from natural sources and 26% from anthropogenic sources. Releases from terrestrial ecosystems comprise about 89% of the natural sources and aquatic ecosystems, about 11%. Burning of biomass to clear land for agriculture or other uses is believed to be the largest anthropogenic source of ethylene emissions (77%); the combustion of various fossil fuels also accounts for a significant fraction (21%) of anthropogenic emissions (Sawada & Totsuka, 1986).

1.3.1 *Natural occurrence*

Ethylene is a natural product emitted by fruits, flowers, leaves, roots and tubers (Altshuller, 1983). The rate of release varies during the life cycle of the plant. Plants that normally produce 0.6–6 μg/kg fresh weight per hour may produce up to 120 μg/kg per hour during ripening of fruits and during senescence and loss of leaves (Dörffling, 1982; Tille *et al.*, 1985). Ethylene is also produced endogenously by humans and other mammals (see section 4.1).

Other natural sources of ethylene include volcanic emissions and natural gas. Volcanos emit only trace concentrations of ethylene, and leaked natural gas contains mainly saturated hydrocarbons (Sawada & Totsuka, 1986).

1.3.2 *Occupational exposure*

The National Occupational Exposure Survey conducted by the US National Institute for Occupational Safety and Health between 1981 and 1983 indicated that 12 280 US employees were potentially exposed occupationally to ethylene (US National Institute for Occupational Safety and Health, 1993). The estimate is based on a survey of US companies and did not involve measurements of actual exposures.

There is thought to be little opportunity for occupational exposure to ethylene during its manufacture in a closed system. Exposure may occur as a result of leaks, spills and other accidents and from work in tanks that contained ethylene (Dooley, 1983). No data on measured levels of exposure to ethylene during its manufacture or processing were available to the Working Group. Hogstedt *et al.* (1979) estimated that during the period 1941–47, ethylene levels in an ethylene oxide production plant in Sweden would have been approximately 600 mg/m^3.

Personal and stationary monitoring of ethylene in a company where this gas was used for controlling the ripening of bananas showed air concentrations to be in the range of 0.02–3.35 ppm [0.02–3.85 mg/m^3], with an estimated average concentration of 0.3 ppm [0.35 mg/m^3] (Törnqvist *et al.*, 1989a). In a study on exposure of firefighters, samples taken during the 'knockdown' phase of a fire showed a concentration of 46 ppm [53 mg/m^3] ethylene; none was detected during the 'overhaul' phase (Jankovic *et al.*, 1991).

1.3.3 *Air*

Ethylene concentrations in ambient air at rural and remote sites worldwide are generally in the range of < 1–5 μg/m^3 (Altshuller, 1983; Anlauf *et al.*, 1985; Colbeck & Harrison, 1985; Davidson *et al.*, 1986; Van Valin & Luria, 1988; Kanakidou *et al.*, 1989; Lightman *et al.*, 1990; Hov *et al.*, 1991; Mowrer & Lindskog, 1991; Satsumabayashi *et al.*, 1992).

In urban and indoor air contaminated with combustion products, ethylene concentrations typically range from a few to over 1000 μg/m^3. For example, a median concentration of 21.4 ppb as carbon (ppbC) [12.3 μg/m^3] ethylene, with a maximum of 1001 ppbC [573 μg/m^3], was measured in over 800 ambient air samples obtained from 39 US cities during 1984–86 (Seinfeld, 1989). In 1985, geometric mean atmospheric concentrations of ethylene ranging from 3.2 to 45.8 ppb [3.7–52.7 μg/m^3] were determined in an industrial suburb of Bombay, India (Rao & Pandit, 1988). In northwest England, geometric mean ambient air concentrations of ethylene during the summer of 1983 were 41.2 ppbC [23.6 μg/m^3] in urban air samples and 1.5 ppbC [0.86 μg/m^3] in rural air samples (Colbeck & Harrison, 1985). Ethylene concentrations averaged 4.0 ppb [4.6 μg/m^3] in 1980 and 2.2 ppb [2.5 μg/m^3] in 1981 in 258 air samples taken over Tokyo, Japan (Uno *et al.*, 1985).

One of the major sources of atmospheric ethylene globally—the burning of biomass (Sawada & Totsuka, 1986)—can also be a source of locally high concentrations. A mean ethylene concentration of 490 ppbC [281 μg/m^3] was measured in the indoor air of rural Nepali houses where biomass combustion is the main source of energy; the mean concentration in outdoor air at Katmandu was 2.1 ppbC [1.2 μg/m^3] (Davidson *et al.*, 1986).

Vehicle exhaust emissions make an important contribution to urban air concentrations of ethylene. Estimates in the mid-1980s for countries of the European Union (Table 3) show that emissions from gasoline- and diesel-fuelled vehicles make a significant contribution in that region (Bouscaren *et al.*, 1987).

Although ethylene is not a fuel component, it is present in motor vehicle exhaust as a result of fuel-rich combustion of hydrocarbon fuels (Stump *et al.*, 1989). Mean ethylene emissions from 25 vehicles in the United Kingdom were 211.94 mg/km in urban road tests, 123.20 mg/km in suburban road tests and 93.9 mg/km in rural road tests (Bailey *et al.*, 1990a,b). The following levels of ethylene were determined in air samples representative of various traffic emissions in Sweden: 68 and 64 μg/m^3 (two sites, urban intersection); 13 and 9.8 μg/m^3 (two sites, fast suburban traffic); and 56 μg/m^3 (cold starts at a garage exit) (Löfgren & Petersson, 1992). Ethylene concentrations of 51–405 μg/m^3 were measured in the Tingstad Tunnel in Göteborg, Sweden (Barrefors & Petersson, 1992).

Industrial emissions of ethylene to the air in the USA in 1991 were reported to amount to 17 400 tonnes (US National Library of Medicine, 1993); industrial emissions in the countries of the European Union are shown in Table 3.

Cigarette smoke is also a significant source of exposure to ethylene, as 1–2 mg ethylene are released per cigarette. The exposure of the average cigarette smoker to ethylene is roughly 10 times that from urban air pollution (Persson *et al.*, 1988; Shaikh *et al.*, 1988). In two studies of smokey tavern air, the ethylene levels were 56 and 110 μg/m^3; the corresponding outdoor air concentrations at the time were 16 and 12 μg/m^3 ethylene (Löfroth *et al.*, 1989).

Table 3. Estimated ethylene emissions in member states of the European Union (thousand tonnes/year)

Country	Source			
	Road traffic		Chemical industry[a]	Other sources
	Gasoline	Diesel		
Belgium	4.7	1.3	1	0.9
Denmark	2	0.7	NR	NR
Germany	27	9.5	2.2	11
France	28	8.8	2.5	1
Greece	2.8	1.4	NR	0.01
Ireland	1.3	0.2	NR	NR
Italy	28	8.1	2	1
Luxemburg	0.23	0.05	NR	NR
Netherlands	5.1	1.6	2.6	3.1
Portugal	1.1	1.3	0.3	0.1
Spain	8.9	4.4	1	0.8
United Kingdom	33	5.5	1	1.5
Total (approximate)	145	45	13	20

From Bouscaren *et al.* (1987); NR, not reported
[a]Production of ethylene and ethylene polymers and copolymers

In laboratory studies, ethylene has been detected as a thermal degradation product of polyethylene and polypropylene (Hoff *et al.*, 1982; Frostling *et al.*, 1984).

Ethylene is degraded in the troposphere mainly by reactions with OH radical and ozone. Its average atmospheric lifetime is estimated at two to four days (Sawada & Totsuka, 1986; Rudolph *et al.*, 1989).

1.3.4 *Water*

Although ethylene is only slightly soluble in water, low concentrations have been measured in various surface waters. Pacific and Atlantic Ocean surface waters (77° N to 75° S) contained 0.7–12.1 nl/L, fresh water lakes and rivers in the USA from 4.8 to 13.0 nl/L, and more polluted waters in the Mississippi River delta and near the shore in Miami, FL, from 26 to 35 nl/L (Sawada & Totsuka, 1986).

1.4 Regulations and guidelines

Ethylene has been classified in several countries as an asphyxiant because its presence at high concentrations in air lowers the available oxygen concentration. Countries in which it is classified as an asphyxiant include Australia, Belgium, Canada, Finland, Hungary, the Netherlands, the United Kingdom and the USA. Nevertheless, the major hazard is due to its inflammable and explosive character. No exposure limits have been recommended in most

countries, but Switzerland established a time-weighted average occupational exposure limit of 11 500 mg/m^3 (about one-half the lower exposure limit) in 1987 (ILO, 1991; American Conference of Governmental Industrial Hygienists, 1993; UNEP, 1993). In Germany, no exposure limit is given for ethylene because it is 'justifiably suspected of having carcinogenic potential' (Deutsche Forschungsgemeinschaft, 1993).

In the USA, ethylene is exempted from the requirement of a tolerance for residues when it is used as a plant regulator on fruit and vegetable crops and when it is injected into the soil to cause premature germination of witchweed for a variety of crops (US Environmental Protection Agency, 1992). The US Food and Drug Administration (1993) permits use of ethylene-containing polymers in products in contact with food.

2. Studies of Cancer in Humans

Some cohorts involved in the manufacture of ethylene oxide are likely to have been exposed to ethylene; however, in the only study in which exposure to ethylene was assessed (Hogstedt *et al.*, 1979), described in detail on pp. 89–90, the risk for cancer in relation to ethylene was not assessed separately.

3. Studies of Cancer in Experimental Animals

3.1 Inhalation exposure

Rat: Groups of 120 male and 120 female Fischer 344 rats, six to seven weeks of age, were exposed by inhalation to 0, 300, 1000 or 3000 ppm (0, 345, 1150 or 3450 mg/m^3) ethylene (> 99.9% pure) for 6 h per day on five days per week for up to 24 months, at which time the experiment was terminated. The high dose was chosen to avoid the hazard of explosion. Necropsies were performed at six (5 rats/dose and per sex), 12 (5 rats/dose and per sex), 18 (19–20 rats/dose and per sex) and 24 (all survivors) months. All rats that died spontaneously were also necropsied. There was no significant difference in survival between control and treated groups. The high-dose and control animals were examined histologically. The authors reported that there was no evidence of treatment-related toxicity and no increase in tumour incidence (Hamm *et al.*, 1984).

3.2 Induction of enzyme-altered foci in a two-stage liver system

Rat: Groups of male and female Sprague-Dawley rats, three to five days of age, were exposed by inhalation to 0 (5 male and 9 female rats) or 10 000 ppm (11 500 mg/m^3, 2 males and 10 females) ethylene [purity unspecified] for 8 h per day on five days per week for three weeks. One week later, the rats received oral administrations of 10 mg/kg bw Clophen A 50 (a mixture of polychlorinated biphenyls [not otherwise specified]) by gavage twice a week for up to eight additional weeks (promotion), at which time the experiment was terminated and the livers were examined for ATPase-deficient foci. The number of ATPase-deficient foci in

the rats exposed to ethylene did not exceed the control values. In the same experiment, ethylene oxide, administered as a positive control, produced a significant increase in the incidence of ATPase-deficient foci in females (Denk *et al.*, 1988).

3.3 Carcinogenicity of metabolites

See the monograph on ethylene oxide.

4. Other Data Relevant for an Evaluation of Carcinogenicity and Its Mechanisms

The toxicology of ethylene has been reviewed (National Research Council Canada, 1985; Gibson *et al.*, 1987; Angerer *et al.*, 1988; Greim, 1993).

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

The inhalation pharmacokinetics of ethylene have been investigated in human volunteers at atmospheric concentrations of up to 50 ppm [57.5 mg/m^3] by gas uptake in a closed spirometer system (Shen *et al.*, 1989; Filser *et al.*, 1992). The uptake, exhalation and metabolism of ethylene can be described by first-order kinetics.

Uptake of ethylene into the body is low. Clearance due to uptake, which reflects the transfer rate of ethylene from the atmosphere into the body, was 25 L/h for a man of 70 kg. This value represents only 5.6% of the experimentally obtained alveolar ventilation rate of 450 L/h. The majority (94.4%) of ethylene inhaled into the lungs is exhaled again without becoming systemically available via the blood stream. Maximal accumulation of ethylene in the same man, determined as the thermodynamic partition coefficient whole body:air (K_{eq} = $Conc_{animal}/Conc_{air}$), was 0.53. The concentration ratio at steady state was even smaller (0.33), owing to metabolic elimination. Clearance due to metabolism, in relation to the concentration in the atmosphere, was calculated to be 9.3 L/h for a man of 70 kg. This indicates that at steady state about 36% of systemically available ethylene is eliminated metabolically and 64% is eliminated by exhalation as the unchanged substance, as can be calculated from the values of clearance of uptake and of clearance of metabolism. The biological half-life of ethylene was 0.65 h. The alveolar retention of ethylene at steady state was calculated to be 2% (Filser *et al.*, 1992). From theoretical considerations of the lung uptake of gases and vapours (Johanson & Filser, 1992), it can be deduced that the low uptake rate of ethylene is due to its low solubility in blood: Ostwald's solubility coefficient for human blood at 37 °C, 0.15 (Steward *et al.*, 1973).

(a) Endogenous formation

Endogenous production of ethylene can be deduced from its exhalation by unexposed subjects (Ram Chandra & Spencer, 1963; Shen *et al.*, 1989; Filser *et al.*, 1992). For a man of

70 kg, a mean production rate of 32 nmol/h [0.9 μg/h] and a corresponding mean body burden of 0.011 nl/ml tissue [equivalent to 0.44 nmol/kg bw or 0.012 μg/kg bw] was calculated for ethylene gas (Filser *et al.*, 1992). The amount of ethylene in the breath of women is increased significantly at the time of ovulation; no difference was observed in the basal ethylene outputs of non-pregnant and pregnant women and of men (Harrison, 1981). The biochemical sources of ethylene are unknown; however, several mechanisms by which it might be produced in mammals are discussed below.

(*b*) *Haemoglobin adducts*

The ethylene metabolite, ethylene oxide, reacts with nucleophilic centres in cellular macromolecules (see monograph on ethylene oxide). In several studies, the haemoglobin (Hb) adducts *N*-(2-hydroxyethyl)histidine (HOEtHis) and *N*-(2-hydroxyethyl)valine (HOEtVal) have been used as internal dose monitors of the formation of ethylene oxide from ethylene. In nonsmokers, the background levels of HOEtVal range between 11 and 188 pmol/g Hb (Törnqvist *et al.*, 1986b; Bailey *et al.*, 1988; Törnqvist *et al.*, 1989a; Sarto *et al.*, 1991; Filser *et al.*, 1992; Törnqvist *et al.*, 1992; van Sittert *et al.*, 1993; van Sittert & van Vliet, 1994). Farmer *et al.* (1986) reported background levels of 30–930 pmol/g Hb in three subjects, without considering smoking habits. In Hb of subjects presumed not to be exposed to ethylene, the levels of 2-hydroxyethyl adducts were 1500–4300 pmol/g Hb *N*-(2-hydroxyethyl)cysteine (HOEtCys) in three subjects, 30–530 pmol/g Hb HOEtVal in five subjects; 60 and 300 pmol/g Hb N^{π}-HOEtHis in two subjects and 110–290 pmol/g Hb N^{τ}-HOEtHis in five. Tobacco smoke, urban air and endogenous production were included as possible sources of ethylene (Calleman, 1986). HOEtHis levels in 31 control subjects ranged from < 20 to 4700 pmol/g Hb. Smoking did not contribute to these background alkylations (van Sittert *et al.*, 1985).

Exposure to environmental ethylene concentrations of 10–20 ppb [11.5–23 μg/m^3] was associated with an HOEtVal increment of 4–8 pmol/g globin at steady state (Törnqvist & Ehrenberg, 1990). Background levels of HOEtVal were predicted on the basis of pharmacokinetic parameters of ethylene and ethylene oxide, together with the rate constant of the reaction of ethylene oxide with the N-terminal valine in Hb and confirmed by measured data. HOEtVal levels resulting from endogenous ethylene only were calculated to be about 12 pmol/g Hb. Those resulting from both endogenous and environmental ethylene (15 ppb [17.25 μg/m^3]) in the area of Munich (Germany) were computed to be about 18 pmol/g Hb; the measured level was about 20 pmol/g Hb and, hence, in close agreement with that predicted (Filser *et al.*, 1992). No difference in HOEtVal adduct levels was seen in nonsmoking workers in an ethylene plant and in nonsmoking controls not occupationally exposed (van Sittert & van Vliet, 1994).

Significantly higher levels of HOEtVal (129–690 pmol/g Hb) were found in cigarette smokers (10–30 cigarettes/day) than in nonsmokers (Törnqvist *et al.*, 1986b; Passingham *et al.*, 1988; Persson *et al.*, 1988; Törnqvist *et al.*, 1989a; Sarto *et al.*, 1991). Ethylene (0.25 mg/cigarette; Elmenhorst & Schultz, 1968) and ethylene oxide (0.005 mg/cigarette; Binder & Lindner, 1972) present in tobacco smoke were considered to be major causes of the elevated adduct levels (Törnqvist *et al.*, 1986b; Persson *et al.*, 1988; Törnqvist *et al.*, 1989a). Smoking

10 cigarettes per day was associated with an additional 60–114 pmol/g Hb HOEtVal (Törnqvist *et al.*, 1986b; Bailey *et al.*, 1988; Passingham *et al.*, 1988; van Sittert *et al.*, 1993).

Nonsmoking fruit store workers exposed occupationally to atmospheric ethylene (0.02–3.35 ppm [0.023–3.85 mg/m^3]) used for the ripening of bananas had levels of 22–65 pmol/g Hb HOEtVal, whereas nonsmoking controls had 12–27 pmol/g Hb. On the basis of a mean exposure concentration of 0.3 ppm [0.345 mg/m^3], it was estimated that about 3% (range, 1–10%) of inhaled ethylene was metabolized to ethylene oxide (Törnqvist *et al.*, 1989a). This percentage is equal to the alveolar retention at steady state calculated from inhalation pharmacokinetics (see above). The two values are in agreement. An increment of 100–120 pmol/g Hb HOEtVal was estimated for a time-weighted average exposure (40 h/week) to 1 ppm ethylene [1.15 mg/m^3] (Kautiainen & Törnqvist, 1991; Ehrenberg & Törnqvist, 1992).

On the basis of the relationship between HOEtVal levels and exposure levels of ethylene or ethylene oxide, an 'uptake' (i.e. amount metabolized) of 1 mg ethylene/kg bw was calculated to be equivalent to a tissue dose of ethylene oxide of 0.7×10^{-6} mol×h/L [0.03 mg×h/kg bw] (Törnqvist *et al.*, 1988). This value is in agreement with the value of 0.5×10^{-6} mol×h/L that can be calculated from the pharmacokinetic data for ethylene and ethylene oxide published by Filser *et al.* (1992).

4.1.2 *Experimental systems*

Four male CBA mice (average body weight, 31 g) were exposed together for 1 h in a closed glass chamber (5.6 L) to ^{14}C-ethylene (22 mCi/mmol) in air at 17 ppm×h [22.3 (mg/m^3)×h, equivalent to about 1 mg/kg bw]. Blood and organs from two mice were pooled 4 h after the end of exposure. Radioactivity was about the same in kidney (0.16 μCi/g wet weight) and liver (0.14 μCi/g) but lower in testis (0.035 μCi/g), brain (0.02 μCi/g) and Hb (0.0094 μCi/g Hb). Urine was collected from the two other mice during 48 h, and blood was collected after 21 days. *S*-(2-Hydroxyethyl)cysteine was identified as a metabolite of ethylene in urine (3% of ^{14}C in urine) by thin-layer chromatography. The radioactivity in Hb was 0.011 μCi/g Hb. These data, together with those on specific hydroxyethyl derivatives at amino acid residues of Hb (see below), indicated that ethylene was metabolized to ethylene oxide (Ehrenberg *et al.*, 1977).

In several experiments, disposition of ^{14}C-ethylene (free of ^{14}C-acetylene or ≥ 97% pure) in male Fischer 344 rats (170–220 g) was determined over 36 h following 5-h exposures in a closed chamber (35 L) to 10 000 ppm [11 500 mg/m^3]. In each experiment, up to four rats were exposed together in a single chamber. Within about 1 min after the end of exposure, animals were transferred to individual all-glass metabolism cages. Most of the eliminated ^{14}C was exhaled as ethylene (18 μmol [504 μg] per rat exposed to acetylene-containing ethylene); smaller amounts were excreted in urine (2.7 μmol ethylene equivalents/rat) and faeces (0.4 μmol) and exhaled as CO_2 (0.16 μmol). Radioactivity was also found in blood (0.022 μmol ethylene equivalents/ml), liver (0.047 μmol ethylene equivalents/liver), gut (0.034 μmol ethylene equivalents/gut) and kidney (0.006 μmol ethylene equivalents/kidney). Pretreatment of animals with a mixture of polychlorinated biphenyls (Aroclor 1254; 500 mg/kg bw; single intraperitoneal injection five days before exposure) had no measurable influence on ethylene exhalation but resulted in a significant ($p < 0.05$) increase in exhaled $^{14}CO_2$ (2.04 μmol ethylene equivalents/rat) and of ^{14}C in urine (11.1 μmol ethylene equivalents/rat)

and in blood (0.044 μmol ethylene equivalents/ml). The organ burden of ^{14}C was one to two orders of magnitude greater in Aroclor 1254-treated than in untreated animals. Radioactivity also became detectable in lungs, brain, fat, spleen, heart and skeletal muscle. The data were interpreted as indicating that the metabolism of ethylene can be stimulated by an inducer of the mixed-function oxidase system (Guest *et al.*, 1981).

The pharmacokinetics of inhaled ethylene have been investigated in male Sprague-Dawley rats using closed exposure chambers in which the atmospheric concentration–time course was measured after injection of a single dose into the chamber atmosphere (Bolt *et al.*, 1984; Bolt & Filser, 1987; Shen *et al.*, 1989; Filser, 1992). Uptake of ethylene into the body was low. Clearance due to uptake (as described above) was 20 ml/min for one rat of 250 g, which represents only 17% of the alveolar ventilation (117 ml/min; Arms & Travis, 1988). Most (83%) inhaled ethylene that reaches the lungs is exhaled again without becoming systemically available via the blood stream. Maximal accumulation of ethylene in the organism, determined as the thermodynamic partition coefficient, whole body:air (K_{eq} = $Conc_{animal}/Conc_{air}$), was 0.7. The concentration ratio at steady-state whole body:air was somewhat lower owing to metabolic elimination, and it decreased from 0.7 to 0.54 at exposure concentrations below 80 ppm [92 mg/m^3]; however, at very low atmospheric concentrations, the concentration ratio at steady-state whole body:air increased again, owing to endogenous production of ethylene: For instance, it was almost twice the value of the thermodynamic partition coefficient whole body:air at an exposure concentration of 0.05 ppm [0.06 mg/m^3] (calculated using the pharmacokinetic parameters and equation 18 of Filser, 1992). At concentrations between 80 and 0.1 ppm [92 and 0.12 mg/m^3], clearance was seen, due to metabolism related to the concentration in the atmosphere of about 4.7 ml/min for a 250-g rat. In that concentration range at steady state, therefore, about 24% of systemically available ethylene is eliminated by metabolism and 76% by exhalation of the unchanged substance (taking into account values of clearance of uptake and clearance of metabolism). The alveolar retention of ethylene at steady state was 3.5%, and the biological half-life was 4.7 min (Filser *et al.*, 1992). At atmospheric concentrations greater than 80 ppm [92 mg/m^3], metabolism of ethylene became increasingly saturated, reaching a maximal rate of metabolism (V_{max}) of 0.035 μmol/(min×250 g bw) [0.24 mg/(h×kg bw)] at about 1000 ppm [1150 mg/m^3]. The apparent Michaelis constant (K_m) related to the average concentration of ethylene gas within the organism was 130 nl/ml tissue, which corresponds to an atmospheric concentration of 208 ppm [239 mg/m^3] at $V_{max/2}$, calculated by means of the kinetic parameters given by Filser (1992).

Gas uptake studies with male Fischer 344 rats gave values for V_{max} of 0.24 mg/(h×kg bw) and an 'inhalational K_m' (related to the atmospheric concentration) of 218 ppm [251 mg/m^3] (Andersen *et al.*, 1980).

Involvement of cytochrome P450-dependent monooxygenases in the metabolism of ethylene in male Sprague-Dawley rats was suggested by the complete inhibition of metabolic elimination after intraperitoneal treatment with 200 mg/kg diethyldithiocarbamate 15 min before exposure and by an increase in the rate of its metabolism with a V_{max} of about 14 μmol/(h×kg bw) [0.33 mg/(h×kg bw)], after treatment with a single dose of Aroclor 1254 (500 mg/kg bw) six days before the experiment (Bolt *et al.*, 1984).

The metabolism of ^{14}C-ethylene in 15 male CBA mice kept for 7 h in a closed exposure chamber (11 L), in which the atmospheric concentration–time course was measured after generation of an initial atmospheric concentration of 10 ppb [11.5 μg/m^3], was reduced by co-exposure to propylene at 1260 ppm [1267 mg/m^3], suggesting inhibition of ethylene metabolism by propylene (Svensson & Osterman-Golkar, 1984).

In liver microsomes prepared from male Sprague-Dawley rats, ethylene at concentrations of up to 10% [115 g/m^3] in the gas phase was metabolized to ethylene oxide in the presence of an NADPH regenerating system (1 h, pH 7.5, 37 °C). The rate of formation of ethylene oxide was saturable (V_{max}, 0.67 nmol/h per mg protein) and could be reduced by the addition of diethyldithiocarbamate or β-naphthoflavone to the microsomal suspension. Treatment of the rats with phenobarbital (single intraperitoneal injection of 80 mg/kg bw followed by three days of 0.1% in drinking-water) before preparation of liver microsomes did not change the V_{max} (Schmiedel *et al.*, 1983).

Male Sprague-Dawley rats exposed to ethylene exhaled ethylene oxide. In these experiments, two animals were kept together up to 21 h in a closed exposure chamber (6.4 L). The concentration of ethylene in the atmosphere of the chamber was maintained at greater than 1000 ppm [1150 mg/mg^3] by repeated additions, in order to maintain V_{max} conditions for ethylene. One hour after the beginning of exposure, the atmospheric concentration of exhaled ethylene oxide reached a peak value of 0.6 ppm [0.69 mg/m^3]. After about 2.5 h, the concentration had decreased to about 0.3 ppm [0.345 mg/m^3] and then remained constant. On the basis of the concentration–time courses of atmospheric ethylene, it was speculated that this decrease was due to rapid induction of ethylene oxide metabolizing enzymes, whereas the rate of ethylene metabolism remained unaffected (Filser & Bolt, 1984). In male Sprague-Dawley rats exposed to concentrations greater than 1000 ppm, the amount of ethylene taken up per unit time from the atmosphere of a closed chamber remained constant over exposure times of up to 30 h (Bolt *et al.*, 1984). Pharmacokinetic data for ethylene and ethylene oxide indicated that under steady-state conditions only 29% of metabolized ethylene is available systemically as ethylene oxide. Therefore, assuming that the liver is the principal organ in which ethylene is metabolized, an intrahepatic first-pass effect for the intermediate ethylene oxide was suggested (Filser & Bolt, 1984).

In view of the saturability of ethylene metabolism, the maximal possible average body concentration of its metabolite, ethylene oxide, was calculated to be 0.34 nmol/ml tissue [15 μg/kg bw] in an open exposure system (infinitely large atmospheric volume). The same value was computed to result from exposure to ethylene oxide at an atmospheric concentration of 5.6 ppm [10.2 mg/m^3] at steady state (Bolt & Filser, 1987).

Ethylene oxide was found in the blood of male Fischer 344/N rats during exposure to an atmospheric ethylene concentration of 600 ppm [690 mg/m^3]. A maximal value of about 3 μg/g blood of ethylene oxide was seen 8 min after the start of exposure to ethylene; this value was followed 4 min later by an immediate decrease to about 0.6 μg/g, and the level remained constant for the following 46 min. During exposure, the cytochrome P450 content in the liver was reduced to 94% after 20 min and to 68% after 360 min. It was speculated that an ethylene-specific cytochrome P450 isozyme was rapidly deactivated during exposure to ethylene, resulting in reduced formation of ethylene oxide (Maples & Dahl, 1993). This speculation is based on results obtained by an unspecific method for the determination of

cytochrome P450 which is not suitable for the determination of cytochrome P450 isozymes; however, under certain conditions, suicide metabolism of ethylene in rat liver does seem to occur, as indicated from experiments of induction of cytochrome P450-dependent monooxygenases. In male Sprague-Dawley rats treated with phenobarbital (80 mg/kg bw, intraperitoneal injection daily for four days, exposure to ethylene on day 5) and then exposed for 3 h to a mixture of commercial ethylene (contaminated with about 10 ppm acetylene) and air (1:1 v/v), a green pigment was found in the liver 4 h after exposure. The same pigment was formed *in vitro* during incubation of acetylene-free ethylene with the 9000 × *g* supernatant of a rat liver homogenate (from phenobarbital-pretreated animals) in the presence of NADPH. No controls were used (Ortiz de Montellano & Mico, 1980). The pigment was identified as a *N*-(2-hydroxyethyl)protoporphyrin IX, an alkylation product of the prosthetic haem of cytochrome P450-dependent monooxygenases. It was concluded that the phenobarbital-inducible form of cytochrome P450 was destroyed during oxidative metabolism of ethylene (Ortiz de Montellano *et al.*, 1980, 1981).

The further metabolic fate of ethylene oxide is described in the monograph on that chemical.

(*a*) *Endogenous formation*

Four possible sources of endogenous ethylene have been suggested: lipid peroxidation (Lieberman & Mapson, 1964; Lieberman & Hochstein, 1966; Frank *et al.*, 1980; Sagai & Ichinose, 1980; Törnqvist *et al.*, 1989b; Kautiainen *et al.*, 1991); enzyme- (Fu *et al.*, 1979), copper- (Lieberman *et al.*, 1965) or iron- (Kessler & Remmer, 1990) catalysed oxidative destruction of methionine; oxidation of haemoglobin (Clemens *et al.*, 1983); and the metabolism of intestinal bacteria (Törnqvist *et al.*, 1989b).

Ethylene is also exhaled by untreated rats (Frank *et al.*, 1980; Sagai & Ichinose, 1980; Shen *et al.*, 1989). The endogenous production rate in a Sprague-Dawley rat (250 g bw) was determined to be 2.8 nmol/h [0.31 μg/(h×kg bw)], resulting in a body burden of ethylene gas of 0.032 nl/ml tissue [0.036 μg/kg bw] (Filser, 1992). The corresponding exhalation rate may be calculated from the pharmacokinetic parameters of Filser (1992) as 0.24 μg/(h×kg bw).

(*b*) *Haemoglobin adducts*

Hydroxyethyl adducts at cysteine, histidine and the N-terminal valine of Hb were identified in several animal species exposed to ethylene and have been ascribed to the formation of ethylene oxide (Ehrenberg *et al.*, 1977; Osterman-Golkar *et al.*, 1983; Segerbäck, 1983; Törnqvist *et al.*, 1986a, 1988, 1989b; Kautiainen *et al.*, 1991). Background levels of Hb adducts, partially due to exposure to endogenous and environmental ethylene, are listed in Table 4.

In male CBA mice exposed for 70 h to an atmospheric concentration of 9100 ppm ethylene [10 465 mg/m^3], the level of the Hb adduct HOEtCys was 7200 pmol/g Hb (Ehrenberg *et al.*, 1977).

Further support for the proposal that ethylene oxide is the reactive metabolite of ethylene arose from the finding of similar relative patterns of the Hb adducts HOEtCys, HOEtHis and HOEtVal in male CBA mice either exposed in a closed chamber to atmospheric ^{14}C-ethylene at initial concentrations of 0.25, 1.1 or 11 ppm [0.29, 1.27, 12.7 mg/m^3]

(exposure dose 1, 6.5 or 50 ppm×h [1.15, 7.48, 57.5 mg×h/m^3]) or treated intraperitoneally with ^{14}C-ethylene oxide (44 μmol/kg bw [1.9 mg/kg bw]) (Segerbäck, 1983).

Table 4. Hydroxyethyl (HOEt) haemoglobin adducts measured in animals after endogenous and environmental exposure to ethylene and related metabolites

Species and strain	Sex	Haemoglobin adducts measured (pmol/g Hb)			Reference
		HOEtCys	HOEtHis	HOEtVal	
CBA mouse	Male	1400			Ehrenberg *et al.* (1977)
Mouse	NR			20–120	Törnqvist *et al.* (1986a)
B6C3F$_1$ mouse	Male			58	Walker *et al.* (1992a)
F344 rat	Male		1300, 2800		Osterman-Golkar *et al.* (1983)
Rat	NR			~100	Törnqvist *et al.* (1986a)
F344 rat	Male, female			75, 60	Törnqvist *et al.* (1988)
F344 rat	Male			42	Walker *et al.* (1992a)
Syrian hamster	NR			~100	Törnqvist *et al.* (1986a)
Syrian hamster	Male, female			120, 105	Törnqvist *et al.* (1988)

NR, not reported

It was calculated from the value of 2–2.4 pmol HOEtCys/g Hb per (ppm h) of ethylene and the value of 30 pmol HOEtCys/g Hb per (ppm × h) of ethylene oxide that 7–8% of inhaled ethylene is metabolized in male CBA mice to ethylene oxide (Ehrenberg *et al.*, 1977; Segerbäck, 1983). These mice had been exposed to ethylene at concentrations below 20 ppm [23 mg/m^3], at which first-order kinetics of metabolism can be assumed. The value is equal to the alveolar retention of ethylene at steady state and is similar to the values calculated for rats and humans (see above).

HOEtVal was determined in Hb of male and female Fischer 344 rats and male and female Syrian hamsters exposed for six months to gasoline and diesel exhausts (mean atmospheric concentrations of ethylene, < 0.1–2.28 ppm [< 0.115–2.62 mg/m^3]). In hamsters, the levels of HOEtVal increased almost linearly with dose. The increments at the highest dose were similar in female rats (505 pmol/g Hb) and hamsters (615 pmol/g Hb) and in male rats (450 pmol/g Hb) and hamsters (420 pmol/g Hb). These values were about 50–90% of those predicted from the data on mice, indicating that ethylene behaves similarly in these species. It was estimated from the results of studies on animals that an uptake (i.e. amount metabolized) of 1 mg ethylene/kg bw is associated with a tissue dose of ethylene oxide of 0.7×10^{-6} mol×h/L [0.03 mg×h/kg bw], similar to the value obtained for humans (Törnqvist *et al.*, 1988).

4.1.3 *Comparison between humans and experimental animals*

Formation of ethylene oxide was determined directly in rats exposed to ethylene, but no such data are available for humans. Assuming that the metabolism of ethylene in humans proceeds quantitatively via ethylene oxide, however, the average body burden of ethylene

oxide resulting from exposure to ethylene can be calculated from pharmacokinetic parameters obtained for the two compounds. A value for ethylene oxide of 0.17 pmol/ml tissue [7.5 ng/kg bw] would result from ethylene produced endogenously; taking into account additional exposure to 15 ppb [17.3 μg/m^3] atmospheric ethylene, as measured in Munich, Germany, the body burden of ethylene oxide can be computed as 0.25 pmol/ml tissue [11 ng/kg bw] (Filser *et al.*, 1992).

For exposure concentrations below 50 ppm [57.5 mg/m^3], the pharmacokinetic parameters of inhaled ethylene obtained in rats were extrapolated to humans by means of an allometric method based on a surface factor equal to two-thirds of body weight (Filser, 1992). The deviation between the values predicted from rats and the measured values did not exceed a factor of 2.3.

4.2 Toxic effects

4.2..1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Exposure to atmospheric ethylene alone did not lead to toxic effects, whether after single exposures of male Holtzman rats (4 h up to 57 000 ppm [65 550 mg/m^3]) or male Fischer 344 rats (5 h to 10 000 ppm [11 500 mg/m^3]) (Conolly & Jaeger, 1977; Conolly *et al.*, 1978; Conolly & Jaeger, 1979; Guest *et al.*, 1981), after 90-day exposures of male and female Sprague-Dawley rats (6 h/day, 5 days/week, up to 10 000 ppm [11 500 mg/m^3]) (Rhudy *et al.*, 1978) or after two-year exposures of male and female Fischer 344 rats (6 h/day, 5 days/week, up to 3000 ppm [3450 mg/m^3]) (Hamm *et al.*, 1984). This lack of toxicity, which might be predicted from results obtained for ethylene oxide, is due to saturation of the metabolic activation of ethylene (see section 4.1.2).

Single exposures of male Holtzman rats to atmospheric ethylene (4 h; 10 000, 23 000–30 000, 50 000–57 000 ppm [11 500, 26 450–34 500, 57 500–65 550 mg/m^3]) one day after treatment with Aroclor 1254 (100 mg/kg bw, equivalent to 300 μmol/kg bw, once daily by gavage for three days induced dose-dependent acute hepatotoxicity. Hepatic effects were indicated 24 h after beginning of exposure by elevated serum concentrations of sorbitol dehydrogenase and of alanine-α-ketoglutarate transaminase and by histological findings such as cell ballooning and haemorrhagic necrosis in centrilobular zones (Conolly & Jaeger, 1977; Conolly *et al.*, 1978; Conolly & Jaeger, 1979). Treatment 0.5 h before start of the exposure with diethylmaleate (0.5 ml/kg bw), in order to deplete reduced glutathione, or with trichloropropene oxide (0.1 ml/kg bw), in order to inhibit epoxide hydrolase, had no effect on the hepatotoxicity of ethylene in Aroclor 1254-pretreated rats (Conolly & Jaeger, 1979).

In two male Fischer 344 rats treated with Aroclor 1254 (500 mg/kg; single intraperitoneal injection five days before exposure), a 5-h exposure to 10 000 ppm [11 500 mg/m^3] ^{14}C-ethylene (free of ^{14}C-acetylene) in a closed recirculating system (35 L) caused uniform hepatic centrilobular necrosis, which was seen 36 h after exposure. Treatment with Aroclor 1254 without subsequent exposure to ethylene resulted in slight

hypertrophy of centrilobular liver cells without hepatocellular necrosis. The authors suggested that Aroclor 1254 affects the metabolism of ethylene in such a way that a toxic metabolite is produced in sufficient quantities to elicit hepatotoxicity (Guest *et al.*, 1981).

4.3 Reproductive and prenatal effects

No data were available to the Working Group.

4.4 Genetic and related effects (see also Table 5 and Appendices 1 and 2)

4.4.1 *Humans*

In the DNA of peripheral lymphocytes of eight people not occupationally exposed to ethylene or ethylene oxide, 7-(2-hydroxyethyl)guanine (7-HOEtGua) was detected at a background level of 8.5 ± 5.7 nmol/g DNA. Possible sources for this DNA adduct were not discussed (Föst *et al.*, 1989).

No other data were available to the Working Group.

4.4.2 *Experimental systems*

(*a*) *DNA adducts*

The ratio between 7-HOEtGua in DNA in various organs and HOEtVal in Hb of rats exposed to ethylene oxide was over 100 times higher in unexposed than in animals exposed for four weeks (Walker *et al.*, 1992a,b). [This suggests that factors other than ethylene oxide are involved in the formation of 7-HOEtGua.]

7-HOEtGua was found by gas chromatography–mass spectrometry at background levels of 2–6 nmol/g DNA in DNA of lymphocytes from blood of untreated male Sprague-Dawley rats (Föst *et al.*, 1989) and in DNA of various tissues from male Fischer 344 rats and B6C3F1 mice (Walker *et al.*, 1992b). Alkylation of 7-guanine was measured in DNA from liver, spleen and testis of mice 14 h after exposure by inhalation to ^{14}C-ethylene at an initial concentration of 11 ppm [12.9 mg/m^3] (exposure dose, 50 ppm×h [58.5 mg×h/m^3]) for 8 h. The values of degree of alkylation were 0.17 for liver, 0.098 for spleen and 0.068 nmol/g DNA for testis, representing < 10% of the background levels. The ratios of 7-guanine in DNA to N$^{\tau}$-His in Hb were approximately the same as those obtained after intraperitoneal injection of ethylene oxide (Segerbäck, 1983).

(*b*) *Mutation and allied effects*

Gene mutations were not induced in *Salmonella typhimurium* TA100 exposed for 7 h to 20% ethylene in air, either with or without an exogenous metabolic system. Ethylene did not induce micronuclei in bone-marrow cells of rats or of mice exposed to up to 3000 ppm (3500 mg/m^3) for 6 h/day, five days/week for four weeks.

Table 5. Genetic and related effects of ethylene

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	225.0000[c]	Victorin & Ståhlberg (1988)
MVM, Micronucleus test, mouse bone-marrow cells *in vivo*	–		1200, inhal. 6 h 5 d/wk 4 wks	Vergnes & Pritts (1994)
MVR, Micronucleus test, rat bone-marrow cells *in vivo*	–		725, inhal. 6 h 5 d/wk 4 wks	Vergnes & Pritts (1994)
BVD, Binding (covalent) to mouse DNA *in vivo*	+		5.9000, inhal. 8 h	Segerbäck (1983)
Protein binding				
BHP, Binding (covalent) to human haemoglobin *in vivo*	+		0.075, inhal. 8 h	Törnqvist *et al.* (1989a)
BHP, Binding (covalent) to human haemoglobin *in vivo*	+		0.0000	Filser *et al.* (1992)

[a] +, positive; –, negative
[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw
[c] Atmospheric concentration in exposure chamber

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Ethylene, the petrochemical manufactured in largest volume worldwide, is produced primarily by the steam-cracking of hydrocarbons. It is used mainly as a chemical intermediate in the production of polymers and other industrial chemicals; small amounts are used to promote the ripening of fruits and vegetables. Ethylene is introduced into the environment from both natural and man-made sources, including emissions from vegetation, as a product of burning of organic material (such as cigarettes) and of incomplete combustion of fossil fuels, and in its production and use. Few data are available on levels of occupational exposure.

5.2 Human carcinogenicity data

The available data did not allow the Working Group to evaluate the carcinogenicity of ethylene to humans.

5.3 Animal carcinogenicity data

Ethylene was tested for carcinogenicity in one experiment in rats exposed by inhalation. No increase in tumour incidence was reported.

5.4 Other relevant data

Endogenous but unidentified sources of ethylene exist in man and experimental animals. Steady-state alveolar retention of ethylene is less than 10% in both man and rat. The biological half-time of ethylene in humans is about 0.65 h. In rats and man, the processes of uptake, exhalation and metabolism are described by first-order kinetics, at least up to 50 ppm; in rats, ethylene metabolism follows first-order kinetics up to about 80 ppm. The maximal rate of metabolism in rats is reached at about 1000 ppm, the initial metabolite being ethylene oxide; hydroxyethyl cysteine is a urinary metabolite in mice. Because ethylene metabolism can be saturated, the maximal possible concentration of ethylene oxide in rat tissues is about 0.34 nmol/ml (15 ng/g bw).

Exposure to ethylene results in the formation of adducts with proteins. In nonsmokers, the background concentrations of the hydroxyethyl valine adduct of haemoglobin were 12–188 pmol/g haemoglobin. Environmental ethylene contributes to these concentrations; the endogenous contribution was calculated to be about 12 pmol/g haemoglobin in nonsmoking control subjects. The increment of N-terminal hydroxyethyl valine formed during a 40-h work week has been estimated as 100–120 pmol/g haemoglobin per part per million of ethylene. Tobacco smoke contributes to formation of this adduct: smoking 10–30 cigarettes/day was reported to result in 600–690 pmol/g haemoglobin.

Background concentrations of 7-hydroxyethyl guanine were 8.5 nmol/g DNA in one study of human peripheral lymphocytes and ranged from 2 to 6 nmol/g DNA in various

tissues of rats and mice. A single exposure of mice to 50 ppm ethylene for 1 h resulted in 0.1–0.2 nmol/g DNA.

No data were available on the genetic and related effects of ethylene in exposed humans. In a single study, no micronuclei were induced in bone-marrow cells of mice and rats exposed *in vivo*. Gene mutation was not induced in *Salmonella typhimurium*. Although the genetic effects of ethylene have not been well studied, its metabolite, ethylene oxide, is genotoxic in a broad range of assays.

5.5 Evaluation[1]

There is *inadequate evidence* in humans for the carcinogenicity of ethylene.

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

Overall evaluation

Ethylene *is not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

Altshuller, A.P. (1983) Review: natural volatile organic substances and their effect on air quality in the United States. *Atmos. Environ.*, **17**, 2131–2165

American Conference of Governmental Industrial Hygienists (1991) *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 6th Ed., Cincinnati, OH, pp. 598–599

American Conference of Governmental Industrial Hygienists (1993) *1993–1994 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*, Cincinnati, OH, p. 21

Amoco Chemical Co. (1993) *Ethylene Specification*, Chicago, IL

Andersen, M.E., Gargas, M.L., Jones, R.A. & Jenkins, L.J., Jr (1980) Determination of the kinetic constants for metabolism of inhaled toxicants *in vivo* using gas uptake measurements. *Toxicol. appl. Pharmacol.*, **54**, 100–116

Angerer, J., Herrmann, H., Jungen, H., Täuber, U. & Wenzel-Hartung, R.P. (1988) *Wirkung von Ethylen auf Mensch und Tier* [Effects of Ethylene on Man and Animals] (Project 174-4), Hamburg, DGMK Deutsche Wissenschaftliche Gesellschaft für Erdöl, Ergas und Kohle eV

Anlauf, K.G., Bottenheim, J.W., Brice, K.A., Fellin, P., Wiebe, H.A., Schiff, H.I., Mackay, G.I., Braman, R.S. & Gilbert, R. (1985) Measurement of atmospheric aerosols and photochemical products at a rural site in SW Ontario. *Atmos. Environ.*, **19**, 1859–1870

Anon. (1985) Facts & figures for the chemical industry. *Chem. Eng. News*, **63**, 22–86

Anon. (1987) Facts & figures for the chemical industry. *Chem. Eng. News*, **65**, 24–76

Anon. (1988) Facts & figures for the chemical industry. *Chem. Eng. News*, **66**, 34–82

Anon. (1989) Facts & figures for the chemical industry. *Chem. Eng. News*, **67**, 36–90

[1]For definition of the italicized terms, see Preamble, pp. 27–30.

Anon. (1990) Facts & figures for the chemical industry. *Chem. Eng. News*, **68**, 34–83

Anon. (1991a) Facts & figures for the chemical industry. *Chem. Eng. News*, **69**, 28–69

Anon. (1991b) Chemical profile: ethylene. *Chem. Mark. Rep.*, **239**, 19, 46

Anon. (1992) Facts & figures for the chemical industry. *Chem. Eng. News*, **70**, 32–75

Anon. (1993) Facts & figures for the chemical industry. *Chem. Eng. News*, **71**, 38–83

Arms, A.D. & Travis, C.C. (1988) *Reference Physiological Parameters in Pharmacokinetic Modeling* (Technical Report No. EPA/600/6-88/004), Washington DC, US Environmental Protection Agency

Bailey, E., Brooks, A.G.F., Dollery, C.T., Farmer, P.B., Passingham, B.J., Sleightholm, M.A. & Yates, D.W. (1988) Hydroxyethylvaline adduct formation in haemoglobin as a biological monitor of cigarette smoke intake. *Arch. Toxicol.*, **62**, 247–253

Bailey, J.C., Gunary, K., Schmidl, B. & Williams, M.L. (1990a) Speciated hydrocarbon emissions from a sample of UK vehicles on the road over a range of speeds. *Sci. total Environ.*, **93**, 199–206

Bailey, J.C., Schmidl, B. & Williams, M.L. (1990b) Speciated hydrocarbon emissions from vehicles operated over the normal speed range on the road. *Atmos. Environ.*, **24A**, 43–52

Barrefors, G. & Petersson, G. (1992) Volatile hazardous hydrocarbons in a Scandinavian urban road tunnel. *Chemosphere*, **25**, 691–696

Binder, H. & Lindner, W. (1972) Detection of ethylene oxide in smoke of guaranteed untreated cigarettes. *Fachliche Mitt. Austria Tabakwerte AG*, **13**, 215–220 (in German)

Bolt, H.M. & Filser, J.G. (1987) Kinetics and disposition in toxicology. Example: carcinogenic risk estimate for ethylene. *Arch. Toxicol.*, **60**, 73–76

Bolt, H.M., Filser, J.G. & Störmer, F. (1984) Inhalation pharmacokinetics based on gas uptake studies. V. Comparative pharmacokinetics of ethylene and 1,3-butadiene in rats. *Arch. Toxicol.*, **55**, 213–218

Bouscaren, R., Frank, R. & Veldt, C. (1987) *Hydrocarbons. Identification of Air Quality Problems in Member States of the European Communities* (Report No. EUR-10646-EN; US NTIS PB88-187992), Luxembourg, European Commission

Bridgen, M.P. (1985) Gases in the greenhouse. *Soc. Am. Florists*, **May**, 30–41

Calleman, C.J. (1986) Monitoring of background levels of hydroxyethyl adducts in human hemoglobin. *Prog. clin. biol. Res.*, **209B**, 261–270

Chemical Information Services Ltd (1991) *Directory of World Chemical Producers 1992/93 Edition*, Dallas, TX, p. 274

Clemens, M.R., Einsele, H., Frank, H., Remmer, H. & Waller, H.D. (1983) Volatile hydrocarbons from hydrogen peroxide-induced lipid peroxidation of erythrocytes and their cell compounds. *Biochem. Pharmacol.*, **32**, 3877–3878

Colbeck, I. & Harrison, R.M. (1985) The concentrations of specific C_2–C_6 hydrocarbons in the air of NW England. *Atmos. Environ.*, **19**, 1899–1904

Conolly, R.B. & Jaeger, R.J. (1977) Acute hepatotoxicity of ethylene and halogenated ethylenes after PCB pretreatment. *Environ. Health Perspectives*, **21**, 131–135

Conolly, R.B. & Jaeger, R.J. (1979) Acute hepatotoxicity of vinyl chloride and ethylene: modification by trichloropropene oxide, diethylmaleate, and cysteine. *Toxicol. appl. Pharmacol.*, **50**, 523–531

Conolly, R.B., Jaeger, R.J. & Szabo, S. (1978) Acute hepatotoxicity of ethylene, vinyl fluoride, vinyl chloride, and vinyl bromide after Aroclor 1254 pretreatment. *Exp. mol. Pathol.*, **28**, 25–33

Davidson, C.I., Lin, S.-F., Osborn, J.F., Pandey, M.R., Rasmussen, R.A. & Khalil, M.A.K. (1986) Indoor and outdoor air pollution in the Himalayas. *Environ. Sci. Technol.*, **20**, 561–567

Denk, B., Filser, J.G., Oesterle, D., Deml, E. & Greim, H. (1988) Inhaled ethylene oxide induces preneoplastic foci in rat liver. *J. Cancer Res. clin. Oncol.*, **114**, 35–38

Deutsche Forschungsgemeinschaft (1993) *MAK and BAT Values 1993* (Report No. 29), Weinheim, VCH Verlagsgesellschaft, p. 46

Dooley, A.E. (1983) Ethylene. In: Parmeggiani, L., ed., *Encyclopedia of Occupational Health and Safety*, 3rd rev. ed., Geneva, ILO, pp. 792–794

Dörffling, K. (1982) *Das Hormonsystem der Pflanzen* [Hormonal System of Plants], Stuttgart, Thieme, pp. 72–90, 115–129, 170–175

Dow Chemical Co. (1989) *Sales Specification: Ethylene*, Midland, MI

Ehrenberg, L. & Törnqvist, M. (1992) Use of biomarkers in epidemiology: quantitative aspects. *Toxicol. Lett.*, **64/65**, 485–492

Ehrenberg, L., Osterman-Golkar, S., Segerbäck, D., Svensson, K. & Calleman, C.J. (1977) Evaluation of genetic risks of alkylating agents. III. Alkylation of haemoglobin after metabolic conversion of ethene to ethene oxide *in vivo*. *Mutat. Res.*, **45**, 175–184

Elmenhorst, H. & Schultz, C. (1968) Volatile components of tobacco smoke. Chemical composition of gas–vapour phase. *Beitr. Tabakforsch.*, **4**, 90–123 (in German)

European Commission (1993) *Panorama of EC Industry 93*, Luxembourg, Office for Official Publications of the European Union, pp. 6–15

Farmer, P.B., Bailey, E., Gorf, S.M., Törnqvist, M., Osterman-Golkar, S., Kautiainen, A. & Lewis-Enright, D.P. (1986) Monitoring human exposure to ethylene oxide by the determination of haemoglobin adducts using gas chromatography–mass spectrometry. *Carcinogenesis*, **7**, 637–640

Filser, J.G. (1992) The closed chamber technique—uptake, endogenous production, excretion, steady-state kinetics and rates of metabolism of gases and vapors. *Arch. Toxicol.*, **66**, 1–10

Filser, J.G. & Bolt, H.M. (1984) Inhalation pharmacokinetics based on gas uptake studies. VI. Comparative evaluation of ethylene oxide and butadiene monoxide as exhaled reactive metabolites of ethylene and 1,3-butadiene in rats. *Arch. Toxicol.*, **55**, 219–223

Filser, J.G., Denk, B., Törnqvist, M., Kessler, W. & Ehrenberg, L. (1992) Pharmacokinetics of ethylene in man; body burden with ethylene oxide and hydroxyethylation of hemoglobin due to endogenous and environmental ethylene. *Arch. Toxicol.*, **66**, 157–163

Föst, U., Marczynski, B., Kasemann, R. & Peter, H. (1989) Determination of 7-(2-hydroxyethyl)guanine with gas chromatography/mass spectrometry as a parameter for genotoxicity of ethylene oxide. *Arch. Toxicol.*, **Suppl. 13**, 250–253

Frank, H., Hintze, T. & Remmer, H. (1980) Volatile hydrocarbons in breath, an indication for peroxidative degradation of lipids. In: Kolb, B., ed., *Applied Headspace Gas Chromatography*, London, Heyden & Son, pp. 155–164

Frostling, H., Hoff, A., Jacobsson, S., Pfäffli, P., Vainiotalo, S. & Zitting, A. (1984) Analytical, occupational and toxicological aspects of the degradation products of polypropylene plastics. *Scand. J. Work Environ. Health*, **10**, 163–169

Fu, P.C., Zic, V. & Ozimy, K. (1979) Studies of ethylene-forming system in rat liver extract. *Biochim. biophys. Acta*, **585**, 427–434

Gibson, G.G., Clarke, S.E., Farrar, D. & Elcombe, C.R. (1987) Ethene. In: Snyder, R., ed., *Ethel Browning's Toxicity and Metabolism of Industrial Solvents*, Vol. 1, *Hydrocarbons*, Amsterdam, Elsevier, pp. 339–353

Giménez, E.R., Rodríguez, C.A. & Capone, L. (1990) Potential human exposure resulting from the chemical industry in Argentina. In: Johnson, B.L., ed., *Advances in Neurobehavioral Toxicology: Applications in Environmental and Occupational Health*, Chelsea, MI, Lewis Publishers, pp. 75–77

Grantom, R.L. & Royer, D.J. (1987) Ethylene. In: Gerhartz, W., Yamamoto, Y.S., Kaudy, L., Rounsaville, J.F. & Schulz, G., eds, *Ullmann's Encyclopedia of Industrial Chemistry*, 5th rev. ed., Vol. A10, New York, VCH Publishers, pp. 45–93

Greim, H., ed. (1993) Ethylene. In: *Gesundheitsschädliche Arbeitsstoffe. Toxikologischarbeitsmedizinische Begründung von MAK-Werten (Maximale Arbeitsplatz-Konzentrationen)* [Toxic Substances at Work. Toxicological, Occupational and Medical Establishment of MAK Values (Maximal Concentrations at the Workplace)], Weinheim, VCH Verlagsgesellschaft, pp. 1–17

Guest, D., Barrow, C.S., Popp, J.A. & Dent, J.G. (1981) Effects of Aroclor 1254 on disposition and hepatotoxicity of ethylene in the rat. *Toxicol. appl. Pharmacol.*, **57**, 325–334

Hamm, T.E., Jr, Guest, D. & Dent, J.G. (1984) Chronic toxicity and oncogenicity bioassay of inhaled ethylene in Fischer-344 rats. *Fundam. appl. Toxicol.*, **4**, 473–478

Hansch, C. & Leo, A. (1979) *Substituent Constants for Correlation Analysis in Chemistry and Biology*, New York, John Wiley & Sons, p. 175

Harrison, V.C. (1981) Ethylene, an ovulatory hormone? (Letter to the Editor) *Lancet*, **i**, 438

Hoff, A., Jacobsson, S., Pfäffli, P., Zitting, A. & Frostling, H. (1982) Degradation products of plastics. Polyethylene and styrene-containing thermoplastics—analytical, occupational and toxicologic aspects. *Scand. J. Work Environ. Health*, **8** (Suppl. 2), 1–60

Hogstedt, C., Rohlén, O., Berndtsson, B.S., Axelson, O. & Ehrenberg, L. (1979) A cohort study of mortality and cancer incidence in ethylene oxide production workers. *Br. J. ind. Med.*, **36**, 276–280

Hov, Ø., Schmidbauer, N. & Oehme, M. (1991) C_2–C_5 hydrocarbons in rural south Norway. *Atmos. Environ.*, **25A**, 1981–1999

IARC (1979) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 19, *Some Monomers, Plastics and Synthetic Elastomers, and Acrolein*, Lyon, pp. 157–186

ILO (1991) *Occupational Exposure Limits for Airborne Toxic Substances: Values of Selected Countries* (Occupational Safety and Health Series No. 37), 3rd Ed., Geneva, pp. 194–195 (Substance No. 962)

Jankovic, J., Jones, W., Burkhart, J. & Noonan, G. (1991) Environmental study of firefighters. *Ann. occup. Hyg.*, **35**, 581–602

Japan Petrochemical Industry Association (1993) *Petrochemical Industry of Japan*, Tokyo, pp. 7, 19

Johanson, G. & Filser, J.G. (1992) Experimental data from closed chamber gas uptake studies in rodents suggest lower uptake rate of chemical than calculated from literature values on alveolar ventilation. *Arch. Toxicol.*, **66**, 291–295

Kader, A.A. (1986) Biochemical and physiological basis for effects of controlled and modified atmospheres on fruits and vegetables. *Food Technol.*, **40**, 99–104

Kader, A.A. & Kasmire, R.F. (1984) Effects of ethylene on commodities during postharvest handling. *Outlook Agric., March–April*, 15–16

Kanakidou, M., Bonsang, B. & Lambert, G. (1989) Light hydrocarbons vertical profiles and fluxes in a French rural area. *Atmos. Environ.*, **23**, 921–927

Kautiainen, A. & Törnqvist, M. (1991) Monitoring exposure to simple epoxides and alkenes through gas chromatographic determination of hemoglobin adducts. *Int. Arch. occup. environ. Health*, **63**, 27–31

Kautiainen, A., Törnqvist, M., Anderstam, B. & Vaca, C.E. (1991) In vivo hemoglobin dosimetry of malonaldehyde and ethene in mice after induction of lipid peroxidation. Effects of membrane lipid fatty acid composition. *Carcinogenesis*, **12**, 1097–1102

Kessler, W. & Remmer, H. (1990) Generation of volatile hydrocarbons from amino acids and proteins by an iron/ascorbate/GSH system. *Biochem. Pharmacol.*, **39**, 1347-1351

Khalil, M.A.K. & Rasmussen, R.A. (1992) Forest hydrocarbon emissions: relationships between fluxes and ambient concentrations. *J. Air Waste Manag. Assoc.*, **42**, 810–813

Lide, D.R., ed. (1991) *CRC Handbook of Chemistry and Physics*, 72nd Ed., Boca Raton, FL, CRC Press, pp. 3–241, 6–69, 6–83

Lieberman, M. & Mapson, L.W. (1964) Genesis and biogenesis of ethylene. *Nature*, **204**, 343–345

Lieberman, M. & Hochstein, P. (1966) Ethylene formation in rat liver microsomes. *Science*, **152**, 213–214

Lieberman, M., Kunishi, A.T., Mapson, L.W. & Wardale, D.A. (1965) Ethylene production from methionine. *Biochem. J.*, **97**, 449–459

Lightman, P., Kallend, A.S., Marsh, A.R.W., Jones, B.M.R. & Penkett, S.A. (1990) Seasonal variation of hydrocarbons in the free troposphere at mid-latitudes. *Tellus*, **42B**, 408–422

Locke, D.C., Feldstein, M., Bryan, R.J., Hyde, D.L., Levaggi, D.A., Rasmussen, R.A. & Warner, P.O. (1989) Determination of C_1 through C_5 atmospheric hydrocarbons. In: Lodge, J.P., Jr, ed., *Methods of Air Sampling and Analysis*, 3rd ed., Chelsea, MI, Lewis Publishers, pp. 243–248

Löfgren, L. & Petersson, G. (1992) Proportions of volatile hazardous hydrocarbons in vehicle-polluted urban air. *Chemosphere*, **24**, 135–140

Löfroth, G., Burton, R.M., Forehand, L., Hammond, S.K., Seila, R.L., Zweidinger, R.B. & Lewtas, J. (1989) Characterization of environmental tobacco smoke. *Environ. Sci. Technol.*, **23**, 610–614

Maples, K.R. & Dahl, A.R. (1993) Levels of epoxides in blood during inhalation of alkenes and alkene oxides. *Inhal. Toxicol.*, **5**, 43–54

Matuška, P., Koval, M. & Seiler, W. (1986) A high resolution GC-analysis method for determination of C_2–C_{10} hydrocarbons in air samples. *J. high Resolut. Chromatogr. Chromatogr. Commun.*, **9**, 577–583

Mowrer, J. & Lindskog, A. (1991) Automatic unattended sampling and analysis of background levels of C_2–C_5 hydrocarbons. *Atmos. Environ.*, **25A**, 1971–1979

National Research Council Canada (1985) *Ethylene in the Environment: Scientific Criteria for Assessing its Effects on Environmental Quality* (NRCC No. 22496), Ottawa

Nickell, L.G. (1982) Plant growth substances. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 18, New York, John Wiley & Sons, pp. 1–23

Ortiz de Montellano, P.R. & Mico, B.A. (1980) Destruction of cytochrome P-450 by ethylene and other olefins. *Mol. Pharmacol.*, **18**, 128–135

Ortiz de Montellano, P.R., Kunze, K.L. & Mico, B.A. (1980) Destruction of cytochrome P-450 by olefins: *N*-alkylation of prosthetic heme. *Mol. Pharmacol.*, **18**, 602–605

Ortiz de Montellano, P.R., Beilan, H.S., Kunze, K.L. & Mico, B.A. (1981) Destruction of cytochrome P-450 by ethylene. Structure of the resulting prosthetic heme product. *J. biol. Chem.*, **256**, 4395–4399

Osterman-Golkar, S., Farmer, P.B., Segerbäck, D., Bailey, E., Calleman, C.J., Svensson, K. & Ehrenberg, L. (1983) Dosimetry of ethylene oxide in the rat by quantitation of alkylated histidine in hemoglobin. *Teratog. Carcinog. Mutag.*, **3**, 395–405

Passingham, B.J., Farmer, P.B., Bailey, E., Brooks, A.G.F. & Yates, D.W. (1988) 2-Hydroxyethylation of haemoglobin in man. In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention* (IARC Scientific Publications No. 89), Lyon, IARC, pp. 279–285

Persson, K.-A. & Berg, S. (1989) Automatic determination of selected C2–C_4 hydrocarbons in urban air by solid sorbent sampling and gas chromatography. *Chromatographia*, **27**, 55–59

Persson, K.-A., Berg, S., Törnqvist, M., Scalia-Tomba, G.-P. & Ehrenberg, L. (1988) Note on ethene and other low-molecular weight hydrocarbons in environmental tobacco smoke. *Acta chem. scand.*, **B42**, 690–696

Ram Chandra, G. & Spencer, M. (1963) A micro apparatus for absorption of ethylene and its use in determination of ethylene in exhaled gases from human subjets. *Biochim. biophys. Acta*, **69**, 423–425

Rao, A.M.M. & Pandit, G.G. (1988) Concentrations of C_2–C_5 hydrocarbons in atmospheric air at Deonar, Bombay, in relation to possible sources. *Atmos. Environ.*, **22**, 395–401

Reid, M.S. (1985) Ethylene in the care and handling of ornamentals. *Soc. Am. Florists*, **June**, 22–24

Reineke, F.J. & Bächmann, K. (1985) Gas chromatographic determination of C_2–C_8 hydrocarbons and halocarbons in ambient air by simultaneous use of three detectors. *J. Chromatogr.*, **323**, 323–329

Rhudy, R.L., Lindberg, D.C., Goode, J.W., Sullivan, D.J. & Gralla, E.J. (1978) Ninety-day subacute inhalation study with ethylene in albino rats (Abstract No. 151). *Toxicol. appl. Pharmacol.*, **45**, 285

Rudolph, J., Koppmann, R., Johnen, F.-J. & Khedim, A. (1989) The distribution of light nonmethane hydrocarbons in the troposphere and their potential impact on photochemical ozone formation. In: Bojkov, R.D. & Fabian, P., eds, *Ozone in the Atmosphere*, Hampton, VA, DEEPAK Publishing, pp. 561–564

Sadtler Research Laboratories (1991) *Sadtler Standard Spectra, 1981–1991 Supplementary Index*, Philadelphia, PA

Sagai, M. & Ichinose, T. (1980) Age-related changes in lipid peroxidation as measured by ethane, ethylene, butane and pentane in respired gases of rats. *Life Sci.*, **27**, 731–738

Sarto, F., Törnqvist, M., Tomanin, R., Bartolucci, G.B., Osterman-Golkar, S.M. & Ehrenberg, L. (1991) Studies of biological and chemical monitoring of low-level exposure to ethylene oxide. *Scand. J. Work Environ. Health*, **17**, 60–64

Satsumabayashi, H., Kurita, H., Chang, Y.-S., Carmichael, G.R. & Ueda, H. (1992) Diurnal variation of OH radical and hydrocarbons in a polluted air mass during long-range transport in central Japan. *Atmos. Environ.*, **26A**, 2835–2844

Sawada, S. & Totsuka, T. (1986) Natural and anthropogenic sources and fate of atmospheric ethylene. *Atmos. Environ.*, **20**, 821–832

Schmidbauer, N. & Oehme, M. (1985) Analysis of light hydrocarbons (C_2–C_6) at ppt levels by high resolution gas chromatography. *J. high Resolut. Chromatogr. Chromatogr. Commun.*, **8**, 404–406

Schmiedel, G., Filser, J.G. & Bolt, H.M. (1983) Rat liver microsomal transformation of ethene to oxirane *in vitro*. *Toxicol. Lett.*, **19**, 293–297

Scientific & Technical Information Research Institute of the Ministry of Chemical Industry of China (1984) *World Chemical Industry Yearbook, 1984: China Chemical Industry* (English ed.), Beijing, pp. 504, 536

Segerbäck, D. (1983) Alkylation of DNA and hemoglobin in the mouse following exposure to ethene and ethene oxide. *Chem.-biol. Interactions*, **45**, 139–151

Seinfeld, J.H. (1989) Urban air pollution: state of the science. *Science*, **243**, 745–752

Shaikh, G.N., Pandit, G.G., Rao, A.M.M. & Mishra, U.C. (1988) Determination of ethylene and other reactive hydrocarbons in tobacco smoke and evaluation of risk from their inhalation. *Sci. total Environ.*, **74**, 67–73

Shen, J., Kessler, W., Denk, B. & Filser, J.G. (1989) Metabolism and endogenous production of ethylene in rat and man. *Arch. Toxicol.*, **Suppl. 13**, 237–239

van Sittert, N.J. & van Vliet, E.W.N. (1994) Monitoring occupational exposure to some industrial chemicals by the determination of hemoglobin adducts. *Clin. Chem.*, **40**(7) (in press)

van Sittert, N.J., de Jong, G., Clare, M.G., Davies, R., Dean, B.J., Wren, L.J. & Wright, A.S. (1985) Cytogenetic, immunological, and haematological effects in workers in an ethylene oxide manufacturing plant. *Br. J. ind. Med.*, **42**, 19–26

van Sittert, N.J., Beulink, G.D.J., van Vliet, E.W.N. & van der Waal, H. (1993) Monitoring occupational exposure to ethylene oxide by the determination of hemoglobin adducts. *Environ. Health Perspectives*, **99**, 217–220

Steward, A., Allott, P.R., Cowles, A.L. & Mapleson, W.W. (1973) Solubility coefficients for inhaled anaesthetics for water, oil and biological media. *Br. J. Anaesthesiol.*, **45**, 282–293

Stump, F., Tejada, S., Ray, W., Dropkin, D., Black, F., Crews, W., Snow, R., Siudak, P., Davis, C.O., Baker, L. & Perry, N. (1989) The influence of ambient temperature on tailpipe emissions from 1984–1987 model year light-duty gasoline motor vehicles. *Atmos. Environ.*, **23**, 307–320

Svensson, K. & Osterman-Golkar, S. (1984) Kinetics of metabolism of propene and covalent binding to macromolecules in the mouse. *Toxicol. appl. Pharmacol.*, **73**, 363–372

Tille, K.J.W., Savelsberg, M. & Bächmann, K. (1985) Airborne measurements of nonmethane hydrocarbons over western Europe: vertical distributions, seasonal cycles of mixing ratios and source strengths. *Atmos. Environ.*, **19**, 1751–1760

Törnqvist, M. & Ehrenberg, L. (1990) Approaches to risk assessment of automotive engine exhausts. In: Vainio, H., Sorsa, M. & McMichael, A.J., eds, *Complex Mixtures and Cancer Risk* (IARC Scientific Publications No. 104), Lyon, IARC, pp. 277–287

Törnqvist, M., Mowrer, J., Jensen, S. & Ehrenberg, L. (1986a) Monitoring of environmental cancer initiators through hemoglobin adducts by a modified Edman degradation method. *Anal. Biochem.*, **154**, 255–266

Törnqvist, M., Osterman-Golkar, S., Kautiainen, A., Jensen, S., Farmer, P.B. & Ehrenberg, L. (1986b) Tissue doses of ethylene oxide in cigarette smokers determined from adduct levels in hemoglobin. *Carcinogenesis*, **7**, 1519–1521

Törnqvist, M., Kautiainen, A., Gatz, R.N. & Ehrenberg, L. (1988) Hemoglobin adducts in animals exposed to gasoline and diesel exhaust. I. Alkenes. *J. appl. Pharmacol.*, 8, 159–170

Törnqvist, M., Almberg, J.G., Bergmark, E.N., Nilsson, S. & Osterman-Golkar, S.M. (1989a) Ethylene oxide doses in ethene-exposed fruit store workers. *Scand. J. Work Environ. Health*, **15**, 436–438

Törnqvist, M., Gustafsson, B., Kautiainen, A., Harms-Ringdahl, M., Granath, F. & Ehrenberg, L. (1989b) Unsaturated lipids and intestinal bacteria as sources of endogenous production of ethene and ethylene oxide. *Carcinogenesis*, **10**, 39–41

Törnqvist, M., Magnusson, A.-L., Farmer, P.B., Tang, Y.-S., Jeffrey, A.M., Wazneh, L., Beulink, G.D.T., van der Waal, H. & van Sittert, N.J. (1992) Ring test for low levels of *N*-(2-hydroxyethyl)valine in human hemoglobin. *Anal. Biochem.*, **203**, 357–360

UNEP (1993) *IRPTC Data Profile on Ethylene*, Geneva

Uno, I., Wakamatsu, S., Wadden, R.A., Konno, S. & Koshio, H. (1985) Evaluation of hydrocarbon reactivity in urban air. *Atmos. Environ.*, **19**, 1283–1293

US Environmental Protection Agency (1992) Ethylene; exemption from the requirement of a tolerance. *US Code fed. Regul.*, Title 40, Part 180.1016, pp. 430–431

US Food and Drug Administration (1993) Food and drugs. *US Code fed. Regul.*, **Title 21**, Parts 173.20, 175.105, 175.300, 176.170, 176.180, 177.1200, 177.1210, 177.1330, 177.1340, 177.1390, 177.1395, 177.1520, 177.2600, pp. 105, 129–144, 171–200, 219–226, 233–236, 240–244, 252–262, 309–313

US National Institute for Occupational Safety and Health (1993) *National Occupational Exposure Survey (1981–1983)*, Cincinnati, OH, p. 10

US National Library of Medicine (1993) *Toxic Chemical Release Inventory (TRI) Data Banks* [TRI87, TRI88, TRI89, TRI90, TRI91], Bethesda, MD

Van Valin, C.C. & Luria, M. (1988) O_3, CO, hydrocarbons and dimethyl sulfide over the western Atlantic Ocean. *Atmos. Environ.*, **22**, 2401–2409

Vergnes, J.S. & Pritts, I.M. (1994) Effects of ethylene on micronucleus formation in the bone marrow of rats and mice following four weeks of inhalation exposure. *Mutat. Res.* (in press)

Victorin, K. & Ståhlberg, M. (1988) A method for studying the mutagenicity of some gaseous compounds in *Salmonella typhimurium*. *Environ. mol. Mutag.*, **11**, 65–77

Walker, V.E., MacNeela, J.P., Swenberg, J.A., Turner, M.J., Jr & Fennell, T.R. (1992a) Molecular dosimetry of ethylene oxide: formation and persistence of *N*-(2-hydroxyethyl)valine in hemoglobin following repeated exposures of rats and mice. *Cancer Res.*, **52**, 4320–4327

Walker, V.E., Fennell, T.R., Upton, P.B., Skopek, T.R., Prevost, V., Shuker, D.E.G. & Swenberg, J.A. (1992b) Molecular dosimetry of ethylene oxide: formation and persistence of 7-(2-hydroxyethyl)guanine in DNA following repeated exposures of rats and mice. *Cancer Res.*, **52**, 4328–4334

Watada, A.E. (1986) Effects of ethylene on the quality of fruits and vegetables. *Food Technol.*, **40**, 82–85

Weast, R.C. & Astle, M.J. (1985) *CRC Handbook of Data on Organic Compounds*, Vol. I, Boca Raton, FL, CRC Press, p. 619