資料　９

OECD: Screening Information Data Set(SIDS)
（経済開発協力機構：審査情報データセット：エチレン
1998 年 10 月

ETHYLENE

CAS N°: 74-85-1

（後半に和訳を添付）

FOREWORD INTRODUCTION

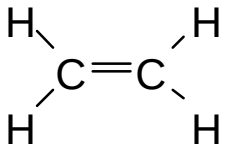
ETHYLENE

CAS N°: 74-85-1

SIDS DOSSIER ON ETHYLENE

Summary of Responses to the OECD Request for Available Data on HPV Chemicals

SIDS PROFILE

1.01 A	CAS NO.	**74-85-1**
1.01 C	CHEMICAL NAME	Ethylene
1.01 G	STRUCTURAL FORMULA	
	OTHER CHEMICAL IDENTITY INFORMATION	
1.5	QUANTITY	Millions metric tonnes per year: (capacity for 1996) Norway: 0.4 World: 83.0
1.7	USE PATTERN	Chemical industry; as raw material for synthesis of chemicals, petrochemicals and resins. Minor quantities used for fruit ripening and as anaesthetic gas.
1.9	SOURCES OF EXPOSURE	Fuel, coal and gas combustion. Leakage from chemical industry. Rural areas: < 1 - 5 $\mu g/m^3$ (0.9 - 4.3 ppb) Heavy traffic areas: up to 1.0 mg/m^3 (0.9 ppm) Petrochemical plants: up to 5 mg/m^3 (4.3 ppm)
ISSUES FOR DISCUSSION (IDENTITY, IF ANY)	No further testing required	

1. GENERAL INFORMATION

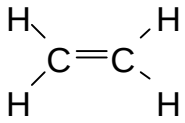
A. **CAS number:** 74-85-1

B. **Name** (IUPAC): Ethylene

C. **Name** (OECD): Ethylene

F. **Molecular formula:** CH_2CH_2

G. **Structural formula:**



H. **Substance group:** Industrial chemical; as raw material for synthesis of chemicals, petrochemicals and resins.

J. **Molecular Weight:** 28.05

1.02 OECD INFORMATION

A. **Sponsor Country:** Norway

B. **Lead Organisation:**
Norwegian Pollution Control Authority (SFT),
P.O. Box 8100 Dep.,
N-0032 Oslo
NORWAY

Contact person:
Marit Kopangen

Tel.: +47 22 573400
Fax.: +47 22 676706

C. **Name of responder:**
Noretyl ANS,
Petrochemical division,
Norsk Hydro ANS,
N-0240 Oslo
NORWAY

1.1 GENERAL SUBSTANCE INFORMATION

A. **Type of Substance:** Organic, hydrocarbon

B. **Physical state** (at 20 °C and 1.013 hPa): Gaseous

C. **Purity:**

1) High purity : > 99.9 %
2) Commercial purity : about 99.9 %

1.2 SYNONYMS

Ethene, acetene, bicarburetted hydrogen, olefiant gas, elayl.

1.3 IMPURITIES

Western Europe product, (ppm range)**:**
Methane + ethane (50-200), propylene and heavier (7-200), CO_2 (2.2-50), H_2(0.1-10), O_2 (0.6-10), acetylene (1.4-10), total sulphur (1-10), water (0.6-20) and CO (0.15-10) [3].

1.4 ADDITIVES

None known.

1.5 QUANTITY

More than 1,000,000 tonnes per annum.
Capacity for 1996 [2]:
Norway: 405,000 tonnes
World: 83,000,000 tonnes

1.6 LABELLING AND CLASSIFICATION

EEC: Fx, R12 (Extremely flammable).
S 2 (Keep out of reach of children.
S 9 (Keep container in well-ventilated place)
S 16 (Keep away from sources of ignition - No smoking)
S 33 (Take precautionary measures against static discharges)

Norway: F, R13 (Extremely flammable liquid gas)
S 9-16-33

According to IARC Monograph Volume 60, (1994):
Ethylene: The agent is not classifiable as to its carcinogenicity to humans [3].

1.7 USE PATTERN

Ethylene is the petrochemical product produced in largest quantities world-wide. More than 95% of the annual commercial production of ethylene is currently based on steam cracking of petroleum hydrocarbons [4].

About 80 % of the ethylene consumed in US, Western Europe and Japan is used for production of ethylene oxide, ethylene dichloride and low density, linear low density and high density polyethylene. Significant amounts are also used to make ethylbenzene, alcohols, olefins, acetaldehyde and vinylacetate. Most of these products are further prosessed into products such as film, blow and injection moulding, extrusion coating, cable insulation and PVC. Minor quantities have been used as anaesthetic gas, for fruit ripening and for welding and cutting metals.

A. General

	Type of use:	Category:
a)	Main industrial use	Use in closed systems Chemical Industry: used in synthesis Raw material
b)	Main industrial use	Non dispersive use Agricultural Industry As fruit ripener

B. Uses in Consumer Products
Not known

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUE

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 [3].

1.9 SOURCES OF EXPOSURE

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 [5].
The main anthropogenic sources are from combustion of gas, fuel, coal and biomass. Maximal exposure of ethylene to humans is considered to be through fossil combustion by vehicles. The total ethylene emission from the global surface has been estimated to be 18-45 $\cdot 10^6$ t/y, of which approximately 74% is released from natural sources and 26 % from anthropogenic sources. Emission from oil combustion is estimated to 1.54 $\cdot 10^6$ t/y [5]. Ethylene produced and consumed in chemical industry is kept in closed systems and the production facility is normally next door to the factory using ethylene as a raw material. Exposure to ethylene from industrial sources are thus mainly due to uncontrolled leakage or blow outs. Such events occur at a rate of once every 2.0 $\cdot 10^6$ t/y of produced ethylene and may result in an immediate release of about 1 ton.

1.10 ADDITIONAL REMARKS

A. Option for disposal
Incineration.

B. Other remarks
No data.

2. PHYSICAL-CHEMICAL DATA

2.1 MELTING POINT

-169.15 °C [4]

2.2 BOILING POINT

-103.71 °C [4]

2.3 DENSITY

d = 0.57 g/cm^3 at boiling point [4].
Gas density at STP 1.2603 g/l [4].
Density relative to air 0.9686 [4].

2.4 VAPOUR PRESSURE

4.27 MPa at 0 °C [4].

2.5 PARTITION COEFFICIENT $\log_{10}P_{ow}$

$\text{Log}_{10}\,P_{ow}$ = 1.13 (calculated) [6].

2.6 WATER SOLUBILITY

A. Solubility

According to Merck Index, "One volume of ethylene gas dissolves in 4 vol of water at 0°C" [7].
One volume of ethylene gas dissolves in 9 volumes of water at 25 °C [8].
Solubility: 131 mg/l at 20°C [9].
At 15 °C the solubility in water is 200 mg/l [10].

B. pH Value, pKa Value

No data available. There is no chemical evidence to suggest a reaction between dissolved ethylene and water and pH remains unchanged.

2.7 FLASH POINT

- 136.11 °C [11].

2.8 AUTO FLAMMABILITY

Autoignition temp: 543°C [7].
Ignition temp: 425-527°C [4].

2.9 FLAMMABILITY

Extremely flammable - liquefied gas.

2.10 EXPLOSIVE PROPERTIES

Explosive limits in air (0.1 MPa and 20°C) [4] :
Lower explosive limit (LEL): 2.75 vol %
Upper explosive limit (UEL): 28.6 vol %

2.11 OXIDIZING PROPERTIES

No information

2.12 OXIDATION:REDUCTION POTENTIAL

No information.

2.13 ADDITIONAL DATA

A. Partition co-efficient between soil/sediment and water (Kd).

No information

B. Other data

Conversion factor for ethylene in air:
1 ppm in air = 1.15 mg/m^3 = 912 nl/l [1,4]

Odour threshold:
Odour low: 299 mg/m^3
Odour high: 4600 mg/m^3 [12]

3. ENVIRONMENTAL FATE AND PATHWAYS

3.1 STABILITY

3.1.1 STABILITY IN AIR

The fate of atmospheric ethylene emitted from natural and anthropogenic sources has been estimated by Sawada and Totsuka, 1986 [5]. They concluded that 89 % was destroyed in the troposphere by reaction with OH radical, and 8 % in the reaction with O_3. The remaining 3 % was transported into the stratosphere. The atmospheric lifetime of ethylene was estimated to be between 2 and 4 days.

Indirect calculation of photodegradation with O_3 as a sensibilizer gave a lifetime of 9.4 days [13]. Using OH as the sensibilizer a lifetime of 2.7 days was calculated [14].

The following lifetimes are according to Howard, P.H. et al (1991) [15]: Handbook of environmental degradation rates:

		Lifetimes:
Air:	High:	3.36 days
	Low:	0.37 days

This is based upon combined, measured photoxidation rate constants for $^{\cdot}OH$ and O_3.
If the calculation procedures for organic compounds in atmosphere of Atkinson, R. (1996) [75] are used the following depletion rates are found:

		Lifetimes	
Air	Due to $^{\cdot}OH$ reaction	1.7	days
	Due to O_3 reaction	10	days
	Due to stratospheric removal	1900	days

Stratospheric removal can be calculated according to IPPC (1995) [76], assuming a similar removal of ethylene as CO.

3.1.2 STABILITY IN WATER

No data available

3.1.3 STABILITY IN SOIL

No data available

3.2 MONITORING DATA (ENVIRONMENT)

Rudolph and Johnen, [16] did more than 200 in situ measurements of ethylene and other selected Light Atmospheric Hydrocarbons during, a cruise from Puerto Madryn (Argentina) to Bremerhaven (Germany) in 1987. The measuring locations were remote with low biological activity in the surrounding ocean areas. The ethylene level, expressed as mixing ratio was in the range 10-30 ppt (12-35 ng/m^3) in the southern hemisphere and in the northern hemisphere a factor of 2 higher. The observed ethylene levels were primarily a result of oceanic emissions and the differences were indicated to be caused by changes in oceanic phytoplankton concentration.

The oceanic distribution of ethylene and other low molecular weight (LMW) hydrocarbons has been studied by Swinnerton and Lamontagne, 1974 [17]. They analyzed 452 water samples from the open ocean and near shore for LMW hydrocarbons and found a baseline (average) ethylene of: 4.8 nanoliters/litre (6.0 µg/l) . Upper values were: Mississippi R. Delta ; 35.0 nl/l (44 µg/l) and Miami dockside; 30.0 nl/l (38 µg/l).

Fuel, coal and gas combustion. Leakage from chemical industry. Rural areas: < 1 - 5 µg/m^3, heavy traffic areas: up to 1.0 mg/m^3 [1, 3].

During burning of wood (white pine) an ethylene concentration of about 50 ml/m^3 (63 mg/m^3 was measured in the smoke [18].

3.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS INCLUDING ESTIMATED ENVIRONMENTAL CONCENTRATIONS AND DISTRIBUTION PATHWAYS

In their study of the dynamics of atmospheric ethylene, Sawada and Totsuka, [5] estimated the following emissons of ethylene (in 10^6 t/y):

Natural:		
Terrestrial	23.3	(65.8 %)
Aquatic	2.9	(8.2 %)
Sum	26.2	(74.0 %)
Anthropogenic:		
Fuel oil combustion	1.5	(4.28 %)
Coal cumbustion	0.42	(1.20 %)
Leakage from Industri	0.03	(0.09 %)
Søpel forbrenning	0.10	(0.29 %)
Biomass burning	7.10	(20.1 %)
Sum	9.19	(26.0 %)

Total Natural + Anthropogenic = 35.4 $\cdot 10^6$ t/y

Atmospheric depletion of ethylene:
Ethylene reacts with OH radical to form an adduct which in the presence of O_2 and NO_x forms formaldehyde. The products of reaction of ethylene with O_3 are mostly CO, CO_2, H_2O and CH_2O. Some ethylene is also transported into the stratosphere [76]. Using the most recent

estimates [75] of the depletion rates (lifetime) of ethylene in the atmosphere due to these prosesses give:

:

	lifetime (days)	
Reaction with ·OH radical	1.7	
Reaction with O_3	10	
into the stratosphere	1900	
total lifetime in atmosphere	1.45	
Ethylene sinks (removal capacity, 10^6 tons/y):		
Reaction with ·OH radical	44.4	(85.4%)
Reaction with O_3	7.5	(14.5 %)
Into stratosphere	0.036	(0.07 %)
Sum	52.0	

The ethylene transported into the stratosphere will eventually react with O_3 with the production of a krøger molecule, which again may react with NO regenerating O_3. ethylene is therefore not suspected of being a potential ozone depletor.

3.3.1 TRANSPORT

Physical properties of ethylene indicate that it will rapidly move into the atmosphere from any type of release.

3.3.2 THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

A fugacity level I calculation, using a six compartment model (air, water, soil solids, sedimented solids, suspended sediments and fish) was conducted using the global reference model of OECD [19]. Default values for the environmental parameters were not changed. Entered generic parameters were: melting point - 169.15 ^oC, vapour pressure 4.27 MPa, water solubility 200 g/m^3, $\log_{10}P_{OW}$ 1.13, half-life in air 56 hours, half-life in water, soil and sediment 672 hours. This gave the following distribution:

in air	99.99915 %,
in water	$8.27 \cdot 10^{-4}$ %,
in soil solids	$9.88 \cdot 10^{-6}$ %
in sedimented solids	$2.20 \cdot 10^{-7}$ %.
in suspended sediments	$6.87 \cdot 10^{-9}$ %
in fish	$5.58 \cdot 10^{-10}$ %

This means that for all practical purposes, emitted ethylene is distributed to air only.

3.4 IDENTIFICATION OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE

See 3.3

3.5 BIODEGRADATION

Also a number of research orientated studies were designed to examine the oxidation/hydroxylation and epoxidation of various hydrocarbons by microorganisms isolated from soil, fresh water systems or other natural systems and pure cultures. Generally, results of these studies show that ethylene is subject to biodegradation by various microorganisms and that ethylene oxide and ethylene glycol are most likely initial degradation products [21].

Aqueous biodegradation rates have been estimated both for aerobic and anaerobic conditions [15]:

Aerobic half-life:	High:	672 hours
	Low:	24 hours
Anaerobic half life:	High:	2688 hours
	Low:	96 hours

3.6 BOD_5, COD OR RATIO BOD_5/COD

No data available

3.7 BIOACCUMULATION

Ethylene is not expected to bioaccumulate because of $Log_{10} P_{ow} = 1.13$.
BCF (Bioconcentration factor) is calculated (QSAR) to be 4 on the basis of the toxic action of nonpolar molecules in the freshwater fish Fathead minnow (pimephales promelas), exposure duration 2.00 - 304 days [22].

3.8 ADDITIONAL REMARKS

No data.

4. ECOTOXICOLOGICAL DATA

4.1 ACUTE TOXICITY TO FISH

Little is known about the acute toxicity of ethylene to fish, but the "Water Quality Criteria, California State Water Resources Control Board, 1963" [23] refers to two reports of toxicity of ethylene to Orange-spotted sunfish from 1917 [24] and 1921 [25]. The findings were the following:

Lethal conc after 1 hour :	22 - 25 mg/l [24]
Lethal conc after $\geq$ 1 hour :	22 - 65 mg/l [25]

Calculated (QSAR) values reported in the database Ecotoxicity Profile database [26]:

Fathead minnow (*Pimephales promelas*)	4 days LC_{50} 116 mg/l
Bluegill, (*Lepomis macrochirus*)	4 days LC_{50} 85 mg/l
Channel catfish, (*Ictalurus punctatus*)	4 days LC_{50} 50 mg/l
Rainbow trout, Donaldson trout, (*Onchorhynchus mykiss*)	4 days LC_{50} 55 mg/l

Calculated (QSAR) values reported by Leeuwen et. al. [27]:
Fathead minnow (Pimephales promelas) 4 days LC_{50} 120 mg/l

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

A. Daphnia

Calculated (QSAR) value reported in the database Ecotoxicity Profile [26]:
Water flea, (Daphnia magna) 48 hours LC_{50} 53 mg/l

Calculated (QSAR) value according to Leeuwen et. al. [27]:
Daphnid 48 hours LC_{50} 153 mg/l

B. Other aquatic organisms
No data available.

4.3 TOXICITY TO ALGAE

A growth inhibition test with *Selenastrum capricornutum* was performed according to OECD 201 and conducted according to GLP guidelines in 1996 [74]. The 5 nominal test concentrations in the growth medium ranged from 8.2 to 131 mg/l. During the 72 hr exposure period there was a loss of ethylene, however the mean measured ethylene concentrations (mean of zero time and 72 h measurement) were used for calculation of growth inhibition. Actual test concentrations (mean) were therfore: 3.3, 7.8, 13.9, 32 and 58mg/l. Loss of ethylene during the 72 hr incubation period ranged from 64 to 91 %. EC_{50} for the growth inhibition based on reduction in biomass compared to control, was calculated to be 40 mg/l (95 % conf. lim.36-46 mg/l). Based on the specific growth rate (μ), the 0 - 72 hr EC_{50} was calculated to be 72 mg/l (95 % conf. lim. could not be calculated due to that the EC_{50} value was outside the range of the test). The highest NOEC was 13.9 mg/l. The results agree fairly well with QSAR calculation for *Selenastrum capricornutum* which gave an EC_{50} after 48 hour value of 122.5 mg/l [27].

4.4 TOXICITY TO BACTERIA

E.coli bacteria were treated with ethylene by passing the gas through a bacterial suspension at constant rate for 10 minutes. After 24 hours exposure, the suspensions were plated on agar medium and incubated for 24 hours at 37 ℃. Survival of colonies from gas treated cells was 79 ± 1.3 % of controls. The survival of the *E. coli* Sd-4 strain after the same treatment was 84.2 ±1.6 % compared to controls. It was concluded that treatment seemed to have little if any effect on the survival of both bacteria strains [28].

4.5 CHRONIC TOXICITY TO AQUATIC ORGANISMS

4.5.1 CHRONIC TOXICITY TO FISH

Calculated (QSAR) value reported in the database Ecotoxicity Profile [26]:
Fathead minnow, (Pimephales promelas) 32 days MATC 15.3 mg/l

Calculated (QSAR) value according to Leeuwen et. al. [27]:
Fathead minnow, (Pimephales promelas) 28 days NOEC 13 mg/l

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Calculated (QSAR) value according to Leeuwen et. al. [27]:
Daphnia 16 days NOEC 37.4 mg/l

4.6 TOXICITY TO TERRESTRIAL ORGANISMS

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

No data available

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

A large and diverse literature exists on the effects of ethylene on vascular plants, including several hundred observations of ethylene exposure and effects. This is mainly due to the fact that ethylene acts as a plant hormone, regulating a whole range of different reactions. Most of these reactions can be categorised as growth regulation and include such effects as defloration, ripening, inhibition of elongation, leaf loss and senescence [9,11, 29, 30, 31, 32]. While most of these effects are non reversible, they do not all constitute effects that reduce a plants fitness nor growth and reproduction. One may categorise the effects into 3 groups based on assumed long term effects, where long term effects are associated with reduced fitness, growth or reproduction. In the table below exotic and tropical plants have been excluded in order to present data that give a more realistic view of risks associated with exposure in industrial areas.

Summary table of effects of ethylene exposure to vascular plants. Exotic and tropical plants are not included. Epinasty=leaf curling, Abcission=loss

Effects	exposure time	concentration $\mu g \cdot m^{-3}$	Ref
1) None or small long term effects:			
Epinasty, Lemon		25-50	[77]
Epinasty, tomato	3-4 h	46	[9]
Epinasty, *Chenopodium*		60	[9]
Epinasty, Potato	16 h	60	[9]
2) Effects that may cause long term effects			
Inhib growth, sweet pea, (NOEC)	2 d	12	[77]
Abscission flower, Carnation	2d	58	[77]
Inhibition of photosynth. Pea (NOEL)	2 h	115	[77]
Abscission flower, Snapdragon	1h	575	[33]
3) Long term effects:			
Decreased amount flowers, Oats	100d	8	[77]
Growth inhibition, Potato	28 d	27	[77]
Yield reduction, Tomato	28 d	50	[77]
Growth retardation, Pea		116	[9]
Yield reduction, Garden cress (30 %)	14 d	115	[77]
Yield reduction, Cotton	30 d	700	[9]

Among the more sensitive agricultural or horticultural crops are peas, potatoes, tomatoes and oats where retardation effects were observed at concentrations in the range 8-50 $\mu g/m^3$ (7-40 ppb) . The most susceptible non-woody plant reported, African marigold reacts with leaf epinasty (downward curling of leaves at 1.16 $\mu g/m^3$ (1.0 ppb) ethylene [9], the Cattleya orchid, reacts with sepal tissue collapse (loss of flower) at 2.3 $\mu g/m^3$ (2.0 ppb) after ethylene exposure for 24 hours [33].

4.6.3 TOXICITY TO OTHER NON MAMMALIAN TERRESTRIAL SPECIES (INCLUDING AVIAN)

No data

4.7 BIOLOGICAL EFFECTS MONITORING (INCLUDING BIOMAGNIFICATION)

No data

4.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES

No data

4.9 ADDITIONAL REMARKS

No data

5. TOXICITY

5.1. ACUTE TOXICITY

5.1.1 ACUTE ORAL TOXICITY:

Not relevant. Ethylene is a gas with a low boiling point (-103.71 °C).

5.1.2 ACUTE INHALATION TOXICITY

The acute toxicity of ethylene is low, but very high concentrations may cause asphyxia due to oxygen displacement. The lethal ethylene concentration in air to mice is thus estimated to be 950,000 ppm. [34].

When male rats were exposed to 10, 25 or $57 \cdot 10^3$ ppm for 4 hours, all groups showed increased serum pyruvate and liver weight [35]. Non of the studies were GLP.

5.1.3 ACUTE DERMAL TOXICITY

Not relevant. Very little ethylene is likely to be absorbed through the skin because of ethylene's low solubility in fat and low boiling point.

5.1.4 ACUTE TOXICITY, OTHER ROUTES OF ADMINISTRATION

No information

5.2 CORROSIVENESS/IRRITATION

5.2.1 SKIN IRRITATION/CORROSION

There is no evidence to suggest that the liquid ethylene gas is irritant, but it might cause frost injuries.

5.2.2 EYE IRRITATION

There is no evidence to suggest that the liquid ethylene gas is irritant, but it might cause frost injuries.

5.3 SKIN SENSITISATION

No data.

5.4 REPEATED DOSE TOXICITY

The toxicity of ethylene has been tested in a 90 days inhalation study on 4 exposed and one control groups of 30 rats (15 males, 15 females) [36]. The animals were exposed 6 hours/day 5

days/week for 13 weeks. The exposure groups were T-I: 300 ppm, T-II: 1,000 ppm, T-III: 3,000 ppm and T-IV: 10,000 ppm. The study was not conducted according GLP, but the study held high scientific standard and a quality assurance statement was issued. There were no differences between controls and treated rats with respect to total weights, weight change, food consumption, haematology, clinical chemistry, gross pathology or histopathology. Male rats in the control, T-I and T-IV groups showed red deposits or red discharge around the nose, whereas the male T-II had red deposits around the eyes. Amongst the female rats, a red deposit was observed around left eye of one T-I rat and alopecia around both ears of one T-II rat. Compared with the controls, the liver weights in several groups of exposed rats were significantly lower. There was, however, no dose response relationship for this weight reduction and the cause was unknown. Ethylene was not toxic to rats when administered under a stratified regimen of exposure up to 10,000 ppm.

In an explorative non-GLP study, where a group of six male Sprague-Dawley albino rats (50-60 g) were exposed to a continuous flow of 60% ethylene in oxygen as inhalation for 6 days, effects could be seen on several haematology parameters [37]. There were significant reductions in thrombocyte count (-19.3%) and leukocyte count (-48.2%). A reduction was also seen in the bone marrow cellularity (-30%).

During chronic tests on rats (newborn) exposed to a concentration of 2.62 ppm (continuous as inhalation) for 90 days, a delay in coat appearance, dentition, eye opening and circulation hypotension, cholinesterase activity inhibition, subordination disruption were reported [38]. There were no information on the quality of the study.

In rats treated by inhalation with a concentration of 100 ppm for 70 days, a change in the reflex nerve impulses, a decrease of cholinesterase activity and a reduction of the blood pressure were observed [39]. There were no information on the quality of the study.

5.5 GENETIC TOXICITY IN VITRO

A. Bacterial test

Ethylene at atmospheric concentrations up to 20 % gave no indication of mutagenic potential in Salmonella typhimurium in the presence or absence of a metabolic activation system (Ames test) [40]. The study was not conducted according to GLP, and only one (TA 100) of the four bacterial test strains recommended in the guidelines was tested. Previous testing with the full range of Salmonella strains in the presence and absence of a metabolic activation system have also given negative results [41, 42]. Ethylene showed no gentoxic activity in Escherichia coli. [28].

B. Non-bacterial in vitro test

The effect of ethylene on chromosomes was tested in an in vitro cytogenetics assay using duplicate cultures of CHO cells [71]. The methodology in this study complies with GLP and the OECD Test Guideline 473, "Genetic Toxicology: In vitro Mammalian Cytogenetic Test". Treatments covering a broad range of doses, separated by narrow intervals, were performed both in the absence and presence of metabolic activation (S9) from Aroclor 1254 induced rats. The highest dose level used, approximately 280.5 mg/ml, was equivalent to a concentration of 10 mM, corresponding to about 25 % of ethylene.

Due to the explosive properties of the test article when mixed with air, it was not possible to achieve the maximum concentration required by the Regulatory Guidelines using air as carrier gas. Nitrogen was therefore used as carrier gas, which allowed higher doses to be achieved. There are, however, technical problems associated with continuous treatment in a nitrogen atmosphere, and short (3 hour) pulse treatments were the only practical option.

A preliminary range-finding study was performed to investigate the toxic effects of ethylene on CHO cells. In this trial, treatment in the absence and presence of S9 lasted for 3 hours only followed by a 17 hours recovery period prior to harvest (3+17). The dose levels for the main study were selected by evaluating the effect of ethylene on mitotic index.

The treatment regimes used in the range-finder were repeated in the main study. Chromosomal aberrations were analyzed at three consecutive dose levels. No mitotic inhibition (reduction in mitotic index) was observed at the highest concentration chosen for analysis (280.5 μg/ml) in either the absence or presence of S9.

Appropriate negative (carrier gas) controls were included in the test system in both experiments under each treatment condition. Untreated controls were also included in the main study. The proportion of cells with structural aberrations in the negative and untreated cultures fell within historical solvent control ranges. 4-Nitroquinoline 1-oxide and cyclophosphamide were employed as positive controls in the absence and presence of liver S9 respectively. Cells receiving these were sampled in the main study, 20 hours after the start of treatment; both compounds induced statistically significant increases in the proportion of cells with structural aberrations.

Treatment of cultures with ethylene in the absence and presence of S9 resulted in frequencies of cells with structural aberrations that were similar to, and not significantly different from, those seen in concurrent negative controls. Frequencies seen in treated cultures fell within the normal range.

It is concluded that ethylene did not induce chromosome aberrations in cultured Chinese hamster ovary cells exposed to a concentration of 10 mM (25 %) in the absence and presence of S9.

5.6 GENETIC TOXICITY *IN VIVO*

The effects on micronucleus formation in bone marrow cells of rats and mice have been studied following ethylene inhalation [43]. Each group consisted of 10 animals of each of the two species and they were dosed with concentrations of 0; 40; 1,000 and 3,000 ppm for 6 hours/ day, 5 days a week for 4 weeks. An ethylene oxide control group with both species was exposed using the same conditions at a concentration of 200 ppm. Bone marrow was collected approximately 24 hours after the final exposure. Ethylene did not produce, statistically significant, exposure related increases in the frequencies of micronucleated polychromatic erythrocytes in the bone marrow of either rats or mice, while ethylene oxide exposure resulted in signifcant increases in the frequencies in both species. It is not stated if the study was conducted according to GLP.

Absorption, distribution, elimination of ethylene and formation of haemoglobin and DNA adducts were studied in rats after inhalation of 300 ppm ethylene for 12 hours/day for 3 consecutive days [44]. DNA adduct formation was measured in liver and lymphocytes and haemoglobin adducts determined in erythrocytes. The adduct formation with ethylene was compared to other alkenes and adduct formation decreased with increasing number of carbon atoms in the molecule. This was an explorative study not conducted according to GLP.

Alkylation of 7-guanine was measured in DNA from liver spleen and testis of mice 14 hours after exposure by inhalation of ^{14}C-ethylene at an initial concentration of 11 ppm for 8 hours [45]. The degree of alkylation was much higher in the liver than in the other tissues. This study was an explorative non-GLP study.

5.7 CARCINOGENICITY

The potential carcinogenicity of ethylene has been tested in a two years study with rats (Fischer - 344 inbred) [46]. The study was conducted prior to OECD Guideline 451 for carcinogenicity testing (1981), but still the study comply with this guideline except for some minor points. In the study, 960 rats were randomly divided into 4 groups of 120 animals of each sex and exposed 6 hr/day, 5 days/week to 0(control); 300; 1,000 and 3,000 ppm for up to 24 months.

During the course of the study there were observations of hair loss, deposits on and around the nose and eyes and gross eye abnormalities, but there were no obvious differences among the different treatment groups.

There was an overall increase in the number of animals exhibiting gross tissue masses for the test groups as compared with the control group, although this trend was not statistically significant. The spontaneous mortality (15.7 %) was roughly equal in all treated groups. The final body weights and total weight changes for treated males were higher than those in the control groups, but no dose-related pattern was seen.

There were no statistically significant differences among any of the treatment groups on any of the haematology, blood chemistry or other parameters investigated.

No gross or histopathologic tissue changes attributable to the effects of the test material were observed in any of the treated rats. The summary reports only few findings which could indicate any carcinogenic effect of the treatment, but lacks a conclusion at this point.

In a publication from the carcinogenicity study [41], it was concluded that the results provided "no evidence that ethylene at these concentrations causes chronic toxicity or is oncogenic in Fischer - 344 rats". However, this publication and the summary have later been criticised [47] since they do not discuss the mononuclear cell leukaemia described in the full report. It was claimed that the number of animals affected (out of 90) rose from 12 and 8 in the male and female control groups to 21 and 11, respectively in the groups receiving 3,000 ppm. On the other hand, it has been stated that mononuclear cell leukemia may occur in F344 rats at a background incidence > 75 %, and that a further increase in exposed animals is difficult to interpret with respect to human cancer development.

When the carcinogenic risk of ethylene was evaluated by the International Agency for Research on Cancer (IARC) in 1979 [1], no data were available to the working group on the carcinogenicity or mutagenicity of the substance in animals and humans. In supplement 7 published in 1987 [48] it is still summarised that no adequate data were available and ethylene is stated to be not classifiable as to its carcinogenicity to humans. The latest evaluation of ethylene by the IARC working group (1994) concludes that there is inadequate evidence in humans and in experimental animals for the carcinogenicity of ethylene [3]. Overall, ethylene was evaluated as not being classifiable as to its carcinogenicity to humans.
In the Ecotoxicity Profile database it is stated to be no information in the QSAR system which would suggest that this chemical is a potential carcinogen or mutagen [26].

In another recent evaluation of ethylene as a cancer risk factor it was concluded that it was a risk factor of concern [49]. This conclusion was based on the observed metabolism of ethylene to ethylene oxide, a compound which has been shown to be both mutagenic and carcinogenic. The linearity hypothesis for dose response relationship can not be applied in this case, since there is a saturation of the metabolism of ethylene. The findings from administration of high doses to animals can thus not be extrapolated to the human exposure level.

The carcinogenic potential of ethylene has also been reviewed in the BIBRA Bulletin [50]. This review concludes also on the basis of metabolic production of ethylene oxide that it is timely with

a detailed reconsideration of the possible carcinogenic risks of inhaling ethylene. The evaluation also calls for re-evaluation of the need for a specific industrial limit of ethylene.

5.8 TOXICITY TO REPRODUCTION

The potential effects of ethylene inhalation on male and female rat reproduction and on growth and development of the offspring has been studied [70]. The experimental study was carried out according to GLP (OECD Guideline 421; Reproduction/Development Toxicity Screening Test).

Four groups of rats (10 females and 10 males per group) were dosed by head only inhalation for 6 hours daily; air only (control); 200; 1,000 or 5,000 ppm of ethylene (corresponding to 0; 230; 1,150 or 5,750 mg/m^3). This dosing regime was calculated to give about 80; 400 and 2,000 mg/kg/day of ethylene for the three dosed groups respectively. Since the uptake from the lungs most likely is in the range of 5-10 % , the absorbed dose probably was substantially less than the figures given above.

The test material was administered to parent animals for two weeks prior to mating, during the mating period and until the day prior to necropsy for the males (minimum 28 days) and until day 20 of gestation for the females. The females were allowed to litter and rear their offspring to day 4 post-partum, when they and their offspring were killed.

Morbidity, mortality, clinical condition, weight and food intake were observed throughout the study, and mating was carefully observed. For each female, litter data and also observations for each offspring were recorded. At termination of the study, all animals were subject to macroscopic examination for structural or pathological changes. Ovaries, testes and epididymides of the control and high dose animals were subject to a histopathological examination.

There were no deaths attributable to the test article, and body weight gain was not adversely affected during the pre-pairing, gestation or lactation periods. The treatment had no effect on fertility or fecundity and all females became pregnant. Litter size, sex ratio, mean pup weight and pup growth and clinical condition were not adversely affected by treatment.

Necropsy revealed no macroscopic finding suggestive of toxicity due to test article administration. There was no evidence of any toxic effect on the testis due to test substance administration and there were no other microscopic findings suggestive of toxicity due to test article administration.

In conclusion, head-only administration of ethylene at nominal concentrations of 200; 1,000 or 5,000 ppm was without evidence of toxicity or adverse effects on male and female reproductive performance, fertility, pregnancy, maternal and suckling behaviour and growth and development of the offspring from conception to Day 4 post-partum.

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

It is referred to the experimental study [70] carried out according to the OECD Guideline 421; Reproduction/Development Toxicity Screening Test. The study is summarised under point 5.8 above.

5.10 OTHER RELEVANT INFORMATION

A. Specific toxicities (neurotoxicity, immunotoxicity etc.)
No data

B. Toxicodynamics, toxico-kinetics

Cowles, A.L. et al [51], studied the uptake and distribution of four inhalation anaesthetics in dogs. In a series of 21 experiments, 13 large mongrel dogs were ventilated with a constant concentration of ethylene (1.4 % = 12 g/m^3) and three other inhalation anaesthetics. Concentrations of the anaesthetic were measured by gas chromatography in alveolar gas, arterial blood, brain, muscle and central venous blood. The average times necessary for the partial pressure of ethylene to reach 50 % of the inspired partial pressure (1.4 %) were: alveolar gas, <2.0 min; arterial blood, <2.0 min; brain, 3.7 min; muscle, 8.2 min and central venous, 5.2 min.

Biotransformation of ethylene to ethylene oxide

Ehrenberg et. al, 1977 [52] showed that ^{14}C-labelled ethylene was metabolized to ethylene oxide when administered to male CBA mice by inhalation. This metabolism is of significant concern since ethylene oxide is a potent alkylating agent, a carcinogen and a gentoxicant, and hence more toxic than ethylene. The amount of epoxide formed was quantitatively determined from the degree of alkylation of cysteine and histidine residues in haemoglobin.

In a later study from the same laboratory [45], it was shown that ethylene oxide alkylated nucleophilic sites of mouse DNA. Since the ratio between the degree of alkylation of DNA and that of haemoglobin was the same when exposed to ethylene and ethylene oxide, it was concluded that the latter was the reactive intermediate formed from ethylene in vivo. A comparison of the degrees of alkylation obtained per unit exposure of ethylene oxide and ethylene, showed that at low levels of ethylene, about 8% of the inhaled amount was metabolized to ethylene oxide. The rate of ethylene oxidation followed saturation kinetics with increasing ethylene concentration. At 218 ppm ethylene, the oxidation rate was half of the maximal rate (K_m value). It was estimated that the maximal rate of metabolism (V_{max}) of ethylene corresponds to exposure to an air level of 4 ppm of ethylene oxide.

After exposing rats to automotive engine exhaust, Törnqvist et. al., 1988 [53] identified alkylated amino acids in haemoglobin. These resulted from conversion of about 5-10 % of inhaled ethylene and propylene to their respective epoxides which again alkylated the nucleophilic sites in haemoglobin. This quantification of the fraction of ethylene to be oxidised form agreed very well with the conversion factor of around 8 % found for the mouse in the above mentioned study [45].

Results from Törnqvist and Ehrenberg in 1990, estimate that in humans, some 6 % of inhaled ethylene in mainstream smoke is converted to ethylene oxide in smokers [54] and some 3 % in non-smokers [55].

Metabolic conversion of ethylene to ethylene oxide results in the formation of adducts to DNA and proteins, and this offers a means for identifying ethylene exposure in vivo. Determination of haemoglobin adducts using the N-alkyl Edman method has proven valuable [53]. This method has been used for monitoring adduct formation after ethylene exposure from different sources [49].

Toxicity of ethylene oxide

Ethylene oxide causes dose-related increases in the incidence of gliomas, peritoneal mesotheliomas and mononuclear cell leukemias in F 344 rats and lymphomas and adenomas/adenocarcinomas of the lung, uterus, harderian gland and mammary gland in B6C3F1 mice (for a review see Walker et. al., 1990 [56]).

Epidemiologic data on ethylene oxide support the anticipation that ethylene oxide is a carcinogenic agent. When mortality and incidence of cancer in totally 733 workers exposed to

ethylene oxide were assessed, 8 cases of leukaemia and 6 cases of stomach cancer occurred, while the expected numbers were 0.8 and 0.65 respectively [57].

In vivo as well as in vitro, ethylene oxide is seen to react both with amino acid residues in proteins and with the purine bases in DNA. When mouse, human or rat erythrocytes were exposed to ethylene oxide, the main reaction products with haemoglobin were 2-hydroxyethylations of cysteines, N-terminal valine, imidazole nitrogens of histidines and carboxylic groups [58]. The main reaction product after reaction with calf thymus DNA was N-7-(2-hydroxyethyl) guanine, whereas O-6-(2-hydroxyethyl)guanine was only about 0.5 % of this. Species differences were also observed, as rat and mouse erythrocytes were more susceptible to alkylation than the human erythrocytes.

The alkylation of DNA-bases with ethylene oxide has been studied further after exposure of rats to ethylene oxide by inhalation [59, 56, 60]. The main alkylation site both in vivo and in vitro is the N-7 position in guanine, resulting in 7-(2-hydroxyethyl) guanine, and this modification is probably the reason for its carcinogenic and mutagenic effects.

The IARC working group evaluated ethylene oxide in 1994 and came to the overall conclusion that it was carcinogenic to humans [61]. This was mainly based on the evidence for carcinogenicity from experimental studies in animals.

Effects of PCB-pre-treatment on ethylene toxicity and biotransformation

It has been demonstrated that ethylene, as well as halogenated ethylenes are acute hepatotoxic in rats pretreated with polychlorinated biphenyl (PCB) [62]. The hepatotoxicity was evident as increased serum alanine-α-ketoglutarate transaminase (SAKT) and sorbitol dehydrogenase (SDH) in rats pretreated with PCB and exposed to 20,000 ppm ethylene for 4 hours. Without pretreatment with PCB, ethylene and halogenated ethylenes are not acute toxic. From these findings it was suggested that the acute toxicity was mediated through epoxide intermediates formed by hepatic mixed function oxidases induced by the PCB pre-treatment.

When rats were exposed to ethylene in a closed desiccator jar chamber, the rate of metabolic elimination of the compound is influenced by pretreatment with PCB (single dose of Aroclor 1254, 500 mg/kg in oil 6 days prior to the experiment) [63]. Biotransformation of ethylene lead to ethylene oxide which was exhaled.

The effects of PCB pre-treatment and high exposure levels of ethylene, due to induction of mono-oxygenases and increased formation of ethylene oxide, demonstrates that the toxicity of ethylene is of concern for organisms also exposed to mono-oxygenase inducers. However, it should be kept in mind that the concentrations used are far above actual exposure levels.

5.11 EXPERIENCE WITH HUMAN EXPOSURE

Ethylene was in general use as an anaesthetic for many years. It has been replaced by more modern anaesthetics, mostly due to the high explosion risk. Chronic injury in humans resulting from prolonged and repeated exposure to low concentrations of ethylene (less than 2.5 %) was not reported in "Patty's Industrial Hygiene and Toxicology (1981)" [11].

Inhalation pharmacokinetics

The inhalation of ethylene was investigated in human volunteers at atmospheric concentrations of up to 50 ppm. The uptake, exhalation and metabolism could be described by first-order kinetics [64]. The clearance due to uptake was low, only 5.6 %, while the rest was exhaled without entering the blood stream. Clearance due to metabolism was 36 % of systemic available ethylene. The biological half-life of ethylene was 0.65 hours. The alveolar retention of ethylene at steady

state was calculated to be 2 %. The low uptake rate of ethylene was considered due to its low solubility in blood.

Reproduction effects
In a preliminary study, the miscarriage rate (six out of 15 pregnancies) amongst Swedish women who had worked in the local petrochemical industry was higher than that seen in 1549 women outside the industry. Ethylene was the main product in four of the five local petrochemical plants. No data were provided on occupational levels but measurements made in areas surrounding the plants indicated that ethylene was present in concentrations up to tenfold higher than the other pollutants (propylene, ethane, propane and phenol) [65].

A brief abstract notes that there was a higher than expected rate of miscarriage and gynaecological disease among female operatives of a polyethylene plant who were exposed to ethylene concentrations in the range of about 40-60 ppm and high levels of noise [66].

Carcinogenicity
A preliminary study found no increase in lung cancer incidence in 31 workers exposed to ethylene (at unspecified levels) at a US petrochemical factory [67].

A study of workers at an US petrochemical plant found that an increased risk of developing brain cancer was associated with exposure to (unspecified levels of) a number of chemicals including ethylene. However, the investigators were unconvinced that the association reflected a casual relationship [68].

Work Place Exposure
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). In a study on exposure of fire-fighters, samples taken during the "knockdown" phase of a fire showed a concentration of 46 ppm (53 mg/m^3) ethylene, while none was detected during the "overhaul" phase [3]

A study was carried out among workers at a Swedish petrochemical plant using measurements of haemoglobin adducts formed from ethylene oxide for monitoring of ethylene exposure [69]. The study was carried out in two parts, part one in 1989 and part two in 1993. Eight workers exposed to high levels of ethylene (4 mg/m^3) and 3 workers exposed to low levels (0.1 -0.3 mg/m^3) were compared to nine controls exposed to 0.01 mg/m^3. All exposed workers showed elevated levels of haemoglobin adducts and adduct formation was dose-related. The results indicated that about 1 % of the inhaled ethylene was metabolized to ethylene oxide.

The second part of the study, which included four workers, was designed to more accurately determine the exposure levels, which turned out to have a mean of 4.5 mg/m^3. The results confirmed part one, showing that about 1 % of inhaled ethylene was metabolized to ethylene oxide and the maximum fraction to be converted was estimated to be 4 %.

The peak level of ethylene reported for human exposure is about 50 ppm (57.5 mg/m^3), while 3.5 ppm (4.0 mg/m^3) has been characterized as a high average level for longer term exposure. The conversion will then correspond to maximum 2 ppm (3.6 mg/m$^{3)}$ of ethylene oxide for the peak level and to maximum 0.14 ppm (0.25 mg/m^3) for the high averaged level. Given occupational exposure limit levels for ethylene oxide (time-weighted averages) are 1.8 mg/m^3 (Denmark, Japan, USA, Norway) and 2.0 mg/m^3 (France, Canada, Sweden) [3].

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SIDS　エチレン評価文書

OECD からの HPV 化学物質に関する利用可能なデータの要求に対する回答の要約

SIDS プロファイル

1.01A	CAS NO.	
1.01C	化学名	
1.01G	分子式	
	その他の化学的性質情報	
1.5	量	数百万トン／年（1996 年生産量） ノルウェー：0.4 世界：83.0
1.7	利用パターン	化学工業;化学薬品、石油化学製品および樹脂の合成用原料として。 少量は果実の成熟、および麻酔薬ガスとして使用される。
1.9	曝露源	燃料、石炭およびガス燃焼。 化学工業からの漏出。 田園地帯:<1 - 5mg/m3(0.9 -4.3ppb) 渋滞エリア:1.0mg/m3(0.9ppm)以内 石油化学プラント:5mg/m3(4.3ppm)以内
議論のための出版物(もしあれば同一性)	さらなる試験を要しない。	

1. 一般情報

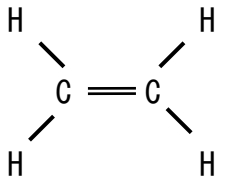
A. CAS number: 74-85-1

B. Name (IUPAC): エチレン

C. Name (OECD): エチレン

F. 分子式: CH_2CH_2

G. 構造式:



H. 物質グループ: 産業化学薬品;化学薬品、石油化学製品および樹脂の合成用原料として。

J. 分子量: 28.05

1.02 OECD 情報

A. スポンサー国: ノルウェー

B. 指導組織:

ノルウェー汚染管理局 (SFT),
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NORWAY

1.1 一般的な物質情報

A. 物質のタイプ: 有機物, 炭化水素

B. 物理的形状 (20℃、1.013hPaにおいて): 気体

C. 純度:

1) 高純度: > 99.9 %

2) 商業的純度 : 約 99.9 %

1.2 同意語

Ethene, acetene, bicarburetted hydrogen, olefiant gas, elayl.

1.3不純物

西ヨーロッパ製, (ppm range):

Methane + ethane (50-200), propylene and heavier (7-200), CO2 (2.2-50), H2(0.1-10), O2 (0.6-10), acetylene (1.4-10), total sulphur (1-10), water (0.6-20) and CO (0.15-10) [3].

1.4 添加剤

知られていない

1.5 生産量

年間1,000,000 トン以上

1996年の生産 [2]:

ノルウェー: 405,000 トン

世界: 83,000,000 トン

1.6 表示と分類

EEC: Fx, R12 (非常に可燃性).

S 2 (子どもの手の届かない場所).

S 9 (よく換気された場所に容器で保存)

S 16 (発火源から離しておくー禁煙)

S 33 (静電気放電に対して予防策をとる)

Norway: F, R13 (非常に可燃性の液体ガス)

S 9-16-33

IARC モノグラフ Volume 60, (1994)による:

Ethylene:人間に対する発癌性物質には分類されていない。[3].

1.7 用途

エチレンは、世界中の大多数で石油製品として生産されている。現在、エチレンの

毎年の商業生産の95%以上は石油の炭化水素のスチームクラッキング(無触媒水蒸気改質）によっている[4]。

米国、西欧、および日本で消費されたエチレンの約80%は酸化エチレン、二塩化エチレン、低密度、直鎖状低密度、および高密度ポリエチレンの生産に使用されている。 また、かなりの量は、エチルベンゼン、アルコール、オレフィン、アセトアルデヒド、およびビニルアセテートを作るのに使用されている。これらの製品の大部分はさらにフィルムや、吹き出し、射出成形や、押出コーティングや、ケーブル絶縁やPVCなどの製品に加工される。 少量が麻酔薬のガス、果実の熟成と金属の溶接と切断に使用されている。

A. 一般

	利用形態：	**カテゴリー：**
a)	主	閉鎖系における利用
	産業	化学工業： 合成に利用
	利用	原材料
b)	主	非分散的利用
	産業	農産業
	利用	果実熟成剤として

B. 消費者向け製品

知られていない

1.8 職業上の曝露限界

被曝限界はほとんどの国で勧告されていないが、スイスでは時間加重平均による職業的被曝限界を11 500mg/m^{3}と制定した。

1.9 曝露源

エチレンは自然および人工を発生源として環境中のどこにでもある。主たる発生源は全てのタイプの植物からの自然の産物である[5]。

主な人為的発生源はガス、石油、石炭、およびバイオマスの燃焼による。人に対するエチレンの最大の曝露は自動車による化石燃料の燃焼を通してと考えられている。地球上の総エチレン排出量は18-45.10^6 t/yであり、うち約74%は自然源、26%は人為的発生源から放出されていると見積もられている。石油の燃焼からの排出量は1.54 .10^6 t/y [5]と推定される。化学産業で生産されて消費されるエチレンは、

閉鎖システム内に保たれており、通常、生産施設はエチレンを原材料として使用している工場に隣接している。その結果、産業からのエチレンの曝露は主に制御できない漏出か破裂によるものである。そのような出来事は年間２百万トンのエチレン製造につき一度の割合で起き、約１トンの直接放出の結果となるかも知れない。

1.10　追加の特記事項

A.　処分に対するオプション

焼却

B.　その他の注意

データ無し

2.　物理化学データ

2.1　融点

-169.15 °C [4]

2.2　沸点

-103.71 °C [4]

2.3 密度

d = 0.57 g/cm3　　沸騰点下 [4].

ガス密度　STP 1.2603 g/l [4].

空気比密度 0.9686 [4].

2.4　蒸気圧

4.27 MPa　　at　　0 °C [4]**.**

2.5　分配係数$\log_{10}P_{ow}$

$Log_{10}\,P_{ow}$ = 1.13 (calculated) [6].

2.6　水溶性

A.　溶解度

メルクインデックスによると,"０℃においてエチレンガスは４倍量の水に溶ける" [7]。25℃では９倍量の水に溶ける。[8].

溶解度：　131 mg/l　20°C　[9]

200 mg/l　15 °C　[10].

B. 水素イオン指数 pH 価,　　酸解離定数 pKa 価

有効なデータ無し。溶解したエチレンと水との間の反応およびpHが残って変化しないことを示唆する化学的証拠はない。

2.7 引火点

- 136.11 °C [11].

2.8 自然発火性

自然発火温度： 543°C [7].

点火温度： 425-527°C [4].

2.9 引火性

強燃性－液化ガス.

2.10 爆発性

空気中における爆発限界： (0.1 MPa and 20$_{o}$C) [4] :

下限爆発限界 (LEL): 2.75 vol %

上限爆発限界 (UEL): 28.6 vol %

2.11 酸化特性

情報無し

2.12 酸化：還元電位

情報無し

2.13 追加データ

A. 土壌／沈殿物と水との間の分配係数 (Kd).

情報無し

B. その他のデータ

空気中のエチレンに対する換算要素：

1 ppm in air = 1.15 mg/m$_{3}$ = 912 nl/l [1,4]

臭い閾値:

臭いの下限： 299 mg/m$_{3}$

臭いの上限： 4600 mg/m3 [12]

3. 環境中運命および経路

3.1 安定性

3.1.1 空気中安定性

自然および人為起源の大気中エチレンの運命は沢田と戸塚によって1986年に推定された[5]。89%は対流圏においてOHラジカルと反応して、８％はオゾンとの反応によって破壊されたと彼等は結論した。残りの３％は成層圏に運ばれた。エチレンの大気中の寿命は２～４日間と推定された。

増感剤としてオゾンを用いた光分解性による間接的な計算では、9.4日間の寿命であった。OHラジカルを用いた場合は2.7日と算出された。以下の寿命はHoward, P.H. らの (1991) [15] 環境的分解率ハンドブックによるものである。

		寿命
空気：	高	3.36日
	低	0.37日

これはOHとオゾンに対して測定された光分解率に基づいている。
もしAtkinson, R. (1996) [75]による大気中の有機化合物に対する計算手順が使用されるなら、以下の減少率が認められる。

		寿命
空気：	OHに帰する反応	1.7日
	オゾンに帰する反応	10日
	成層圏への移動	1900日

成層圏へのエチレンへの移動がCOと同じと仮定すれば、IPPC (1995) [76]の方法によって計算できる。

3.1.2 水中における安定性

有効なデータはない。

3.1.3 土壌中における安定性

有効なデータはない。

3.2 監視データ（環境中）

Rudolph and Johnen, [16] は、1987年にプエルト・マドリン(アルゼンチン)からブレ

ーマーハーベン (ドイツ)までの航海中に、200以上の場所でエチレンとその他の選択された大気中炭化水素成分を測定した。測定場所は周辺に生物活動が少ない遠い海域であった。混合率で表されたエチレンのレベルは南半球では10-30 ppt (12-35 ng/m3)の範囲であり、北半球では２倍であった。観測されたエチレン値は主として海洋放出の結果であり、示された差は海洋性植物プランクトンの集まり方の変化によって引き起こされていた。

エチレンとその他の低分子炭化水素（ＬMW）の海洋における分布はSwinnerton and Lamontagne, 1974 [17] によって調べられた。彼等は遠洋および沿海から452の海水サンプルから低分子炭化水素を分析し、エチレンの平均的な基準値は4.8 nanoliters/litre (6.0 µg/l)であることを発見した。高い方の値は、ミシシッピのR.. Deltaの35.0 nl/l (44 µg/l)およびマイアミのドック側の地域の30.0 nl/l (38 µg/l)であった。

燃料、石炭、ガスの燃焼、化学産業からの漏出。農村：< 1 - 5 µg/m3、交通量の多い地域：1.0 mg/m3 まで[1, 3]

森林（モミ）火災の時に煙の中から約50 ml/m3 (63 mg/m3）の濃度のエチレンが計測された。

3.3 推定環境濃度を含む環境区画間の移動と分布および分布経路

沢田と戸塚[5]による大気中のエチレンの動態に関する研究では、以下のようなエチレン（in 10^6 t/y）の排出が推定された。

自然：		
陸上	23.3	(65.8%)
水中	2.9	(8.2%)
計	26.2	(74.0%)
人為：		
石油燃焼	1.5	(4.28%)
石炭燃焼	0.42	(1.20%)
工場からの漏出	0.03	(0.09%)
焼却	0.10	(0.29%)
山火事	7.10	(20.1%)
計	9.19	(26.0%)

分布経路合計　自然＋人為＝35.4*10$_6$ t/y

エチレンの大気中の減少

エチレンはOHラジカルと反応して、酸素と窒素酸化物があればフォルムアルデヒドを形成する付加体を作る。エチレンとオゾンの反応による産物はほとんど一酸化炭素、二酸化炭素、水およびフォルムアルデヒドである[76]。いくらかの量のエチレンは成層圏へも移動している。最新の推定による大気中のエチレンの減少率（寿命）は以下のプロセスのようである。

	寿命（日）
OHラジカルとの反応	1.7
オゾンとの反応	10
成層圏へ	1900
大気中における合計寿命	1.45

エチレン（移動容量、10$_6$ tons/y)	
OHラジカルとの反応	44.4（85.4%）
オゾンとの反応	7.5（14.5%）
成層圏へ	0.036（0.07）
計	52.0

成層圏へ移動するエチレンは結局はオゾンと反応してkrüger分子を産生し、それはふたたび一酸化窒素と反応してオゾンを再生するかもしれないので、エチレンは潜在的なオゾンの破壊者としては疑われない。

3.3.1 移動

エチレンの物理的性質は、それがどんなタイプの解放においても大気中に急速に移動するであろうことを示唆している。

3.3.2 理論的分配 (逃散能計算)

６区画モデル(空気、水、固体土壌、沈殿土壌、浮遊土砂および魚)を使用した逃散能レベルⅠの計算が、OECDの世界的な参考モデルを用いて行われた[19]。環境変数としてのデフォルト値は変えられなかった。 入力された一般的な変数は以下の通りである: 融点－169.15℃、蒸気圧は4.27メガパスカル、水への溶解性は200g/m3、分配係数のlog10POWは1.13、空気中の半減期56時間、水、固体土壌、沈殿土壌での半減期は672時間であった。このことは以下の分配を与えた：

空気中	99.99915 %,
水中	$8.27.10^{-4}$ %,
固体土壌中	$9.88.10^{-6}$ %
沈殿土壌中	$2.20.10^{-7}$ %.
浮遊物中	$6.87.10^{-9}$ %
魚類中	$5.58.10^{-10}$ %

このことは、すべての実用的な目的において、放出されたエチレンは空気中だけに分配されることを意味している。

3.4 実際の使用での分解性の主なモードの識別

3.3を参照

3.5 生分解

数多くの関連した調査研究は、土壌や淡水系またはその他の自然系や純粋培養から分離された微生物による、様々な炭化水素の酸化／ヒドロキシル化反応とエポキシ化を調べるように設計されていた。一般的に、これらの研究の結果は、エチレンは様々な微生物で生物分解を受けることがあるのを示しており、酸化エチレンとエチレン・グリコールはたぶん初期の分解産物である[21]。

水の微生物分解速度は、有酸素と嫌気性の両方の状態で見積もられている[15]：

有酸素半減期：	高：	672 時間
	低：	24 時間
無酸素半減期：	高：	2688 時間
	低：	96 時間

3.6 BOD_5, COD または BOD_5/COD比

役立つデータはない。

3.7 生物蓄積性

エチレンは$Log_{10} P_{ow} = 1.13$であるために生物蓄積性は期待されていない。

BCF（生物濃縮係数）は淡水魚ファットヘッド・ミノウ (pimephales promelas)において無極性分子の毒性作用に基づき4になるように計算された(QSAR : 定量的構造活性相関)、露出持続時間2.00－304日間であった[22]。

3.8　追加の特記事項

無し

4.　生態毒性データ

4.1　魚類への急性毒性

魚類に対するエチレンの急性毒性についてはあまり知られていない。しかし、1963年の“カリフォルニア州水資源管理部の水質基準[23]”は、オレンジスポッティド・サンフィッシュに対するエチレンの毒性についての1917年[24]と1921年[25]の二つの報告を参照している。研究結果は次のようである：

1 時間後の致死濃度：　22 - 25 mg/l [24]

1 時間以上の致死濃度：　22 - 65 mg/l [25]

Ecotoxicity Profile database [26]で計算値（QSAR：定量的構造活性相関）が報告された。

Fathead minnow (*Pimephales promelas*) 4 days LC_{50} 116 mg/l

Bluegill, (*Lepomis macrochirus*) 4 days LC_{50} 85 mg/l

Channel catfish, (*Ictalurus punctatus*) 4 days LC_{50} 50 mg/l

Rainbow trout, Donaldson trout,

(*Onchorhynchus mykiss*) 4 days LC_{50} 55 mg/l

Leeuwen [27]らによって計算値（QSAR：定量的構造活性相関）が報告された

Fathead minnow (Pimephales promelas) 4 days LC_{50} 120 mg/l

4.2　水棲無脊椎動物に対する急性毒性

A.　ミジンコ

Ecotoxicity Profile [26]のデータベースで計算値(QSAR)が報告された。

Water flea, (Daphnia magna) 48 hours LC_{50} 53 mg/l

Leeuwen ら[27]による計算値は：

Daphnid 48 hours LC_{50} 153 mg/l

B.　その他の水生生物

有効なデータは無い。

4.3　藻類に対する毒性

Selenastrum capricornutum に対する生長阻害試験が1996年にOECD201による GLP(優良試験所基準)のガイドラインに従って実施された[74]。8.2 から131 mg/l.

の間の５つの設定濃度が培養基においてテストされた。72時間の期間中にエチレンの喪失はあったものの、測定された平均エチレン濃度（０と72時間の測定値の平均）が、生長阻害の計算に用いられた。そのため実際の試験濃度は3.3, 7.8, 13.9, 32 and 58mg/l.であった。培養期間の72時間の間のエチレンの損失は64～91％の範囲であった。対照と比較した生体量の減少に基づく生長阻害に対する半数影響度（EC_{50}）は40 mg/l (95 % conf. lim.36-46 mg/l)であろうと算出された。種特有の成長率に基づいて、0-72時間のEC_{50}は72 mg/lと計算された（95 % conf. lim.はEC_{50}が試験した範囲外であったために計算できなかった）。最も高いNOEC（無影響濃度）は13.9 mg/lであった。その結果は、QSARによる*Selenastrum capricornutum*に対して得られた48時間後のEC_{50}：122.5 mg/l [27]とかなり良く一致した。

4.4 細菌に対する毒性

バクテリア懸濁液の中を10分間一定の速度でガスを通過させるやり方で、*E.coli*細菌を処理した。24時間の曝露後に、懸濁液は寒天培地に塗布されて24時間37℃で培養された。ガス処理された細胞からのコロニーの生存数は対照の79 ±1.3 %であった。同様の処理を受けた*E. coli*のSd-4株の生存数は対照と比較して84.2 ± 1.6%であった。その処理は両方の細菌株の生存に何らかの影響があったとしても軽微であるように思われると結論された[28]。

4.5 水生生物に対する慢性毒性

4.5.1 魚類に対する慢性毒性

Ecotoxicity Profile [26]のデータベースに算定値（QSAR）が報告されている。

ファットヘッド・ミノウ（Pimephales promelas）における32日間の最大許容毒性濃度（MATC）は15.3 mg/lである。

Leeuwen et. al. [27]による算定値（QSAR）は

ファットヘッド・ミノウ（Pimephales promelas）における28日間の無影響度（NOEC）は13 mg/l。

4.5.2 水生無脊椎動物に対する慢性毒性

Leeuwen et. al. [27]による算定値(QSAR) ：

ミジンコにおける16日間の無影響度（NOEC）は 37.4 mg/l

4.6 陸生生物に対する慢性毒性

4.6.1 土壌生物に対する慢性毒性

データ無し

4.6.2 陸生植物に対する慢性毒性

エチレンの曝露と影響について数百の観察結果を含む、維管束植物へのエチレンの影響について多数の種々の文献がある。これは主としてエチレンが、異なる反応の範囲の全体を調節する植物ホルモンとして作用しているという事実による。これらの反応の大部分は、摘花、成熟、伸張の抑制、葉の損失と老齢化のような効果を含む成長調節として分類することができる[9,11, 29, 30, 31, 32]。これらの効果のほとんどは非可逆的である一方、植物の生長と繁殖の適合性を減ずるような影響を全くもたらさない。その影響は適合性、生長または繁殖の減少に関連している長期間の影響と想定されることに基づく３グループに分類されるかもしれない。産業地帯における曝露に関連した危険性についてのより現実的な観点を与えている現在のデータに従って、以下の表では熱帯植物は除かれている。

維管束植物へのエチレン露出の効果の概要表。熱帯植物は含まれていない。
上偏生長（Epinasty）=縮葉、器官脱離（Abcission）=喪失

影響	曝露時間	濃度 μ g. m^{-3}	参照
1) 長期間の影響が無しまたは少			
上偏生長,レモン		25-50	[77]
上偏生長,トマト	3-4 h	46	[9]
上偏生長, アカザ属		60	[9]
上偏生長, じゃがいも	16 h	60	[9]
2) 長期間の影響によるかもしれない効果			
生長抑制, スイートピー, (NOEC)	2 d	12	[77]
花の部分欠如, カーネーション	2d	58	[77]
光合成の阻害. エンドウ (NOEL)	2 h	115	[77]
花の部分欠如, キンギョソウ	1h	575	[33]
3) 長期間の影響:			
花の量の減少, エンバク	100d	8	[77]
生長阻害, ジャガイモ	28 d	27	[77]
収量減少, トマト	28 d	50	[77]
成長遅延, エンドウ		116	[9]
収量減少, コショウソウ (30 %)	14 d	115	[77]
収量減少, ワタ	30 d	700	[9]

農業または園芸作物の中ではエンドウ、ジャガイモ、トマトおよびエンバクがよ

り感受性であり、8-50 µg/m3 (7-40ppb)の範囲の濃度において遅延効果が観察された。最も影響されやすい非木本植物がアフリカン・マリーゴールドの葉の上偏生長反応（1.16 µg/m3 (1.0 ppb)のエチレンで下向きの縮葉[9]、カトレヤに対して24時間のエチレン曝露後に2.3 µg/m3 (2.0 ppb)においてガク片の組織崩壊（花の損失）の反応が報告された。

4.6.3 哺乳動物以外のその他の陸生種に対する毒性（鳥類を含む）

データ無し

4.7 生物学的影響のモニタリング(生物濃縮を含む)

データ無し

4.8 環境種における体内変化と動力学

データ無し

4.9 追加の特記事項

データ無し

5. 毒性

5.1. 急性毒性

5.1.1 急性経口毒性：

関係がない。エチレンは沸点の低いガスである（-103.71 □）

5.1.2 急性吸入毒性

エチレンの急性毒性は低いが、非常に高い濃度は酸素置換による窒息を引き起こすかもしれない。 ネズミに対する空気中の致命的なエチレン濃度は95万ppmであると推定されている[34]。

雄のラットを４時間10, 25 or 57·10^3 ppmに曝露した時、全てのグループが血清中のピルビン酸イオンと肝臓の重量増加を示した。GLP（優良試験所基準）に準拠した研究はなかった。

5.1.3 急性経皮毒性

関係がない。エチレンの脂肪に対する低い溶解性と低い沸点のために、エチレンは皮膚を通して吸収されることはほとんど無いと思われる。

5.1.4 管理の他のルートにおける急性毒性

情報がない

5.2 腐食性／刺激性

5.2.1 皮膚刺激／腐食

液体エチレンが刺激性であることを示唆する証拠はないが、霜害を引き起こすかもしれない。

5.2.2 眼刺激性

液体エチレンが刺激性であることを示唆する証拠はないが、霜害を引き起こすかもしれない。

5.3 皮膚感作性

データ無し

5.4 反復投与毒性

エチレンの毒性が４区の曝露処理と無処理に区分したそれぞれ30頭（雄15、雌15）のラット群について90日間の吸入試験でテストされた[36]。ネズミたちは一日６時間、週に５日間で13週の間曝露された。曝露グループはT-I: 300 ppm, T-II: 1,000 ppm, T-III: 3,000ppm および T-IV: 10,000 ppm.であった。研究はＧＬＰに準拠してはいなかったが、高い科学的規格を保持し、品質を保証する声明書が発行された。無処理と処理されたネズミの間には、総重量、体重変化、食糧消費量、血液学、臨床化学、総計の病理学または組織病理学に関して違いが全くなかった。無処理、T-I および T-IV処理グループの雄ネズミは鼻の周りに赤い付着物または排出物を見せた。一方、T-II グループの雄ネズミは眼の周りに赤い付着物があった。雌の中で一頭のT-I の左目の周囲に赤い付着物が、一頭のT-I の両耳の周囲に脱毛が認められた。対照と比較して曝露処理の幾つかのグループにおいて肝臓重量が有意に低かった。しかしながら、この重量減少は無投与との関係が無く、その原因は不明であった。エチレンは段階的に管理された曝露では10,000ppmまではネズミに毒性はなかった。

試行的な非GLP研究では、6匹の雄のSprague‐Dawley系アルビノ・ラット(50-60g)が６日間、吸入剤として酸素中に60％のエチレンの連続フローに曝露されたグループにおいて、いくつかの血液学パラメタで影響を見ることができ [37]、栓球の数(-19.3%)と白血球数(-48.2%)の有意な減少があった。骨髄細胞においても同じ減少(-30%)が見られた。

新生ラットについて90日間2.62ppmの濃度での曝露(連続吸入)した慢性試験中に、発毛の遅延、歯列状態、開眼と低血圧、コリンエステラーゼ活性阻害、従属分裂が報告された[38]。この研究の質に関する情報はない。

濃度100ppmで70日間の吸入処理されたネズミでは、反射神経刺激における変化、コリンエステラーゼ活性の減少、および血圧の減少が観察された[39]。この研究の質に関する情報はない。

5.5 IN VITRO 遺伝毒性

A. 細菌試験

20%までの空気中濃度のエチレンが、ネズミチフス菌（Salmonella typhimurium）に対して、代謝活性化の添加および無添加のシステム(エームス試験)において突然変異性の兆候を示さなかった[40]。研究はＧＬＰに従って行われておらず、ガイダンスで推奨されている四分の一の細菌供試株(TA 100)しかテストされていない。サルモネラ菌の全範囲について代謝活性化システムを添加および無添加の以前のテストでもネガティブの結果が得られている[41, 42]。エチレンはエシュリキア属大腸菌に遺伝的毒性の活性を全く示さなかった[28]。

B. l in vitro での非細菌試験

染色体へのエチレンの影響が、CHO細胞の複製培養を用いてインビトロの細胞遺伝学的分析で試験された。この研究における方法論はＧＬＰとＯＥＣＤの試験ガイドライン473“遺伝毒性：インビトロの哺乳類遺伝学的試験”に従っている。広範囲な投与量をカバーする狭い間隔で分けられた処理が、ラットに導入されたAroclor1254による代謝活性化(S9)の添加および無添加の両方において実施された。使用した中で最も高いレベルの投与量(約280.5mg/ml)は、10mMの濃度に同等であり、エチレンの約25%に一致している。

空気に混ぜた時の試験品の爆発性のために、搬送ガスとして空気を使用する規定ガイドラインによって、必要な最高濃度を達成することは出来なかった。したがって、高投与量の達成を許容する窒素が搬送ガスとして使用された。しかしながら、窒素大気には連続処理に関連している技術的問題があり、短い周期(3時間)の処理が唯一の実用的な選択肢であった。

CHO細胞へのエチレンの毒性効果を調べるための範囲を見つける予備試験が行われた。この試行において、結果を収める前に17時間の回復期が伴ってのみ、S9の添加および無添加処理が３時間続けられた。主たる研究における投与量レベルは、

分裂指数によるエチレンの影響評価によって、選択された。
距離計（range-finder）を使用した処理工程が主たる研究において繰り返された。染色体の異常は3つの連続した投与量レベルで分析されました。解析で選ばれた最も高い濃度(280.5 µg/ml)において、S9を添加してもしなくても、細胞分裂の阻害（分裂指数の減少）は観察されなかった。また、無処理の対照群は主な研究に含まれていました。

適切なネガティブ(搬送ガス)コントロールがそれぞれの処理状態で両方の実験におけるテスト・システムに含まれていた。ネガティブと無処理の培地における構造的な異常を伴う細胞の割合は、歴史的な溶媒によるコントロールの範囲の中にあった。4-Nitroquinoline 1-oxideとシクロフォスファミドがそれぞれ肝臓S9が添加および無添加の陽性対照物質として使われた。これらを受ける細胞が、主な研究で処理開始の20時間後に抽出され、両方の化合物とも構造に異常のある細胞の割合が統計的に有意な増加を引き起こした。

S9の添加および無添加でのエチレンを伴う培養処理は、構造に異常のある細胞の頻度は同じようであったが、陰性対照に伴って見られたそれとは有意な違いはなかった。処理培地で見られた頻度は正常の範囲内にあった。

Ｓ９の添加および無添加のいずれでも10 mM (25 %)の濃度に曝露されたチャイニーズ・ハムスターの卵巣細胞の培養において、エチレンは染色体異常を引き起こさないと結論された。

5.6　*IN VIVO* 遺伝毒性

ラットとマウスの骨髄細胞における小核形成への影響が、次のエチレン吸入で研究された[43]。の2種それぞれ10匹の動物から成る各グループは、一日６時間、週に５日で４週間の期間に0; 40; 1,000 and 3,000 ppmの濃度が投与された。両種の酸化エチレン対照群が、同じ条件で200ppmの濃度で曝露された。骨髄は最後の曝露の約24時間後に集められた。エチレンはどちらのネズミの骨髄において曝露に関係した小核を有する多染性赤血球の頻度の統計的に有意な増加を産み出さなかった。一方、酸化エチレンの曝露は両種ともに有意な増加であった。その研究がＧＬＰに従って運営されたかどうかは記述されていない。

エチレンの吸収、分配、除去と、ヘモグロビンおよびDNAの付加体の形態が、一日12時間の３日連続した300ppmのエチレンの吸入の後のラットで研究された[44]。DNA付加体の形成は肝臓とリンパ球で測られ、ヘモグロビン付加体は赤血球の中

で測定された。エチレンによる付加体形成は他のアルケン類((二重結合を一つ持つ不飽和脂肪族炭化水素))と比較され、付加体形成の減少は分子中の炭素原子の数が増加することでわかる。この研究はＧＬＰの指針によらない試行的な研究であった。

7－グアニンのアルキル化は、８時間の初期濃度が11ppmであるときの14C-エチレンに14時間吸入曝露させたマウスの肝臓、脾臓と睾丸からのDNAで測定された。アルキル化の度合いは他の組織よりはるかに肝臓で高かった。 この研究は試行的な非GLP研究であった。

5.7　発がん性

エチレンの潜在的な発癌性はラット（Fischer -344系）を用いた2年間の研究でテストされた。研究は発癌試験のためのOECD ガイドライン451(1981)に先だって行われたが、それでも、研究はいくつかの小さな点を除いてこのガイドラインに従っている。研究では、960匹のラットから無作為に分けられた雌雄それぞれ120匹の４グループが、0(対照); 300; 1,000 ,3,000 ppm に１日６時間、週５日間、24ヶ月間以上にわたって曝露された。

研究期間中、抜け毛と鼻と目の周りのでき物、総体的な眼の異常が観察されたが、異なる処理グループの間に明確な差はなかった。

対照グループと比べてテストグループに組織肥大を示しているネズミの数の総合的な増加があったけれど、この傾向は統計的に有意ではなかった。自然死亡率(15.7%)はすべての処理グループでほぼ等しかった。処理された雄の最終的な体重と総重量の変化は対照グループよりも大きかったが、投与量に関連したパターンは見られなかった。

血液学的、血液化学的および他の調査したパラメタのいずれにおいても処理グループ間に統計的な有意差はなかった。テスト材料の効果に起因する大まかな、または組織病理的な組織の変化も供試されたラットのいずれにも見られなかった。要約は処理による発がん性効果を示すことができる所見がほんのわずかであると報告し、この点についての結論はない。

発がん性の研究からの発表[41]では、結果が「これらの濃度におけるエチレンが慢性の毒性を引き起こす、またはFischer - 344 ラットに対して発がん因子であると

いう証拠はない」との結果を出して結論づけた。しかしながら、、彼らが単完全なレポートの中で説明されている核細胞白血病について議論していないので、後でこの公表と概要は批評された[47]。影響を受けたネズミの数が（90匹のうち）対照グループでは雄が12匹、雌が８匹なのに比べて3,000 ppmを受けたグループでそれぞれ21と11匹に上がっていると主張されていた。他方では、背景としてF344ラットでは単核細胞白血病が75%以上の発生率があるかもしれず、曝露されたネズミにおける更なる増加は人間のがん発生に関して解釈するのが難しいと述べられている。

エチレンの発がん性リスクが1979年に国際がん研究機関(IARC)によって評価された時[1]、動物と人間における物質の発がん性または変異誘発性のワーキンググループには役立つデータが全くなかった。1987年に公表された補足7 [48]では役立つ十分なデータはないと要約されており、エチレンが人間にとって発がん性であると分類できないと述べられていた。IARCワーキンググループ(1994)によるエチレンの最新の評価は、エチレンの発がん性について人間と実験動物では十分な証拠がないと結論した[3]。総合的に見て、エチレンは人間にとって発がん性と分類できないと評価された。生態毒性プロファイルデータベースではQSARシステムにおいて、この化学物質が潜在的な発がん性または突然変異誘発要因であることを示唆する情報はないと述べられている。

がんの危険因子としてエチレンの別の最近の評価では、それが重要な危険因子であると結論づけられた[49]。この結論は突然変異性と発がん性の双方が示されている酸化エチレンへのエチレンの代謝の観察に基づいていた。エチレンの代謝の飽和があるので、用量反応関係による直線的な仮説をこの場合には適用できない。その結果、動物へ多量に投与した実験における知見からは、人間の曝露レベルに対して推定できない。

エチレンの潜在的発がん性は、BIBRA（British Industrial Biological Research Association） の会報でも総括された。このレビューも、酸化エチレンの代謝産物に基づいて、エチレン吸入の潜在的発がん性リスクの詳細な再考に時宜を得ていると結論している。また、評価はエチレンの明確な産業的制限の必要性の再評価を求めている。

5.8 繁殖への毒性

雄と雌のラットにおける繁殖および子の生長と発育へのエチレン吸入の潜在的影響が研究された[70]。その実験的研究はGLP(OECD Guideline421; 繁殖/発育への毒

性審査テスト)に従って行われた。４グループのラット(1グループあたり匹の雌と10匹の雄)が毎日６時間の頭部だけでの吸入で200; 1,000 or 5,000 ppmのエチレンと、空気だけの投与（0; 230; 1,150 or 5,750 mg/m3に相当）が行われた。この投与制は、投与の３グループに対してそれぞれ80; 400 and 2,000mg/kg/dayを与えるために計算された。肺からの摂取がたぶん5-10%の範囲にあったため、吸収量はたぶん上記の数字より実質的に少なかったであろう。

交配に先立つ２週間、交配期間中、および雄では検死の前日まで(最小28日間)、雌では妊娠の20日目まで、供試物が親ネズミたちに施された。雌は出産と、親子が殺されるまでの分娩後４日間は世話をすることを許された。

病的状態、死亡率、臨床の状態、体重および食物摂取量が研究期間中観察され、また交配が注意深く調べられ。それぞれの雌について、産子数および各子ネズミの測定が記録された。研究の終了時、すべての動物が形態的または病理学的な変化を肉眼で検査された。対照および高投与量動物の卵巣、睾丸、および副睾丸が組織病理学検査を受けた。

テスト品に起因する死亡はなく、交配前、妊娠および授乳期間における体重増加は悪影響を受けなかった。繁殖力や多産性に対して処理の影響はなく、すべての雌が妊娠した。産子数、性比、子ネズミの平均体重、成長および臨床状態は処理による悪影響を受けなかった。

検死は、肉眼による検査がテスト品の投与による毒性を示唆する肉眼的発見がないことを示した。試験物の投与による睾丸への毒性影響に関する証拠はなく、さらに毒性を示唆する顕微鏡的所見もなかった。

結論として、名目上の濃度が200; 1,000 or　5,000 ppmのエチレンの頭部だけの投与は、毒性の証拠または、雄と雌における繁殖行動、繁殖力、妊娠、母と子の行動、および受胎から産後４日目の子の生長と発育への悪影響はなかった。

5.9　発生毒性／催奇形性

それはOECD Guideline421にそって行われた繁殖／発育毒性の選択試験が実験的研究に参照されている。その研究は上記の5.8に要約されている。

5.10　他の関連情報

A.　特異的毒性（神経毒性、免疫毒性など）

データなし

B. 毒力学、毒物動態学

コールズ，A.Lら[51]は犬での４種類の4吸入麻酔薬の摂取と分布を研究した。21の一連の実験では、13頭の大型雑種犬に一定濃度のエチレン(1.4%＝12g/m^3)と他に３種類の吸入麻酔薬を吸入させた。肺胞気、動脈血、脳、筋肉、および中央の静脈血の中の麻酔薬の濃度がガスクロマトグラフィーによって測定された。エチレンの分圧が吸気分圧(1.4%)の50%に達するのに必要な平均時間は以下の通りである： 肺胞気、２分以下、 動脈血　２分以下、 脳、3.7分、筋肉 8.２分、中央の静脈、5.2分

エチレンの酸化エチレンへの生体内変換

エーレンバーグらは1977 [52]、雄のCBAマウスに吸入させた14Cでラベルしたエチレンが酸化エチレンに代謝されたことを示した。酸化エチレンは発癌物質であり遺伝子毒である強力なアルキル化剤(DNAを不可逆修飾する抗悪性腫瘍薬の一群)としてエチレンより毒性が強いので、この代謝はとても重要である。形成されたエポキシドの量はヘモグロビン中に残っているシステインとヒスチジンのアルキル化の度合いから量的に決定された。

同じ実験室における後の研究では[45]、酸化エチレンがマウスのDNAの求核部をアルキル化したことが示された。エチレンと酸化エチレンに曝露された時に、DNAとヘモグロビンのアルキル化の度合いの比率が同じであったので、後者が生体内でエチレンから形成された反応中間物であると結論づけられた。酸化エチレンとエチレンの単位あたりの曝露で得られたアルキル化の度合いの比較は、低レベルのエチレンでは、吸入された量の約8%が酸化エチレンに代謝されたことを示した。エチレン濃度の増加に伴うエチレン酸化の割合は飽和濃度まで続いた。218ppmのエチレンでは、酸化率は最高割合の半分(K_m 値)であった。エチレンの最大限度の代謝速度(Vmax)が空気中濃度4ppmの酸化エチレンへの曝露に対応すると推定された。

Törnqvist ら., 1988 [53]は、自動車エンジンの排気に曝露した後のラットで、ヘモグロビンちゅうにアルキル化されたアミノ酸を確認した。これらは吸入されたエチレンとプロピレンの約5-10%がそれぞれのエポキシドに転換し、さらにヘモグロビンの求核サイトをアルキル化した結果である。約8%の換算率にとてもよく一致していたエチレンの酸化される部分の定量化は、上記の研究の中でのマウスで発見された。Törnqvist とエーレンバーグ1990による結果では、人間では、喫煙家において吸入された主流煙中のエチレンの約6%[54]、非喫煙者で約3%[55]が酸化エ

チレンに変換されると推定された。

エチレンの酸化エチレンへの代謝的変換はDNAとタンパク質付加体の形成をもたらし、これは生体内でエチレン曝露を特定するための手段を提供する。N-アルキル・エドマン法を使用したヘモグロビン付加体の測定は役立つと証明した[53]。この方法は異なるソースからのエチレン曝露後の付加体形成を調べるために用いられた[49]。

酸化エチレンの毒性

酸化エチレンは投与量の増加と関連して、F344ラットでグリオーマ、腹膜悪性中皮腫、単核細胞白血病を、B6C3F1マウスでリンパ腫および肺、子宮、ハーダー腺、乳腺の腺腫/悪性腺腫引き起こす（ウォーカーら、1990によるレビュー1990 [56]）。

酸化エチレンに関する疫学データは酸化エチレンが発がん性作用物であるという予想を支持している。酸化エチレンに曝露された733人の労働者の死亡率と発がん率が調べられた時、それぞれの期待数は0.8と0.65であったが[57]、８例の白血病と６例の胃がんが見つけられた。

生体内と同じく生体外で、酸化エチレンはタンパク質のアミノ酸残基とDNAのプリン塩基の双方に反応しているのが見られる。マウス、人間またはラットの赤血球が酸化エチレンにさらされたとき、主な反応の生成物はヘモグロビンでシステインの2ヒドロキシエチレイション、N-末端バリン、ヒスチジンとカルボキシルグループのイミダゾール窒素であった[58]。仔ウシ胸腺のDNAとの反応の後の主な反応生成物はN7(2-hydroxyethyl)グアニンであったが、O-6(2-hydroxyethyl)のグアニンはこの約0.5%にすぎなかった。
また、ラットとマウスの赤血球がヒトの赤血球よりアルキル化に感受性であったように、種間差が見られた。

酸化エチレンによるDNA 塩基のアルキル化が、吸入によって酸化エチレンに曝露させたラットでさらに研究された[59, 56, 60]。
生体内および生体外ともにおける主なアルキル化部位は7(2-hydroxyethyl)グアニンに由来するグアニンのN-7位置であり、この変更がたぶん発がん性と突然変異的な効果の理由である。

IARC（国際がん研究機関）のワーキンググループは、1994年に酸化エチレンを評価し、人間対して発がん性があるという総体的結論に至った。これは主として動

物に対する発がん性に関する実験的研究からの証拠に基づいていた。

エチレン毒性と体内変化におけるPCBの前処理の効果

ハロゲン化エチレンと同様にエチレンがポリ塩化ビフェニル(PCB)で前処理されたラットに対して急性の肝細胞毒であることが示された[62]。PCBの前処理と2万ppmのエチレンに４時間曝露されたラットにおいて、血清のアラニン・α・ケトグルタル酸塩トランスアミナーゼ(SAKT)とソルビトール脱水素酵素(SDH)の増加で肝毒性は明白であった。PCBの前処理がなければ、エチレンとハロゲン化エチレンは急性毒ではない。これらの発見から、急性毒性がPCBの前処理で引き起こされた肝臓の混合機能酸化酵素によって形成されたエポキシドの仲介を通して成立していることが示唆された。

ラットが閉じている乾燥機瓶の部屋でエチレンに曝露されたとき、化合物を除去する代謝速度はPCB前処理(実験の6日前にアロクロール125を500mg/kg油に入れて単回投与)によって影響を受ける[63]。エチレンの体内変化は酸化エチレンとなって放出された。

PCBプレ処理と高い被ばくレベルのエチレンの影響は、モノオキシゲナーゼの誘導と酸化エチレン形成の増加のために、モノオキシゲナーゼ誘導酸素に曝露された生物にとって、エチレンの毒性が重要であることを示している。しかしながら、使用された濃度が、実際の被ばくレベルをはるかに超えていることを心に留めておくべきである。

5.11 人のばく露経験

一般的にエチレンは麻酔薬として長年にわたって使用された。たいていはその高い爆発の危険性のために、より近代的な麻酔薬に取り替えられた。低濃度のエチレン（2.5 %以下）の長期で反復した曝露の結果としての人における慢性的な障害は「Pattyの産業衛生と毒物学(1981)」の中では報告されなかった[11]。

吸入薬物動態学

エチレンの吸入が人間のボランティアで最大50ppmの大気中濃度で調査された。摂取、発散および代謝は一次反応速度論によって説明できた[64]。摂取による除去はわずか5.6%と低く、残りは血流に入ることなく吐き出された。代謝による除去はシステムで使われたエチレンの36%であった。エチレンの生物学的半減期は0.65時間だった。肺胞に定常的に留まったエチレンは２％と算出された。エチレンの低い摂取率は血液への低い溶解度のためと考えられた。

繁殖への影響

予備的な研究では、地方の石油化学産業で働いていたスウェーデン人女性における流産率(15回の妊娠のうちの6回)は、産業の外部にいた1549人の女性に見られたそれより高かった。エチレンは5ヶ所の地方石油化学工場のうちの4ヶ所における主な生産物であった。職業レベルで提供されたデータは全くないが、領域を囲っている植物での測定では、エチレンがその他の汚染物質(プロピレン、エタン、プロパンおよびフェノール)よりも10倍高い濃度で存在しているのを示した[65]。

簡潔な要約は、約40-60ppmの範囲のエチレン濃度と高いレベルの雑音に曝露されたポリエチレンプラントの女子工員における流産と婦人科病は期待値よりも高い割合であったことが簡潔な要約で言及された[66]。

発がん性

予備的な研究では､米国の石油化学工場でエチレン(不特定のレベルにおける)に曝露された31人の労働者において肺がん発生の増加を全く見つけなかった[67]。

アメリカの石油化学プラント労働者についての研究で、脳腫瘍を発症する危険性の増加がエチレンを含む多くの化学物質の曝露(不特定のレベル)と関連していることが分かった。しかしながら、研究者はその関連性が偶発的な関係を反映していたと確信してはいなかった[68]。

職場の曝露

バナナの成熟を制御するのに使用されている会社における、個人的で定常的なエチレンの観測は、大気中濃度が0.02-3.35ppm(0.02--3.85mg/m3)の範囲にあり、平均濃度は0.3ppm(0.35mg/m3)であったことを示した。

消防士の曝露に関する研究では、炎の「圧倒的な（knockdown）」様相の間に取られたサンプルは、46ppm(53mg/m3)の濃度のエチレンを示した一方、精密検査（overhaul）の間には検出されなかった[3]。

スウェーデンの石油化学プラントの労働者を対象に、エチレン曝露のモニターのために酸化エチレンから形成されたヘモグロビン付加体の測定をする研究が実施された[69]。研究は1989年のパート1および1993年のパート2の2つのパートで実施された。高いレベルのエチレンに曝露された8人の労働者(4mg/m3)と、低レベルに曝露された3人の労働者(0.1 -0.3mg/m3)が、対照とした0.01mg/m3に曝露された9人と比較された。全ての被ばく労働者がヘモグロビン付加体のレベルを上げ、付加

体形成は投与量に関連していた。結果は、吸入されたエチレンの約1%が酸化エチレンに代謝されたことを示した。

4人の労働者を含んでいた研究の第二部は、より正確に被ばくレベル、平均4.5mg/m3となるに設計された。結果はパート1を追認し、吸入されたエチレンの約1%が酸化エチレンに代謝されて、変換されるべき最大区分が4%であると推定された。

ヒトの曝露関して報告されたエチレンのピーク水準は約50ppm(57.5mg/m3)であり、一方3.5ppm(4.0mg/m3)は、より長い期間の曝露の高位平均値とみなされた。そして、ピーク水準に対しては最大の2ppm(3.6mg/m3)、高位平均値に対しては最大0.14ppm (0.25mg/m3)の酸化エチレンへの変換に対応するであろう。酸化エチレン(時間加重平均)について定められた職業被曝限界水準は、1.8mg/m3(デンマーク、日本、米国、ノルウェー)と2.0mg/m3(フランス、カナダ、スウェーデン)である[3]。

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IRPTC（International Register of Potentially Toxic Chemicals　国際有害化学物質登録制度）の法的なファイルからの抽出

資料　１０

欧州経済共同体理事会指令 91/414：評価報告書に対する最終補遺
エタノールについての補遺－第３巻、付属書Ｂ．７
反応および分解生成物の毒性（エチレンおよび酸化エチレン）
2008 年 10 月　　（抜粋、p.80-139 の部分は省略）

Final addendum to the Draft Assessment Report (DAR)

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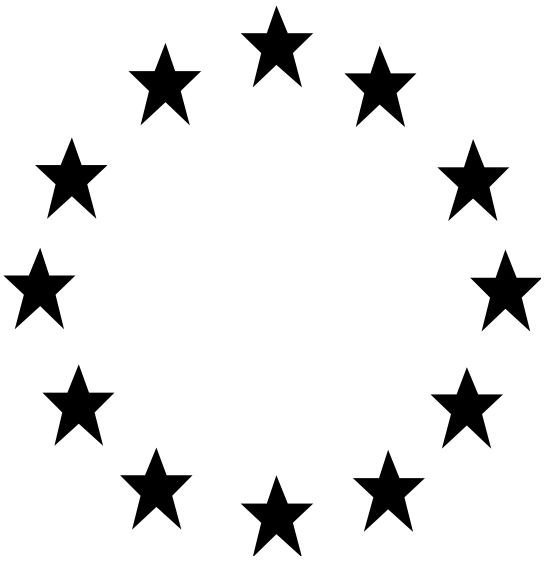


Final addendum to the

Draft Assessment Report (DAR)

- public version -

Initial risk assessment provided by the rapporteur Member State The United Kingdom for the Existing active substance

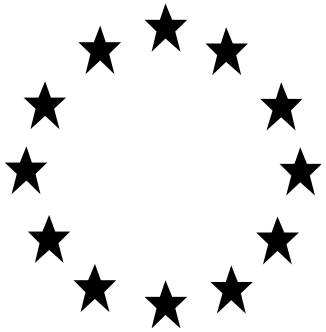
ETHANOL

of the fourth stage of the review programme referred to in Article 8(2) of Council Directive 91/414/EEC

November 2008

Table of contents

Council Directive 91/414/EEC



Ethanol

Volume 4

Annex C

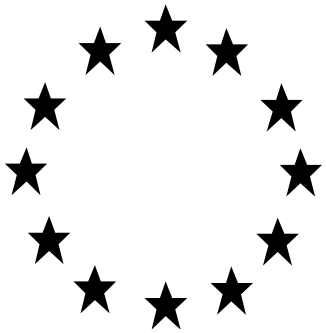
to the Report and Proposed Decision of the United Kingdom made to the European Commission under Article 8(1) of 91/414/EEC

Confidential Information

Draft: August 2008

confidential information available at RMS

Council Directive 91/414/EEC



Ethanol

Addendum 2 to the Report and Proposed Decision of the United Kingdom made to the European Commission under Article 8(1) of 91/414/EEC

Assessment of available information on the toxicology of the reaction and degradation products (ethylene and ethylene oxide)

Note: The sole supported use of ethanol is as a precursor for ethylene. Ethanol is converted to ethylene using a catalytic generator.

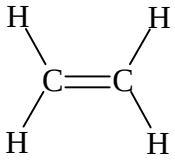
October 2008

B.6 TOXICOLOGY AND METABOLISM

Introduction

Ethylene (or ethene) is the simplest alkene (i.e. an unsaturated hydrocarbon or olefin); it is a very flammable gas and forms explosive mixtures with air. It is an endogenous growth regulator in plants which is used to ripen bananas. The biosynthesis of ethylene in plants is well documented in the literature (Wang *et al*, 2002).

Figure B.6.1 Structure of ethylene



Chemical name: ethylene.
Other names: ethene, acetone, bicarburetted hydrogen and olefiant gas.
CAS Number: 74-85-1.
Molecular weight: 28.05 g/mol.
Molecular shape: planar.
Molecular formula: C_2H_4
Octanol/water partition coefficient: Log Kow = 1.13.
Solubility in water: 131 mg/l at 20ºC.
Vapour pressure: 4.2 x 10^6 Pa.
Physical state: Colourless gas with a slight, sweet and musty odour.
Conversion factors (NTP): i) 1 ppm = 1.15 mg/m^3; ii) 0.86 ppm = 1.0 mg/m^3.

Ethylene is a gas at normal temperature and pressure. It is an asphyxiant and induces hypoxia by reducing the oxygen content of air by dilution.

Ethylene is an important industrial chemical; its uses include the manufacture of polyethylene, ethylene oxide (a fumigant and sterilizing agent), ethylene dichloride, ethylene glycol, linear alcohols, olefins, ethylbenzene, acetaldehyde and vinylacetate. In addition, it is used as a fuel in metal cutting and welding and as an anaesthetic.

Ethylene is ubiquitous in the environment being released into the atmosphere from natural and man made sources. Approximately 75% of the atmospheric ethylene originates from organic sources (e.g. an endogenous growth regulator in plants that is emitted by vegetation and it is produced by micro-organisms as part of their normal metabolism) and 25% from anthropogenic sources (e.g. combustion of gas, fuel, coal and biomass). Atmospheric ethylene can be degraded by ozone (half-life 6.5 days/estimated to destroy 8%), nitrate radicals (half-life 190 days) or by photochemically-produced hydroxyl radicals (half-life 1.9 days/estimated to destroy 89%). The atmospheric lifetime of ethylene has been estimated to be 2-4 days.

Environmental human exposure mainly occurs from the combustion of fossil fuels (e.g. motor vehicle emissions) and the burning of organic matter (e.g. smoking). Ethylene concentrations in ambient air at rural and remote sites are generally in the

range of <0.001-0.005 mg/l and up to 0.05 mg/l in urban and indoor areas (values of up to 1 mg/l have been recorded in heavy traffic). Ethylene is produced endogenously by humans and other mammals and several mechanisms have been proposed for its endogenous production: lipid peroxidation, enzymatic reactions or oxidative destruction of methionione and haemoglobin and by intestinal bacteria.

No metabolism or toxicity studies have been submitted or evaluated for ethylene or its metabolite ethylene oxide (a potent alkylating agent and genotoxic carcinogen). The information and toxicological data cited in this document is entirely dependant on the data cited in the published literature (mainly summarised in the publications listed below). It should be noted that details of the protocols, the dosing patterns and the GLP status of cited studies were minimal and the source, age and quality of the data/information were often unclear and difficult to assess. In addition, no reliable quantitative toxicity data have been submitted for ethylene exposure to experimental animals via the oral route (normally required for determining NOAELs and the setting of reference doses for the consumer risk assessment).

The main publications/sources of information cited in the following ethylene evaluation are as follows:

i) OECD Screening Information Data Set (SIDS): Ethylene. Date not specified. Organisation for Economic Co-operation and Development (OECD: SIDS).

ii) IUCLID Dataset, Ethylene, European Chemicals Bureau, 2000 CD-ROM Edition.

iii) Hazardous Substances Data Bank, No 168, 2003 (HSDB 2003, toxnet.nlm.nih.gov).

iv) IARC Monograph on the Evaluation of Carcinogenic Risks to Humans (1994). Some Industrial chemicals, Vol 60 (Ethylene pages 45-70) (IARC 1994).

v) Proposed Regulatory Decision Document. Ethylene Eco Sprout Guard. Health Canada October 2001 (HC 2001).

Inevitably, the publications listed above are mainly summarising and citing the same studies and data. Since there are minor differences in the reporting of the details by the different sources, individual studies may be cited more than once especially where additional information has been reported. To assist in identifying the studies cited by these publications, the original references (where available) have been cited together with the relevant publication in this evaluation (these references have not been individually evaluated by the RMS). The quality of the studies cited and the extent and depth of the investigations carried out are impossible to ascertain without an extensive evaluation of the individual published studies.

B.6.1 Absorption, distribution, metabolism and excretion (toxicokinetics) (IIA 5.1)

B.6.1.1 Absorption, distribution and excretion

Male Fischer 344 rats (170-220g) were exposed to 14C-ethylene (free of ^{14}C-acetylene or greater than or equal to 97% pure) for 5 hours in a closed chamber (35 litres) to 10000 ppm (11.5 mg/l). In each experiment, up to four rats were exposed together in a single chamber. Within one minute after the end of exposure, animals were transferred to individual all glass metabolism cages and the elimination of radioactivity monitored for up to 36 hours. Most of the eliminated 14C was exhaled as ethylene [(18 µmol (504 µg) per rat exposed to acetylene-containing ethylene; this statement is not consistent with the material tested/no explanation)]; smaller amounts were excreted in urine (2.7 µmol ethylene equivalents/rat) and faeces (0.4 µmol) and exhaled as carbon dioxide. Radioactivity was 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 equivalent/kidney). Pre-treatment of animals with a mixture of polychlorinated biphenyls (Aroclor 1254: 500 mg/kg bw; single intraperitoneal injection 5 days before exposure) had no measurable influence on ethylene exhalation but resulted in a significant ($p< 0.05$) increase in exhaled $14CO_2$ (2.04 µmol ethylene equivalents/rat) and of 14C in urine (11.1 µmol ethylene equivalents/ml). The organ burden of 14C was one to two orders of magnitude greater in Aroclor 1254-treated than in untreated animals. Radioactivity was also detectable in lungs, brain, fat, spleen, heart and skeletal muscle. The data were interpreted as indicating that an inducer of the mixed-function oxidase system can stimulate the metabolism of ethylene.

(Guest *et al*, 1981/IARC 1994)

b) Male Fischer 344 rats (with and without pre-treatment with Aroclor 1254) were exposed to 14C-ethylene (12.56 mg/l= 10000 ppm) for 5 hours. Samples were collected for 36 hr following exposure. Aroclor pre-treatment did not affect the amount of ethylene expired but did cause a 4-fold increase in expired $14CO_2$ and a 2-fold urinary excretion of radioactivity. Aroclor pre-treatment increased the concentrations in blood, gut, kidney, liver and lung by factors of 1.5-, 6-, 8-, 16-, 17-fold; detectable concentrations of radioactivity were also found in brain, heart, fat and muscle. The rats pre-treated with Aroclor showed centrilobular hepatic necrosis (light microscope) which was not seen in the rats exposed to ethylene alone. The author suggested that ethylene metabolism is stimulated by Aroclor treatment.

(Guest *et al*, 1981, IUCLID 2000)

c) Several studies have investigated the pharmacokinetics of inhaled ethylene 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 20ml/min for one rat of 250 g which represents only 17% of the alveolar ventilation (117 ml mins; Arms & Travis, 1980). Most (83%) inhaled ethylene that reaches the lungs is exhaled again without becoming systemically available via the blood stream. Maximum accumulation of ethylene in the organism, determined as the thermodynamic partition coefficient, whole body:air (Keq =

$Conc_{animal}/Conc_{air}$), was 0.7. The concentration ratio at steady-state whole body:air was somewhat lower owing to metabolic elimination ad it decreased from 0.7 to 0.54 at exposure concentrations below 92 mg/m^3 (80 ppm). However, at very low atmospheric concentrations, the concentration ratio at steady-state whole body:air increased, 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 0.06 mg/m^3 (0.05 ppm); calculated using pharmacokinetic parameters and equation 18 of Filser,1992. At concentrations between 92 and 0.12 mg/m^3 (80and 0.1 ppm), clearance was seen, due to metabolism related to the concentration in the atmosphere of about 4.7 ml/min for the 250g 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 value was 3.5% and the biological half-life was 4.7 minutes (Filser *et al*, 1992). At atmospheric concentrations greater than 92 mg/m^3 (80 ppm), metabolism of ethylene became increasingly saturated, reaching a maximum rate of metabolism (V_{max}) of 0.035 µmol/(min x 250 g bw) [0.24 mg/(h x kg bw)] at about 1150 mg/m^3 (1000 ppm). 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 239 mg/m^3 (208 ppm) at $V_{max/2}$, calculated by means of the kinetic parameters given by Filser (1992).

(IARC 1994)

d) In a series of 21 experiments, 13 large mongrel dogs were ventilated with a constant concentration of ethylene (1.4% = 12g/m^3). Concentrations were measured by gas chromatography in alveolar gas, arterial blood, brain, muscle and central venous blood. The average times necessary for the partial pressure of ethylene to reach 50% of the inspired partial pressure (1.4%) were: alveolar gas, <2.0 minutes; arterial blood, <2.0 minutes; brain, 3.7 minutes; muscle, 8.2 minutes and central venous blood, 5.2 minutes.

(Cowles, 1972/OECD: SIDS)

B.6.1.2 Metabolism

A metabolic pathway for the biotransformation of ethylene in mammals was not proposed.

a) Four male CBA mice (average body weight, 31 g) were exposed together for one hour in a closed glass chamber (5.6 litre) to 14C-ethylene (22 mCi/mmol) in air at 17 ppm (0.0223 mg/l) which is equivalent to about 1 mg/kg bw. Blood and organs from two mice were pooled 4 hours after the end of exposure. Radioactivity was about the same in kidney (0.16 µCi/ g) and liver (0.14 µCi/ g) but lower in testis (0.035 µCi/ g), brain (0.02 µCi/ g) and haemoglobin (0.0094 µCi/G Hb). Urine was collected from the two other mice during the 48 hour period and blood was collected after 21 days. A urinary metabolite, 5-(2-hydroxyethyl)cysteine was identified by thin-layer chromatography (3% of 14C in urine). The radioactivity in haemoglobin was 0.011 µCi/g Hb. This data, together with those on specific hydroxyethyl derivatives at amino acid residues of haemoglobin indicates that ethylene was metabolised to ethylene oxide.

(Ehrenberg *et al*, 1977/IARC 1994)

In liver microsomes prepared for male Sprague-Dawley rats, ethylene at concentrations of up to 115 g/m^3 (10%) in the gas phase was metabolized to ethylene oxide in the presence of an NADPH regenerating system (1 hour, pH 7.5, 37ºC). 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 diethyldithiocarbonate or β-naphthoflavone to the microsomal suspension. Treatment of 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/IARC 1994)

b) In mice, it was shown that ethylene oxide alkylated nucleophilic sites of DNA in liver, spleen and testes. Since the ratio between the degree of alkylation of DNA and that of haemoglobin was the same when exposed to ethylene and ethylene oxide, it was concluded that ethylene oxide was an *in vivo* reactive intermediate formed from ethylene. A comparison of the degrees of alkylation obtained per unit exposure of ethylene oxide and ethylene showed that at low levels of ethylene, about 8% of the inhaled amount was metabolised to ethylene oxide. The rate of ethylene oxidation followed saturation kinetics with increasing concentration. At 218 ppm ethylene, the oxidation rate was half of the maximal rate (k_m value). It was estimated that the maximal rate of metabolism (V_{max}) of ethylene corresponds to exposure to an air level of 4 ppm of ethylene oxide.

(Segerback, 1983/OECD:SIDS)

c) 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 diethyldithiocarbonate 15 min before exposure and by an increase in the rate of its metabolism with a V_{max} of about 14 µmol/(h x kg bw) [0.33 mg/(h x kg bw)] after treatment with a single dose of Aroclor 1254 (500 mg/kg bw) six days before the experiment.

(Bolt *et al*, 1984/IARC 1994)

d) Male Sprague-Dawley rats exposed to ethylene exhaled ethylene oxide. In these experiments, two animals were kept together up to 21 hours in a closed chamber (6.4 litres). The concentration of ethylene in the atmosphere of the chamber was maintained at greater than 1115 mg/m^3 (1000 ppm) 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 0.69 mg/m^3 (0.6 ppm). After about 2.5 hours, the concentration had decreased to about of 0.345 mg/m^3 (0.3 ppm) and then remained constant. On the basis of the concentration- courses of atmospheric ethylene, it was speculated that this decease was due to rapid induction of ethylene oxide metabolizing enzymes, whereas the rate of ethylene metabolism remained unaffected (Filser and Bolt, 1984). In male Sprague-Dawley rats exposed to ethylene at concentrations greater than 1115 mg/m^3 (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 hours (Bolt *et al*, 1984). Pharmacokinetic data for ethylene and ethylene oxide indicate that in steady state conditions only 29% of metabolised ethylene is available systemically as ethylene

oxide. Therefore, assuming that the liver is the principle organ in which ethylene is metabolised, an intrahepatic first-pass effect for the intermediate ethylene oxide was suggested (Filser and 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 10.2 mg/m^3 (5.6 ppm) at steady state (Bolt and Filser, 1987).

(IARC 1994)

e) Metabolic conversion of ethylene oxide results in the formation of DNA and haemoglobin adducts that can be used to identify ethylene exposure. Alkylated amino acids in haemoglobin have been shown in rats exposed to automotive engine exhaust. These adducts resulted from the conversion of 5-10% of inhaled ethylene.

(Tornqvist *et al*, 1988/OECD:SIDS)

f) Ethylene oxide was found in the blood of male Fisher 344 rats during exposure to an atmospheric ethylene concentration of 690 mg/m^3 (600 ppm). A maximal value of about 3µg/g blood of ethylene oxide was seen 8 minutes after the start of exposure to ethylene; this value was followed 4 minutes later by an immediate decrease to about 0.6 µg/g blood and this level remained constant for the following 46 minutes. During exposure, "the cytochrome P450 content in the liver was reduced to 94% after 20 minutes and 68% after 360 minutes" (no further details). 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 isozyme which is not suitable for the determination of cytochrome P450 isozymes.

(IARC 1994)

g) In male Sprague Dawley rats treated with phenobarbital (intraperitoneal injection of 80 mg/kg bw/day for 4 days and exposure to ethylene on day 5) and then exposed for 3 hours to a mixture of commercial ethylene (contaminated with about 10 ppm acetylene) and air (1:1 v/v), a green pigment was formed in the liver 4 hours after exposure. The same pigment was formed *in vitro* during incubation of acetylene-free ethylene with 9000 x g supernatant of a rat liver homogenate (from phenobarbital-pre-treated animals) in the presence of NADPH. No controls were used (Ortz 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 conclude that the phenobarbital-inducible form of cytochrome P450 was destroyed during oxidative metabolism of ethylene (Ortz de Montellano *et al*, 1980 & 1981).

(IARC 1994)

h) Ethylene oxide is exhaled by untreated rats (Shen *et al*, 1989). The endogenous production rate in a Sprague-Dawley rat (250g bw) was determined to be 2.8 nmol/h [0.31 µg/(h x kg bw)] resulting in a body burden of ethylene gas of 0.32 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 0.24µg/(h x kg bw). Four

possible sources of endogenous ethylene have been suggested in the literature: lipid peroxidation (Kautiainen *et al*, 1991), enzyme- copper- or iron-mediated catalysed oxidation destruction of methionine (Fu *et al*, 1979; Lieberman *et al*, 1965; Kessler & Remmer, 1990; respectively), oxidation of haemoglobin (Clemens *et al*, 1983) and the metabolism of intestinal bacteria (Tornqvist *et al*, 1989b).

(IARC 1994)

It has been demonstrated that ethylene and halogenated ethylenes are acute liver toxins in rats pre-treated with polychlorinated biphenyl (PCB). Without pre-treatment with PCB and exposed to 20000 ppm ethylene for 4 hours, ethylene and halogenated ethylenes did not induce liver toxicity. The rate of metabolic elimination of ethylene is influenced by pre-treatment with PCB and leads to an increase in exhaled ethylene oxide.

(Conelly and Jaeger, 1977; Filser and Bolt, 1983/OECD: SIDS)

B.6.1.3 Summary of toxicokinetics studies

No ADME studies have been submitted (no oral ADME studies have been cited). The majority of the available data has been generated using inhalation exposure. A metabolic pathway has not been proposed for ethylene in mammals. Apart from ethylene oxide and its metabolites and the urinary metabolite hydroxyethyl cysteine in mice, there appears to be little or no information or investigations into other potential metabolites of ethylene (see B.6.8.1).

Following inhalation of radiolabelled ethylene, absorption appeared to be rapid (within minutes) but the systemic uptake from the lungs was low (low solubility in blood). The uptake, exhalation and metabolism can be described by first-order kinetics. It has been estimated that approximately 83% of the ethylene that reaches the lungs is exhaled unchanged while 17% is absorbed. Distribution is widespread throughout the body (i.e. nervous system, lungs, liver, kidneys, spleen, heart, blood, fat, skeletal muscle and testes). In rats, about 24-29% of systemically available ethylene is eliminated by metabolism and the remainder by exhalation of the unchanged substance. Elimination appears to be rapid. Most of the inhaled ethylene was exhaled unchanged with smaller amounts excreted in urine and faeces and as exhaled carbon dioxide. Pre-treatment with cytochrome P450 inducers increased the amount of $^{14}CO_2$ exhaled and the levels of 14C in urine and tissues.

Ethylene oxide has been identified as a metabolite of ethylene in rodents based on its ability to form DNA and protein adducts (e.g. haemoglobin). The degree of alkylation obtained per unit exposure of ethylene oxide and ethylene shows that at low levels of ethylene, about 5-10% of the inhaled ethylene was metabolised to ethylene oxide in experimental animals. The rate of ethylene oxidation followed saturation kinetics with increasing concentration. *In vitro* studies using rodent liver also demonstrate that ethylene can be metabolised to ethylene oxide. Inducers (PCBs) of the mixed-function oxidase system can stimulate the metabolism of ethylene and increase the levels of exhaled ethylene oxide. A urinary metabolite 5-(2-hydroxyethyl)cysteine, possibly formed from ethylene oxide, was identified in mice.

B.6.2 Acute toxicity, irritancy and skin sensitisation studies (IIA 5.2)

B.6.2.1 Acute oral toxicity (IIA 5.2.1)

No studies submitted (or data cited from the published literature).

B.6.2.2 Acute dermal toxicity (IIA 5.2.2)

No studies submitted (or data cited from the published literature).

B.6.2.3 Acute inhalation toxicity (IIA 5.2.3)

Male rats exposed to ethylene at concentrations of 11.5, 28.8 or 65.6 mg/l of air for 4 hours showed increased serum pyruvate and liver weight at all dose levels (no deaths reported). The LC50 in male F344 rats was greater than 12.518 mg/l for a five hour exposure. The lethal concentration of ethylene in air to mice was stated to be 950000 ppm (estimated to be approximately 1093 mg/l of air). No respiratory irritation has been reported in patients. Therefore, ethylene would not be classifiable via the inhalational route according to EC criteria.

(Flury, 1928; Gaeb *et al*, 1975/OECD: SIDS)

B.6.2.4 Skin irritancy (IIA 5.2.4)

No studies submitted (or data cited from the published literature) but according to the reference there is no evidence that ethylene gas is a skin irritant.

(OECD: SIDS)

B.6.2.5 Eye irritancy (IIA 5.2.5)

No studies submitted (or data cited from the published literature) but according to the reference there is no evidence that ethylene gas is an eye irritant.

(OECD: SIDS)

B.6.2.6 Skin sensitisation (IIA 5.2.6)

No studies submitted (or data cited from the published literature).

B.6.2.7 Summary of acute toxicity, irritancy and sensitisation studies

Based on the cited data, ethylene is not classifiable via the acute inhalation route according to EC criteria. There is insufficient data to classify ethylene via the acute oral and dermal routes, for skin and eye irritancy or for skin sensitisation using the normal EC criteria. However, based on industrial use and practice and its use as an anaesthetic, ethylene gas dose not appear to be classifiable as a skin or eye irritant or a skin sensitiser. It should be noted that liquefied or pressurized ethylene gas can cause frostbite damage (this may trigger part of Directive 2003/82/EC).

B.6.3 Short-term toxicity studies (IIA 5.3)

B.6.3.1 Oral administration to rats

No studies submitted (or data cited from the published literature).

B.6.3.2 Oral administration to mice

No studies submitted (or data cited from the published literature).

B.6.3.3 Oral administration to dogs

No studies submitted (or data cited from the published literature).

B.6.3.4 Administration by other routes

B.6.3.4.1 Inhalation exposure

a) 6-day exploratory study

A group of six male Sprague-Dawley albino rats were exposed to a continuous flow of 60% ethylene in oxygen for 6 days, i.e. 600,000 ppm equivalent to 690 mg/l (1968 publication). Effects were reported on several haematology parameters. There was a significant reduction in thrombocyte count (-19.3%) and leukocyte count (-48.2%) and a reduction was also seen in the bone marrow cellularity (-30%).

(Fink, 1968/OECD: SIDS)

b) Liver damage occurred in mice repeatedly exposed (up to 20 times over 58 days) to atmospheric concentrations of 90% ethylene for periods of 60-90 minutes. There was no cellular injury in the kidney, adrenal, heart or lungs.

(Reynolds, 1926/BIBRA Toxicity Profile 1993)

c) 70-day study

Rats were exposed to ethylene at a concentration of 100 ppm (0.15 mg/l) for 70 days (non-GLP study reported in 1966 of unknown quality and no further exposure details). Changes in the reflex nerve impulses, a decrease in cholinesterase activity and reduced blood pressure were reported (no actual data or indications of the magnitude of these changes were reported).

(Krasovitskaya *et al*, 1966/ OECD: SIDS)

d) 90-day study

Groups of rats (15/sex/concentration) were exposed to ethylene at concentrations of 0, 300, 1000, 3000 or 10000 ppm (0, 345, 1150, 3450, or 11500 mg/$m^{3.}$ respectively) for 6 hours/day, 5 days/week for 13 weeks (a non-GLP study).

There were no differences between controls and treated rats with respect to total body weights, weight change, food consumption, haematology, clinical chemistry, gross pathology or histopathology. Male rats in the 0 (control), 300 and 10000 ppm groups showed red deposits or red discharge around the nose whereas the males in the 1000 ppm group had red deposits around the eyes. Amongst the female rats, a red deposit was discovered around the left eye of one 300 ppm female and alopecia around both ears of one 1000 ppm female. Compared with the controls, the liver weights in several groups of exposed rats were significantly lower (no indication of magnitude in the publication). There was no dose response relationship for this weight reduction and the cause was unknown. Ethylene appeared to have a low toxicity in rats when administered up to 10000 ppm (11.5 mg/l of air). This was considered to be the NOAEL for the 90-day study by the authors.

(Chemical Industry Institute of Toxicology, 1977/OECD: SIDS)

B.6.3.4.2 Dermal exposure

No studies submitted (or data cited from the published literature).

B.6.3.5 Summary of short term toxicity

No data were submitted for the oral or dermal routes of exposure (or cited from the published literature). A summary of the short-term inhalation data is presented in Table B.6.1.

The 6-day exploratory inhalation study in rats showed that at high exposure levels there were marked effects on the thrombocyte and leukocyte counts and on bone marrow cellularity. There are some limited citations that indicated the liver may be a target for ethylene induced toxicity. In the 70-day rat study, changes in the reflex nerve impulses, a decrease in cholinesterase activity and reduced blood pressure were reported. The 90-day inhalation study concluded that the NOAEL was greater than 11.5 mg/l of air for inhalation exposure, the highest dose tested. It should be noted that this study may have been conducted by Industrial Bio-Test Laboratories Inc under contract to the CIIT (see B.6.5). The background to IBT can be found at section 3.1.8 of http://www.oecd.org/dataoecd/13/15/36045203.pdf]

Table B.6.1 Summary of the short-term inhalation toxicity of ethylene

Type of study	NOAELs	LOEL/effects	Reference
6 day exploratory study in rats	Not set	600000 ppm (690 mg/l, the only dose tested): Marked effects on haematological parameters and bone marrow.	Fink, 1968/SIDS
70-day study in rats	Not set	100 ppm (0.15 mg/l): Changes in the reflex nerve impulses, a decrease in cholinesterase activity and reduced blood pressure.	Krasovitskaya *et al*, 1966/SIDS
90-day study in rats	11.5 mg/l	No effects reported at highest dose tested.	CIIT, 1977/SIDS

B.6.4 Genotoxicity studies (IIA 5.4)

B.6.4.1 *In vitro* testing (AII 5.4.1)

a) Bacterial mutations

Ethylene has been tested in an Ames test at atmospheric concentrations up to 20% in one strain (TA 100) of *Salmonella typhimurium* in the presence and absence of metabolic activation (non-GLP study/Victorin and Stalberg, 1988). It was also reported that previous testing in four strains of *Salmonella typhimurium* (non-GLP studies/Hamm *et al*, 1984; Hughes *et al*, 1984) and *in Escherichia coli* (non-GLP study/Landry and Fuerst, 1968) were also negative.

(OECD: SIDS)

b) Mutations in mammalian cells

No studies submitted (or data cited from the published literature).

c) Chromosome aberrations in mammalian cells

Duplicate cultures of Chinese hamster ovarian (CHO) cells were tested in the absence and presence metabolic activation (S9-mix) from Aroclor 1254-induced rats (GLP compliant study conducted to OECD guideline 473). The cells were tested at concentrations up to 280.5 mg/l (approximately 25% ethylene). Due to the explosive properties of ethylene when mixed with air, nitrogen was used as a carrier gas. The cells were exposed to a short 3 hour pulse treatment followed by a 17 hour expression period prior to harvest. Negative (carrier gas, untreated and positive control groups were tested. The positive control groups produced appropriate results. It was concluded that there was no effects on the mitotic index and no increase in the frequency of cells with structural chromosome aberrations.

(Riley, 1996/ OECD: SIDS)

B.6.4.2 *In vivo* genotoxicity in somatic cells (AII 5.4.2)

a) Micronucleus tests

Rats (10/dose) and mice (10/dose) were exposed to concentrations of 0, 40, 1000 or 3000 ppm for 6 hour/day, 5 days a week for 4 weeks (reported in 1994 but not stated whether or not GLP status). Bone marrow samples were collected approximately 24 hours after the final exposure. No significant differences in the PCE to NCE ratios

were observed in any exposure group. It was concluded that ethylene did not induce statistically significant concentration-related increases in the frequencies of micronucleated polychromatic erythrocytes in the bone marrow of rats or mice.

(Vergenes and Pritts, 1994/ OECD: SIDS)

b) Formation of DNA and haemoglobin adducts

Absorption, distribution, elimination of ethylene and formation of haemoglobin and DNA adducts were studied in rats after inhalation of 300 ppm ethylene for 12 hours per day for 3 consecutive days (a non-GLP study reported in 1995). DNA adduct formation was measured in liver and lymphocytes and haemoglobin adducts determined in erythrocytes. The adduct formation with ethylene was compared to other alkenes and adduct formation decreased with increasing number of carbon atoms in the molecule. No actual results or conclusions were provided in the publication (the study was stated to be an explorative study).

(Eide *et al*, 1995/OECD: SIDS)

c) Alkylation of DNA

Alkylation of 7-guanine was measured in DNA from liver spleen and testis of mice 14 hours after exposure by inhalation of 14C-ethylene at an initial concentration of 11 ppm for 8 hours (a non-GLP study reported in 1983). The degree of alkylation was much higher in the liver than in the other tissues. No actual results or conclusions were provided in the publication (the study was stated to be an explorative study).

(Segerback, 1983/OECD: SIDS)

B.6.4.3 *In vivo* studies in germ cells (AII 5.4.3)

No study submitted (or data cited from the published literature) but there are no indications in the available data/information that such a study is necessary.

B.6.4.4 Summary of genotoxicity studies

A summary of the submitted genotoxicity data is provided in Table B.6.2.

The bacterial mutation and chromosome aberration assays conducted with ethylene gas were stated to be negative for genotoxic activity (these conclusions may be equivocal taking into consideration the low solubility of ethylene in aqueous media). However, following *in vivo* inhalation exposure to rats and mice, the bone marrow micronucleus investigations were also reported to be negative (no significant differences in the PCE to NCE ratios). There was insufficient information provided for the DNA and haemoglobin adduct assays to draw any clear conclusions about the potential genotoxicity of ethylene.

The overall genotoxicity database on ethylene is limited, but on the data available there is no evidence for significant genotoxic potential.

Table B.6.2 Summary of the genotoxicity data

Study	Concentrations	Result	Reference
In vitro assays			
Ames test	Atmospheric concentrations up to 20%	Negative	OECD: SIDS
Chromosome aberrations in CHO cells	280.5 mg/l (approximately 25% ethylene)	Negative	Riley, 1996/ OECD: SIDS
In vivo assays (inhalation exposure)			
Bone marrow micronucleus tests in rats and mice.	3000 ppm (approximately 3.45 mg/l)	Negative	Vergenes & Pritts, 1994 OECD: SIDS
Formation of DNA and haemoglobin adducts	300 ppm (approximately 0.345 mg/l)	Adduct formation reported but no quantitative results reported	Eide *et al*, 1995 OECD: SIDS
Alkylation of DNA	11 ppm (approximately 0.0126 mg/l)	Alkylation reported but no quantitative results reported	Segerback, 1983 OECD: SIDS

B.6.5 Chronic toxicity and carcinogenicity studies (IIA 5.5)

A single long-term inhalation study has been summarised by the OECD: SIDS publication (CIIT, 1979/SIDS & by Hamm *et al*, 1984). However, this study was conducted 1977-1979 at the Industrial Bio-Test Laboratories Inc (IBT) under contract to the Chemical Industry Institute of Toxicology (CIIT). It should be noted that IBT was responsible for falsifying data which lead to the implementation of GLP principles and practice in the USA. The background to IBT can be found at section 3.1.8 of http://www.oecd.org/dataoecd/13/15/36045203.pdf]

B.6.5.1 Chronic dietary studies in rats

No studies submitted (or data cited from the published literature).

B.6.5.2 Chronic dietary study in mice

No studies submitted (or data cited from the published literature).

B.6.5.3 Carcinogenicity studies in rats

a) Fischer-344 inbred rats (120/sex/group) were exposed to ethylene at concentrations of 0, 300, 1000 and 3000 ppm for 6 hours per day, 5 day/week for up to 24months (non-GLP study).

The spontaneous mortality (15.7%) was stated to be roughly equal in all treated groups. Hair loss, deposits on and around the nose and eyes and gross eye abnormalities were noted but there were no obvious differences among the treatment groups. There was an overall increase in the number of animals exhibiting gross tissue masses for the test groups as compared with the control group but this trend was not statistically significant.

The final body weights and total weight changes for treated males were higher than those in the control groups but no dose related pattern was seen. There were no significant differences among any of the treatment groups on any of the haematology, blood chemistry or other parameters tested. No gross or histopathological tissue changes attributable to the effects of the test material were observed in any of the treated rats. The summary states that only a few findings were reported that could indicate any carcinogenic effect of the treatment.

In a publication from the above 1979 carcinogenicity study (Hamm *et al*, 1984), it was concluded that the results provided "no evidence that ethylene at these concentrations causes chronic toxicity or is oncogenic in Fischer 344 rats". However, this publication and the summary have been criticised since they do not discuss the mononuclear cell leukaemia described in the full report. It was stated that the number of animals affected (out of 90) rose from 12 and 8 in the male and female control groups to 21 and 11, respectively, in the groups receiving 3000 ppm. On the other hand, it has been stated that mononuclear cell leukaemia may occur in F344 rats at a background incidence > 75% and that a further increase in exposed animals is difficult to interpret with respect to human cancer development.

(Chemical Industry Institute of Toxicology/conducted by IBT, 1979/OECD: SIDS)

b) A summary of a 2-year rat inhalation study was submitted which was down loaded from the Hazardous Substances Data Bank (HSDB) on 5th May (toxnet.nlm.nih.gov). This summary appears to be another summary of the above 1979 inhalation study but provides some further limited information on the methodology. The maximum tolerated dose was not used as concentrations above 3000 ppm were considered hazardous because of the risks associated with the explosive properties of the test mixture. The calculated time weighted average concentrations for the 24 months of exposure were 0, 301, 1003 and 3003 ppm, respectively. Randomly selected animals were necropsied and examined after 6, 12 and 18 months and selected organs and tissues from all animals in the control and 3000 ppm groups were examined microscopically at termination. Histologically, a variety of proliferative, degenerative and inflammatory lesions were observed in both control and 3000 ppm groups. It was stated that these lesions were typical of those seen in this strain of animal and were unrelated to ethylene exposure.

(Hamm *et al*, 1984/HSDB)

c) Criticism of the above 2 year rat inhalation study and the Hamm summary has been published by BIBRA scientists.

"CIIT scientists concluded that there was 'no evidence that ethylene at these concentrations causes chronic toxicity or is oncogenic in Fischer 344 rats. According to the 'executive summary' of the full report (published separately), unusual malignant lung tumours were found in two rats exposed to 1000 ppm and one exposed to 3000 ppm, but the low incidence and lack of other related changes in bronchial epithelium suggested they may have occurred spontaneously. The incidence of mononuclear cell leukaemia is not discussed in the summary, but the full report (available only on microfiche) indicates that it was somewhat increased in both sexes at the top dose level. The number of animals affected (out of 90) rose from 12 and 8 in male and female controls to 21 and 11, respectively, at 3000 ppm. The total number of organs or

tissues affected rose to 106 in males and 83 in females from only 62 and 26, respectively, in controls. Whether it increased at lower doses too is uncertain, since only limited histological examination of the lower dose groups was conducted. In the view of EO to induce this form of cancer (NIOSH Current Intelligence Bulletin 1981, No5, 22 May) it is strange that the incidence of leukaemias is not discussed in the report's executive or by Hamm *et al*, 1984".

"Although one of the CIIT scientists was unable to detect any conversion of ethylene to EO in an *in vitro* preparation of rat-liver microsomes (Hamm *et al*. *loc. cit*.), two other metabolic studies indicate that rats and mice can indeed metabolize ethylene to EO and that both chemicals can lead to the alkylation of proteins and DNA."

(Rostron, 1986, Fd Chem Toxic, Vol 24 No 1)

d) Based on the pharmacokinetics of ethylene and its oxide in the rat, Bolt and Filser, 1987 estimated that exposure at an atmospheric concentration of 1000 ppm ethylene would correspond to a theoretical atmospheric concentration of 5.6 ppm ethylene oxide. Because of saturation kinetics, exposure concentrations of ethylene above 1000 ppm would not result in further increases in systemic ethylene oxide concentration. Thus, the above ethylene bioassay could not expose rats to more than 5.6 ppm ethylene oxide. By extrapolating the tumour/exposure data in the ethylene oxide studies to 5.6 ppm, the investigators concluded that the high ethylene exposures would not result in a tumour incidence of more than 2% above the background incidence. This lead to the conclusion that should ethylene pose a carcinogenic threat to the rat by virtue of its conversion to the oxide, the group sizes normally used in cancer study would be insufficient to produce statistically significant increases tumour yield at attainable ethylene concentrations.

(Hopkins, 1993, Fd Chem Toxic, Vol 32 No 2)

e) Groups of male and female Sprague-Dawley rats, there to five days of age, were exposed by inhalation to 0 (5 males and 9 females) or 11500 mg/m^3 or 10000 ppm (2 males and 10 females) ethylene (purity unspecified) for 8 hours per day on five days per week for three weeks. One week later, the rats received oral administration of 10 mg/bw Clophen A50 (a mixture of PCBs 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 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/IARC 1994)

B.6.5.4 Summary of chronic toxicity/carcinogenicity

No long-term studies were submitted for the oral route of exposure (or data cited from the published literature).

There are several summaries in the published literature of a single long-term inhalation study in the rat. Generally, the authors of these summaries have concluded that there no evidence of chronic toxicity in this study and no evidence of compound-induced carcinogenicity. However, some authors have expressed doubts over the interpretation of the findings in this study (i.e. the mononuclear cell leukaemia). Although IARC

(1994) concluded that the evidence of carcinogenicity in experimental animals and humans was inadequate, Tornqvist (1994) and Hopkins (1993/OECD: SIDS) stated that the possible carcinogenic risk from inhaling ethylene should be reconsidered/re-evaluated based on the potential exposure to ethylene (very high tonnage), the limited database and the metabolism of ethylene to ethylene oxide.

B.6.6 Reproductive and developmental toxicity studies (IIA 5.6)

A multigeneration study has not been submitted instead a summary of a single generation screening test has been submitted to support the application. The limitations of such a protocol for the detection of compound-induced post-natal effects and the small number of animals tested should be noted.

B.6.6.1 Fertility and post-natal developmental toxicity

a) Reproduction/Development Toxicity Screening Test (IIA 5.6.1)

Rats (10/sex/concentration) were exposed to ethylene (head only) at concentrations of 0, 200 (230 mg/m^3), 1000 (1150 mg/m^3) or 5000 ppm (5750 mg/m^3) for 6 hours daily (the number of days/week was no stated). The calculated body burden was approximately 0, 80, 400 and 2000 mg/kg bw/day for the dosing regime. Since the uptake from the lungs is likely to be in the range of 5-10%, the actual absorbed dose would be substantially less than the values given above. This study was GLP compliant and carried out in accordance with OECD Guideline 421 (Reproduction/Development Toxicity Screening Test).

The test material was administered to parent animals for two weeks prior to mating, during the mating period and until the day prior to necropsy for the males (minimum 28 days) and until day 20 of gestation for the females. The females were allowed to litter and rear their offspring to day 4, post-partum, when they and their offspring were killed.

Morbidity, mortality, clinical condition, weights and food intake were observed throughout the study, and mating was carefully observed. For each female, litter data and also observations for each offspring were recorded. At termination of the study, all animals were subject to macroscopic examination for structural or pathological changes. Ovaries, testes and epididymides of the control and high dose animals were subject to a histopathological examination.

There were no deaths attributable to the test article, and body weight gain was not adversely affected during the pre-pairing, gestation or lactation periods. The treatment had no effect on fertility or fecundity and all females became pregnant. Litter size, sex ratio, mean pup weight and pup growth and clinical condition were not adversely affected by treatment.

Necropsy revealed no macroscopic finding suggestive of toxicity due to test article administration. There was no evidence of any toxic effect on the testis due to test substance administration and there were no other microscopic findings suggestive of toxicity due to test article administration.

The summary concluded that at nominal concentrations of 200, 1000 or 5000 ppm there was no evidence of toxicity or adverse effects on male and female reproductive performance, fertility, pregnancy, maternal and suckling behaviour and growth and development of the offspring from conception to Day 4, post-partum. The NOEL was established to be 5000 ppm (equivalent to 5.75 mg/l) with respect to parental toxicity and foetal and reproductive performance.

(Aveyard, 1996/OECD: SIDS)

b) Post natal-development

In a published study, newborn rats exposed to a concentration of 2.62 ppm (approximately 0.003mg/l) for 90-days (continuous inhalation) exhibited a delay in coat appearance, dentition and eye opening; circulation hypotension, cholinesterase inhibition and subordination disruption were also reported. It was stated that there was no information on the quality of this study.

(Krasovitskaya and Mabyarova LK, 1968/OECD: SIDS)

B.6.6.2 Developmental toxicity studies (IIA 5.6.2)

a) Developmental study in rats

No studies submitted (or data cited from the published literature).

b) Developmental study in rabbits

No studies submitted (or data cited from the published literature).

B.6.6.3 Summary of reproductive toxicity

The reproductive screen test concluded there was no compound induced parental or foetal toxicity or developmental toxicity over a single generation (i.e. up to 4 days post partum) at concentrations up to 5.75 mg/l (equivalent to a systemic exposure of 0.575 mg/l). However, some published data (of unknown quality) appears to indicate that post-natal development could be adversely affected at low dose levels.

B.6.7 Neurotoxicity studies (IIA 5.7)

B.6.7.1 Delayed neurotoxicity studies

Ethylene is not of similar or related structure to those compounds such as the organophosphates that are capable of inducing delayed neurotoxicity. Therefore, delayed neurotoxicity studies have not been carried out.

B.6.7.2 Acute and repeat dose neurotoxicity studies

No studies submitted (or data cited from the published literature).

B.6.7.3 Summary of the neurotoxicity studies

No specific neurotoxicity studies have been submitted for evaluation but there are some indications of treatment-related effects on the nervous system. Two papers by the same authors have reported changes in the reflex nerve impulses, a decrease in cholinesterase activity and reduced blood pressure. Although there is no information on the quality of the investigations or the magnitude of the changes in these two papers, it should be noted that nerve impulses, cholinesterase activity and blood pressure have not been routinely investigated in the standard toxicity studies.

B.6.8 Further toxicological studies (IIA 5.8)

B.6.8.1 Relevant metabolites (ethylene oxide)

Since ethylene is metabolised to ethylene oxide in experimental animals and humans, a summary of the submitted published data/information for ethylene oxide has been included in this evaluation. It should be noted that the majority of data for ethylene oxide has been primarily generated using the inhalation exposure route.

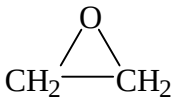
Ethylene oxide is officially classified by the ECB as a Cat: 2 for carcinogenicity (R45) and Cat: 2 for mutagenicity (R46). In addition, the literature indicates that ethylene oxide induces reproductive effects in experimental animals (foetal toxicity in the presence and absence of maternal toxicity, teratogenicity in mice, sperm effects) and there is some limited evidence of spontaneous abortions in humans.

Ethylene oxide is also officially classified by the ECB as Toxic by inhalation (R23) and as an irritant (R36/37/38). The literature also indicates that it can also induce sensitisation responses.

An updated MSDS (2005) obtained from the internet suggests that ethylene oxide may be classifiable for acute oral and dermal toxicity (R24 & 25); an acute oral LD50 value of 72 mg/kg bw is cited by this MSDS.

The current UK cut-off for ethylene oxide in pesticide formulations is the limited of detection (LOD) and the occupational maximum exposure level is 5 ppm; 8-hour TWA (EH64 Summary Criteria for Occupational Exposure Levels, as amended by update supplements up to 2002).

Figure B.6.2 Structure of ethylene of ethylene oxide



ethylene oxide

Chemical name: ethylene oxide.
CAS Number: 75-21-8.
Other names: dihydrooxirene, dimethylene oxide, EO, ETO, 1,2-epoxyethane, epoxyethane, ethene oxide, oxacyclopropane, oxane, oxidoethane and oxirane.
Molecular weight: 44.05 g/mol.
Octanol/water partition coefficient: Log Kow = -0.30.
Solubility in water: infinitely soluble.
Vapour pressure: 146 kPa @ 20 ºC
Physical state: Colourless gas at normal temperature and pressure.
Smell: described as having a characteristic ethereal odour.
Odour threshold: 470 mg/m^3 for perception and 900-1260 mg/m^3 for recognition.
Conversion factors (NTP): i) 1 ppm = 1.8 mg/m^3; at 25ºC, ii) 0.55 ppm = 1.0 mg/m^3.
Methods of production: i) catalytic oxidation of ethylene with air or oxygen, ii) the chlorohydrin process.

Ethylene oxide is an important industrial chemical. It is used as an intermediate in the production of various chemicals (e.g. ethylene glycol & surfactants), as a sterilant, a fumigant and as a component of pest control products. Gas and liquid forms of ethylene oxide may be released into the environment during industrial processes and sterilisation operations (e.g. medical equipment in hospitals). It is also released on combustion of fossil fuels and is present in tobacco smoke.

Ethylene (a natural plant growth regulator) is degraded to ethylene oxide in certain plants and by certain micro-organisms. Ethylene oxide is also produced by some natural sources such as manure and sludge.

Ethylene oxide is used as a sterilant (micro-organisms) and fumigant (insects) on food stuffs at concentrations that range from 250-1500 mg/litre (ECHC 2001).

The data/information in this section has mainly been taken from the following publications:

i) International Programme on Chemical Safety (IPCS). World Health Organisation (WHO). 1985 Environmental Health Criteria 55. Ethylene Oxide (WHO 1985).

ii) Environment Canada & Health Canada. Priority Substances List Assessment Report (September 2001): Ethylene oxide (ECHC 2001).

iii) IARC Monograph on the Evaluation of Carcinogenic Risks to Humans (1994). Some Industrial chemicals, Vol 60 (Ethylene oxide, pages 73-159) (IARC 1994).

iv) IPCS. WHO. Concise International Chemical Assessment Document 54 (2003) (CICADS 2003).

Inevitably, the publications listed above are mainly summarising and citing the same data and studies. Since there are minor differences in the reporting of the details by the different sources, individual studies may be cited more than once especially where additional information has been reported.

B.6.8.1.1 Absorption, distribution, excretion and metabolism

Absorption, distribution and excretion

a) Inhalation studies in mice show that ethylene oxide is very soluble in blood and the pulmonary uptake is expected to be rapid and to depend only on the alveolar ventilation rate and the concentration of ethylene oxide in the inspired air. The rate of uptake of ethylene oxide was 1.1µg/kg bw per min at an exposure level of 1 mg/m^3. This corresponds to nearly 100% absorption of ethylene oxide from 1.1 litre of air per min and per kg bw which is the reported rate of alveolar ventilation in resting mice. Approximately 74% of labelled ethylene oxide inhaled by mice was excreted in the urine within 24 hours in the form of unidentified metabolites.

(Ehrenberg *et al*, 1974/WHO, 1985)

b) Ethylene oxide is rapidly distributed throughout the body. In mice, whole body autoradiograms 2 min after intravenous injection showed that concentrations of ethylene oxide in the liver, kidneys, and pancreas were 3-4 times those in the blood. Between 20 minutes and 4 hours after exposure, radioactivity was distributed throughout the body. Directly after inhalation by mice, the highest concentrations of labelled ethylene oxide were found in the liver, kidney, and lung. The radioactivity in the liver and kidney dropped exponentially and approached the levels in the lung, testes, spleen, and brain within 4 hours, indicating rapid metabolism and excretion (Appelgren *et al*, 1977). On the basis of tissue alkylation data (Ehrenberg *et al*, 1976) or haemoglobin alkylation data (Osterman-Golkar *et al*, 1976), a half-life of approximately 10 min was estimated for the first-order clearance of ethylene oxide from mouse or rat tissues. A similar value for man was estimated on the basis of haemoglobin alkylation data (Calleman *et al*, 1978).

(WHO, 1985)

c) When the degree of protein and DNA alkylation was investigated in mice and rats, only small variations were observed between the different tissues in the species. Apparently, most organs receive a more or less equal dose of ethylene oxide after distribution throughout the body. The extent of protein alkylation was approximately equal in the lung, liver, kidney, and spleen of mice, 120 min after inhalation of 2 mg ethylene oxide/m^3 air, for 75 min, but in the testes, it was about 50% lower. When the vapour concentration was increased (up to 59 mg/m^3), the degree of protein alkylation in the liver increased relative to that in the other tissues. In all the tissues investigated, protein alkylation increased linearly with the dose up to an exposure level of 59 mg/m^3 and was relatively constant for at least 3.5 hours following exposure.

(Ehrenberg *et al*, 1974/WHO, 1985)

d) When 0.4 mg ethylene oxide/kg body weight was administered intraperitoneally to mice, DNA alkylation in the testes and spleen was, respectively, 50 and 40% of that in the liver, 5 hours after exposure. The approximate half-lives of the alkylation products were 24 hours in the spleen, 10 hours in the testes, and 12 hours in the liver. For the spleen, this half-life was found to be shorter *in vivo* than *in vitro,* indicating active removal.

(Segerback, 1983/WHO, 1985)

Metabolism

The available animal data indicate two possible pathways for the metabolism of ethylene oxide, i.e., hydrolysis to 1,2-ethanediol and conjugation with glutathione (Fig. B.6.2).

a) In dogs, peak levels of 13 and 33 mg 1,2-ethanediol/litre blood-plasma were measured between 1 and 3 hr after intravenous administration of 25 or 75 mg ethylene oxide in water/kg body weight, respectively. As the half-life for hydrolysis is about 60 h at 40 °C in neutral fresh water, the involvement of an epoxide hydrolase has been suggested, but this has not yet been confirmed. The peak concentration of 1,2-ethanediol at 25 mg ethylene oxide/kg body weight represented approximately 25% of the dose of ethylene oxide. Within 24 hr, 7-24% of the dose was excreted in the urine as 1,2-ethanediol.

(Martis *et al*, 1982/WHO, 1985)

b) In the serum of workers exposed to ethylene oxide (0.54-27 m^3 air; mean 7.56 m^3 air,), for an average of 5.3 years, the blood concentration of 1,2-ethanediol was elevated compared with that of unexposed controls.

(Wolfs *et al*, 1983/WHO, 1985)

c) The results of studies in rats, rabbits and monkeys have shown that some 1,2-ethanediol is metabolised but most of it is excreted unchanged in urine.

(Gessner *et al*, 1961; McChessney *et al*, 1971/WHO, 1985)

d) When a single dose of 2 mg labelled ethylene oxide in propanediol was administered intravenously to rats 43% was excreted in urine within 50 hours (41% within 24 hours); 9% as S-(2-hydroxyethyl)cysteine and 33% as N-acetyl- S-(2-hydroxyethyl)cysteine. Ethylene oxide (1%) and labelled carbon dioxide (1.5%) were also excreted via the lungs.

(Jones and Wells, 1981/WHO, 1985)

e) As ethylene oxide can react with chloride ions, and this reaction is acid catalysed, 2-chloroethanol might be expected to be a metabolite, especially after oral administration. However, neither 2-chloroethanol (also called ethylene or glycol chlorohydrin), nor its metabolites have been found in the plasma, tissues, or urine of species exposed to ethylene oxide.

(Grunow & Altman, 1982/WHO, 1985)

B.6.8.1.2 Dermal penetration

a) *In vitro*

The permeation rate of a solution of 1% ethylene oxide in water (w/v) through excised human skin at 30ºC was determined to be 0.125 mg/cm^2/hour.

(Baumbach *et al*, 1987/IARC 1994)

b) *In vivo*

The range of skin penetration of ethylene oxide was reported to be 1-14% from a variety of formulated products.

(Kreuzer, 1992/ECHC 2001)

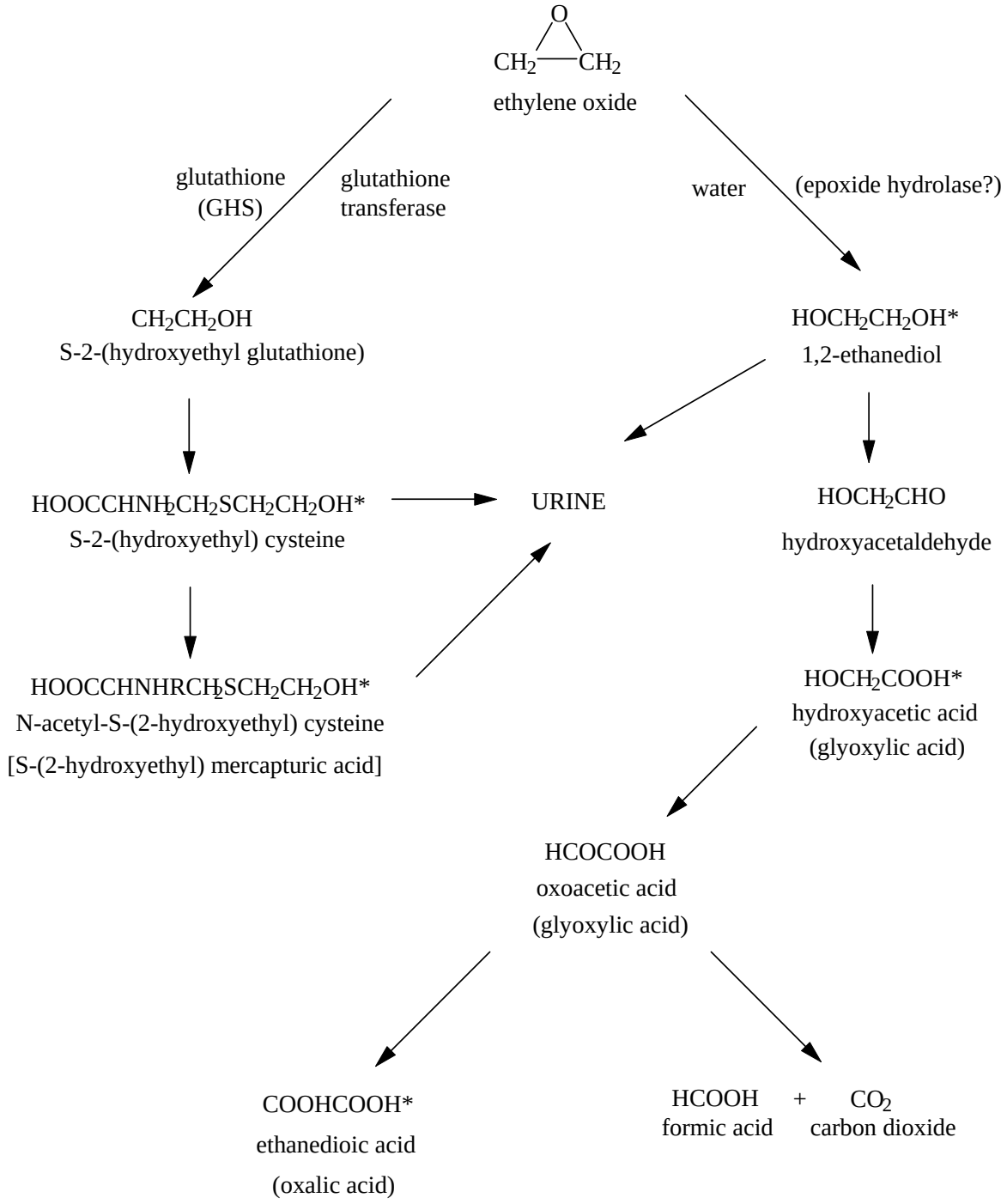
B.6.8.1.3 Summary of ADME studies

No ADME studies using oral administration of ethylene oxide have been submitted (or cited from the literature).

Inhalation and intravenous administration of labelled ethylene indicate that the excretion occurs mainly via urine. Minor amounts of unchanged parent and labelled carbon dioxide are excreted via the lungs. Distribution is widespread based on the protein and DNA alkylation in various organs and tissues (e.g. lung, liver, kidney, spleen and testes).

Two metabolic pathways have been identified in experimental animals and humans, the hydrolysis of ethylene oxide to 1,2-ethanediol and conjugation with glutathione to produce S-(2-hydroxyethyl)cysteine and N-acetyl- S-(2-hydroxyethyl)cysteine.

Figure B.6.3 Proposed pathway for the metabolism of ethylene oxide in mammals



KEY: a) * metabolites identified by Gessnar et al, 1961; McChessney et al, 1971; Jones and Wells, 1981. b) GSH = glutamylcysteinylglycine. c) R = $COCH_3$ d) Taken from WHO, IPCS, Environmental Health Criteria 55, Ethylene Oxide.

B.6.8.1.2 Acute toxicity, irritancy and sensitisation

B.6.8.1.2.1 Acute oral toxicity

a) The acute LD50 values cited for ethylene oxide administered orally (in water) to rodents were 330 mg/kg bw for male rats and 365 and 280 mg/kg bw for male and female mice, respectively.

(Smyth *et al*, 1941; Woodward & Woodward 1971/WHO 1985)

b) A MSDS (updated 2005) reports an acute LD50 value of 72 mg/kg bw for ethylene oxide in the rat.

(http://www.physchem.ox.ac.uk/MSDS/ET/ethylene_oxide.html)

c) After oral administration to rats, the difference between 0.1% mortality (325 mg/kg) and 99.9% mortality (975 mg/kg) was approximately 650 mg/kg body weight.

(Smyth *et al*, 1941/WHO, 1985)

B.6.8.1.2.2 Acute dermal toxicity

A MSDS (updated 2005) states that ethylene oxide is classified as 'Toxic in contact with skin'.

(http://www.physchem.ox.ac.uk/MSDS/ET/ethylene_oxide.html)

B.6.8.1.2.3 Acute inhalation toxicity

a) Ethylene oxide was stated to be toxic by inhalation with 4 hour LC50 values of 1460, 835 and 960 ppm (2672, 1528 and 1757 mg/m^3) for rats, mice and dogs, respectively. No deaths occurred in dogs at 1280 mg/m^3. No guinea pigs died after inhalation of ethylene oxide at a level of 450 mg /m^3 air for 8 hours, the majority died at 2400 mg/m^3. Guinea pigs exposed to ethylene oxide at a concentration of 13000 mg/m^3 for 2.5 hours were found lying on their sides and unable to stand.

In the above studies, the respiratory system and nervous system were the main targets in rodents and dogs. The clinical effects included nasal irritation, scratching the nose, nasal discharge, lachrymation, salivation, respiratory effects (gasping and laboured breathing) vomiting and convulsions. The gross findings in animals that died included congestion and oedema in the lungs, petecchial haemorrhage of the trachea and hyperaemia of the liver and kidneys and parenchymatous changes in the kidneys.

(Jacobson *et al*, 1956; Waite *et al*, 1930/WHO, 1985)

b) A MSDS (updated 2005) states the LC50 for ethylene oxide in the rat for a 4 hour exposure was 800 ppm (920 mg/m^3).

(http://www.physchem.ox.ac.uk/MSDS/ET/ethylene_oxide.html)

c) Male and female mice were exposed to concentrations of up to 1600 ppm (2928 mg/m^3) for 4 hours. At 800 ppm (1464 mg/m^3), all the males and 4 of the 5 females died within six days post exposure.

(Jacobson *et al*, 1956/WHO, 1985)

B.6.8.1.2.4 Skin irritancy

a) Cotton pads moistened with solutions of 100 or 500 g ethylene oxide/litre water were applied to shaved rabbit skin under a plastic cover. After an exposure period of six minutes, skin irritation (with hyperaemia), oedema and scar formation were observed. The intensity of the response was reported to be roughly proportional to the length of exposure time (1 - 60 min) and the concentration.

(Hollingsworth *et al*, 1956/WHO, 1985)

B.6.8.1.2.5 Eye irritancy

a) A maximal non-damaging concentration of 0.1% ethylene oxide in physiological salt solution was established after instillation of 0.05 ml solution, every 10 minutes for 6 hours, into the conjunctival sac of rabbits. The concentration above 1% caused reversible changes in conjunctiva such as hyperanemia and swelling and irreversible opacity both in the cornea and in the lens. *In–vitro* studies with isolated rabbit cornea were in agreement with these results.

(McDonald *et al*, 1973; Edelhauser *et al*, 1983/WHO, 1985)

B.6.8.1.2.6 Skin sensitisation

a) No study submitted (or data cited from the published literature).

b) Ethylene oxide is considered a strong sensitising agent owing to its strong reactivity with various chemical groups (anaphylaxis and contact dermatitis are reported in humans).

(Bommer and Ritz, 1987/ECHC 2001)

B.6.8.1.2.7 Summary of acute toxicity, irritancy and sensitisation

A summary of the cited acute toxicity data is presented in Table B.6.3.

A steep dose response curve was evident for ethylene oxide from the reported mortalities in the acute studies. These studies indicate that the respiratory system, the nervous system and the liver and kidneys are target organs. It should also be noted that liquefied or pressurized ethylene oxide gas can cause frostbite damage (Hine & Rowe, 1981/).

The official ECB classification of ethylene oxide: Cat 2: carcinogenicity, Cat: 2 mutagenicity, Toxic by inhalation (R23) and R/36/37/38 for irritancy.

Table B.6.3 Summary of the acute toxicity, irritancy and skin sensitisation of ethylene oxide

Study	Species	Results/comments	Classification	Reference
Acute oral	Rat	72 mg/kg bw.	Toxic (R25)	physchem.ox.ac.uk
Acute oral	Rat	Males: 330 mg/kg bw	Harmful (R22)	WHO, 1985
Acute oral	Mouse	♂ & ♀: 365 & 280 mg/kg bw, respectively.	Harmful (R22)	
Acute dermal	NS	No details given	Toxic (R24)	physchem.ox.ac.uk
Acute inhalation	Rat	2.672 mg/l	Harmful (R20 & R37)	WHO, 1985
Acute inhalation	Rat	0.92 mg/l	Toxic (R20 & R37)	physchem.ox.ac.uk
Acute inhalation	Mouse	1.528 mg/l	Toxic (R23 & R37)	WHO, 1985
Acute inhalation	Dog	1.757 mg/l	Toxic (R23 & R37)	WHO, 1985
Skin irritation	Rabbit	Aqueous solutions	Irritating to skin (R38)	WHO. 1985
Skin sensitisation	NA	Considered to be a sensitiser based on chemical reactivity.		

Key: a) NS = not stated in MSDS/citation. b) NA = not applicable.

B.6.8.1.3 Short-term toxicity

The cited data for short-term repeat dose toxicity is primarily limited to inhalation studies.

B.6.8.1.3.1 Oral administration to rats

In a reported subacute study, rats orally exposed to ethylene oxide at 100 mg/kg bw/day in olive oil for 5 days/week for 3 weeks (15 doses in 21 days). The findings included loss of body weight, gastric irritation and slight liver damage.

(Hollingsworth *et al*, 1956/WHO 1985)

B.6.8.1.3.2 Oral administration to mice

No studies submitted (or data cited from the published literature).

B.6.8.1.3.3 Oral administration to dogs

No studies submitted (or data cited from the published literature).

B.6.8.1.3.4 Inhalation exposure data/information for experimental animals

a) Groups of Wistar rats (10-20/sex), guinea pigs (8/sex), rabbits (1-2/sex) and Rhesus monkeys (1-2 females) were each exposed to concentrations of ethylene oxide at levels of 0, 90, 200, 370, 640, or 1510 mg/m^3, for 7 hours per day/5 day per week. The female monkeys were not tested at 90 mg/m^3 and an additional 3 male monkeys were tested at 640 mg/m^3. The test period varied with the species tested and the severity of exposure, i.e. approximately 26 weeks at 90 mg/m^3; 25-32 weeks at 200 and 370 mg/m^3; 7-25 weeks at 640 mg/m^3 and 10 days at 1510 mg/m^3.

Guinea pigs, rabbits, and monkeys tolerated 90 and 200 mg/m^3 and rats tolerated exposure to 90 mg/m^3 without adverse effects on general appearance, behaviour, mortality rate, growth, body and organ weight and gross and microscopic examination. Rats showed elevated mortality rates from 370 mg/m^3, rabbits from 640 mg/m^3 and all exposed animals died at 1510 mg/m^3. Secondary respiratory infection was put forward as a cause of death in an appreciable number of rats and mice in these studies.

Surviving rats showed increased relative lung weights after 26-27 weeks at 200 and 370 mg/m^3. At 370 mg/m^3, haemorrhages, hyperaemia, emphysema, and local alveolar collapse were observed in these lungs. Lungs of male rabbits also showed hyperaemia and slight oedema at 370 mg/m^3. Even more severe lung injury was seen in rats at 640 mg/m^3 and the higher exposure. Gross respiratory tract irritation was apparent in all species at 1510 mg/m^3.

Delayed reversible effects were observed on the peripheral nervous system. Monkeys and rabbits exhibited paralysis of the hind legs at 370 mg/m^3 and rats at 640 mg/m^3. This was accompanied by atrophy of the muscles of the hind legs (except in rabbits at 370 mg/m^3). The effects on the peripheral nervous system were investigated further in monkeys and loss of both sensory and motor function was noted at levels of 370 and 640 mg/m^3.

Significant increases in body weight were also observed in rats, at levels of 200 mg/m^3 or more. Rats showed slight but significant increases in the relative weights of kidney and liver at 370 mg/m^3.

(Hollingworth *et al*, 1956/WHO, 1985)

b) Groups of 20 male rats and 30 female mice were exposed to concentrations of ethylene oxide at levels of 0, 180, or 730 mg/m^3 for 6 hours/day/5 days per week. The exposures lasted 26 weeks at 180 mg/m^3 and 6 weeks at 730 mg/m^3. Additional groups of 15 rats and mice at the higher and 60 rats and mice at the lower exposure level were used for interim gross pathology.

No clear toxic effects were reported at 180 mg/m^3. No pathological changes were observed except for marked haemosiderosis in the spleen of a few rats at 730 mg/m^3. The highest exposure (730 mg/m^3) resulted in death for both species without clinical signs in mice. Effects on the respiratory and nervous system were shown by rats as laboured breathing, reddish nasal discharge, diarrhoea, tendency towards a side position, and dragging of the hind-quarters. Rats also lost weight, which was regained by survivors.

(Jacobson *et al*, 1956/WHO, 1985)

c) Groups of 30 B6C3F1 mice of each sex were exposed to concentrations of ethylene oxide at 0, 18, 86, 187, or 425 mg/m^3, for 6 hr/day, and 5 days per week. The exposures lasted for 10 weeks for males and 11 weeks for females. No effects were observed in relation to survival, body weight, clinical signs, white blood cell count, serum clinical chemistry, urinalysis and histopathology. At the highest exposure level, changes at terminal sacrifice included an increased relative liver weight in female mice, and a decreased testicular weight in males. A decreased relative spleen weight was observed at 187 and 425 mg/m^3 in both sexes. In addition, the red blood cell

count, the packed cell volume, and the haemoglobin concentrations were decreased at 425 mg/m^3. Screening of neuromuscular function at week 6 (5 female mice) and weeks 10 or 11 (5 mice/sex) revealed altered reflex responses at 425 mg/m^3 and a dose-related trend in alterations of locomotor function from 86 mg/m^3 upwards.

(Snellings *et al*, 1984a/WHO, 1985)

d) Groups of 3 male beagle dogs each were exposed to concentrations of ethylene oxide of 180 and 530 mg/m^3, for 1-3 days. No effects were observed on mortality rate, body weight, electrocardiogram, blood-calcium and -urea, icteric index and rectal temperature. Anaemia was noted at both exposure levels. Effects on the respiratory and nervous systems were shown at 530 mg/m^3, such as hyperaemia and local alveolar collapse in lungs, vomiting, and occasional slight tremors and transient weakness in the hind legs. Muscular atrophy was also observed.

(Jacobson *et al*, 1956/WHO, 1985)

e) New Zealand rabbits (3 males/dose) were exposed to 0, 18, 90, or 450 mg/m^3.for 12 weeks. No haematological changes were noted.

(Yager & Benz, 1982/WHO, 1985)

f) Fischer rats (groups of 3 or 4 animals) were exposed to 90, 270, or 810 mg/m^3 for 6 hours per day for 3 days. The white blood cell count was depressed but there was a poor correlation with exposure level.

(Kligermann *et al*, 1983/WHO, 1985)

B.6.8.1.3.5 Dermal exposure

No studies submitted (see section B.6.8.1.2).

B.6.8.1.3.6 Summary of short term toxicity

A summary of published short-term toxicity data are presented in Table B.6.4.

Following oral exposure in a subacute study, loss of body weight, gastric irritation and slight liver damage were evident (no further details).

Following inhalation exposure, mortalities and effects on respiratory system, the haematological system (including bone marrow), the nervous system, ocular lens, liver and kidneys, thymus and spleen and the testes were reported. A dose-related in crease in pulmonary adenoma was also seen in mice after 6 mounts of exposure.

Table B.6.4 Subchronic effects of exposure to ethylene oxide, presented in tabulated form (taken from IARC 1994)

Species	Exposure	Effects
General toxicity		
Wistar rats (♂)	0 & 500 ppm (915 mg/m^3), 6 hours/day, 5 days/week for 13 weeks.	**500 ppm** i) Decrease in glutathione reductase in the brain, liver, ocular lens and erythrocytes (and glutathione). ii) Increase in lipid peroxidation in the liver (malondialdehyde liver). iii) Anaemia (normocytic and normochromic) decrease in the haemoglobin concentration. iv) Disturbance of porphyrin-haem metabolism. v) Decrease in hepatic cytochrome P450.
Wistar rats (♂ & ♀)	0 & 250 ppm (458 mg/m^3), 6 hours/day, 5 days/week for 17 weeks.	**250 ppm** i) Decrease in hepatic cytochrome P450 in males. ii) Decrease in hepatic glutathione reductase and an increase in glutathione-S-transferase (both sexes). iii) Increase in hepatic NADPH-cytochrome c reductase and liver weight in females. iv) Increase in hepatic glutathione peroxidase.
B6C3F1 mice (♂ & ♀)	0-250 ppm (0-458 mg/m^3), 6 hours/day, 5 days/week for 10 weeks (♂) or 11 weeks (♀).	**250 ppm** i) Decrease in spleen weight and an increase in liver weight in females. ii) Decrease in absolute testicular weight. iii) Slight decrease in haemoglobin concentration and erythrocyte count. **100 ppm (183 mg/m^3)** i) Decrease in spleen weight in females.
[a]B6C3F1 mice (♂ & ♀)	0-600 ppm (0-1098 mg/m^3), 6 hours/day, 5 days/week for 14 weeks.	**600 ppm (1098 mg/m^3)** i) Renal tubular necrosis. ii) Lymphocytic necrosis of the thymus and spleen in males. **200-600 ppm (366-1098 mg/m^3)** i) Rhinitis of the nasal cavity. **100-400 ppm (366-1098 mg/m^3)** i) Renal tubular degeneration. Also dose-related epithelial damage in the nasal portion of the respiratory tract.
C57BL/6J mice (♂)	0 & 255 ppm (467 mg/m^3), 6 hours/day, 5 days/week for 16 days; 6 hours/day, 5 days/week for 4-10 weeks.	**255 ppm** General depression of cellularity in blood and bone marrow (with large fluctuations) and transient increase in granulocytes.
ddY mice (♂)	0 & 400 ppm (732 mg/m^3), 6 hours/day, 3 days/week for 13 weeks.	**400 ppm** i) Macrocytic anaemia ii) Two-fold increase in hepatic cytochrome P450 iii) Increase in ferricyanide reductase. iv) Decrease in hepatic glutathione reductase and glutathione peroxidase. v) Increase in hepatic glutathione-S-transferase.

Key: a) US National Toxicology Program (1987).

Table B.6.4 Subchronic effects presented in tabulated form (taken from IARC)

Neurotoxicity		
Species	**Exposure**	**Effects**
Wistar rats (♂)	0 & 250 ppm (458 mg/m^3), 6 hours/day, 5 days/week for 9 months.	**250 ppm** i) Preferential distal axonal degeneration of myelinated fibres in sural nerves and gracile fascicles.
Wistar rats (♂ & ♀)	0 & 250 ppm (458 mg/m^3), 6 hours/day, 5 days/week for 17 weeks.	**250 ppm** i) Paresis of hindlegs ii) Degeneration of myelinated fibres in the peroneal nerve, the nerve of the soleus muscle and gracile fascicles. iii) No sex differences.
Wistar rats (♂)	0 & 500 ppm (915 mg/m^3), 6 hours/day, 3 days/week for 13 weeks.	**500 ppm** i) Ataxic gait after 6 weeks ii) Preferential distal axonal degeneration of myelinated fibres in hindleg nerves and gracile fascicles. iii) Decrease in creatine kinase activity in serum, brain and spinal cord after four weeks.
B6C3F1 mice (♂ & ♀)	0-250 ppm (0-458 mg/m^3), 6 hours/day, 5 days/week for 10 weeks (♂) or 11 weeks (♀).	**0-250 ppm** i) Dose-related trend in reduction in locomotor activity and abnormal reflexes. ii) No microscopic findings.

B.6.8.1.4 Genotoxicity

Ethylene oxide is an alkylating agent and is considered to be a mutagen in experimental animals and humans. It has consistently displayed genotoxic activity in almost all *in-vitro* and *in vivo* studies reviewed by the cited publications (see B.6.8.9 for human data/information).

(IARC 1994)

B.6.8.1.4.1 *In vitro* testing

Ethylene oxide is an alkylating agent. It has induced gene mutations in plant, bacteria, fungi, insect, mammalian and human cells (*in vitro* investigations with and without metabolic activation). Numerous studies in mammalian cells are reported in the literature showing gene mutations, micronucleus formation, chromosome aberrations, cell transformation, unscheduled DNA synthesis, DNA strand breaks and sister chromatid exchanges.

(WHO 1985 & IARC 1994)

B.6.8.1.4.2 *In vivo* genotoxicity in somatic cells

The available *in vivo* studies have reported positive results following administration by ingestion, inhalation or intraperitoneal injection of ethylene oxide. Genotoxic activity has been reported in rats, mice, rabbits and monkeys and includes the endpoints list below.

i) Formation of DNA adducts (haemoglobin used as a surrogate for DNA adducts) in brain, kidney, lung and spleen (rats and mice).

ii) Gene mutations in rat and mouse splenic T-lymphocytes (HPRT locus) and in the lung (lacI locus) of transgenic mice.

iii) Sister chromatid exchanges in lymphocytes (rabbits, rats and monkeys) and bone marrow cells (rats and mice).

iv) The induction of sister chromatid exchanges appears to be a more sensitive endpoint than chromosome aberrations and the formation of micronuclei.

v) Micronucleus formation in bone marrow cells (rats and mice).

vi) Chromosome aberrations in lymphocytes (monkey) and bone marrow cells (rats and mice).

(WHO 1985 & IARC 1994)

B.6.8.1.4.3 *In vivo* studies in germ cells

a) Ethylene oxide also induces heritable mutations or effects in germ cells. Dose-related damage to germ cells was established in the mid and late spermatid stages in a mouse dominant lethal assay after one oral dose of 150 mg/kg body. After short-term repeated exposures, dominant lethal effects were induced in mice at intraperitoneal doses from 40 mg/kg body weight (5 times per week for 3 months) and at inhalation exposures from 460 mg/m^3, (6 hours/day, 5 days per week for 11 weeks). Heritable translocations were induced in the germ cells of mice after repeated intraperitoneal exposure at doses of 30 mg/kg body weight (administered on 5 days/week over a 5-week period).

(Generoso *et al*, 1980 & 1983/WHO, 1985)

b) An abstract stated that DNA repair was induced in the germ cells of mice exposed to 540 mg/m^3 for 8 hr. The repair seemed inhibited at higher exposures.

(Cumming & Michaud, 1979/WHO, 1985)

c) Ethylene oxide has induced DNA single strand breaks in mouse sperm and spermatids, dominant lethal effects in mice and rats, chromosome aberrations in mouse spermatocytes.

(IARC 1994)

d) In two studies, male mice were exposed to ethylene oxide by inhalation under similar exposure conditions but using different mating regimens and examining different genetic events. In one study, there were no significant increases in the frequency of specific locus mutations in the offspring (Russell *et al*, 1984) while dominant visible and electrophoretically detected mutations were observed in another (Lewis *et al*, 1986).

(IARC 1994)

B.6.8.1.4.4 Summary of genotoxicity studies

Ethylene oxide is a potent mutagen in different cell lines and experimental animals. It forms DNA adducts and induces gene mutations, chromosome aberrations, cell transformation, unscheduled DNA synthesis, DNA strand breaks, sister chromatid exchanges, dominant lethal mutations and heritable translocations.

B.6.8.1.5 Long-term toxicity and carcinogenicity

Ethylene oxide has been tested in rats (1 oral and 2 inhalation studies) and in mice (2 inhalation studies, 1 topical application study and 1 subcutaneous injection study). However, since most of the studies focussed on carcinogenicity, ethylene-induced non-neoplastic effects have not been investigated extensively.

B.6.8.1.5.1 Dietary studies in rats

a) Groups of 50 female Sprague Dawley rats were orally (gavage) administered 7.5 or 30 mg/kg bw/day ethylene oxide in salad oil. The rats were dosed twice a week for 110 weeks. In addition, there were 50 vehicle controls, 50 untreated controls and 50 positive controls. No statistical analysis was reported.

The mean survival period was over 100 weeks for all groups. The mortality rate increased at 30.0 mg/kg body weight from week 100 onward. Elevated incidences of tumours were only observed in the forestomach, the first tumour appearing in week 79. The incidences of squamous cell carcinomas were 0/50, 8/50, and 29/50 at 0, 7.5, and 30 mg/kg bw/day, respectively. At 30 mg/kg bw/day, invasive growth and metastases were observed in 10 rats and 2 fibrosarcomas were also noted. At 7.5 and 30 mg/kg bw/day, the incidences of hyperplasia, hyperkeratosis, papillomas and/or carcinomas were increased in the forestomach.

(Dunkelberg, 1982/WHO, 1985)

B.6.8.1.5.2 Inhalation studies in rats

a) In a combined toxicity-carcinogenicity study, groups of 120 male and 120 female Fischer 344 rats were exposed to ethylene oxide at concentrations of 18 mg/m^3 (10 ppm), 58 mg/m^3 (32 ppm), and 173 mg/m^3 (96 ppm) for 6 hours per day, 5 day per week, over 25 months. In addition, two control groups each comprising 120 male and 120 female rats were used. There was an exposure-free period of 2 weeks in month 15, because of infection with sialoacryoadenitis virus. Interim sacrifices occurred at 6, 12, and 18 months.

The mortality rates of male and female rats increased significantly from the 22nd or 23rd month, at the highest exposure, with a trend towards an increase at a level of 58 mg/m^3. Male and female body weights were depressed at 173 mg/m^3 from the end of the first week until the end of the study. At 58 mg/m^3, the body weights of female rats were decreased between week 10 and 80.

The ophthalmologic examinations did not reveal any abnormalities.

Haematological changes were found in rats at all doses but mainly at the end of the study in animals exposed to 173 mg/m^3. These changes included an elevated leukocyte count in both sexes, a depressed red blood cell count and depressed haemoglobin values in females (some of these rats had leukaemia).

In females, the relative liver weights were increased in the 18th month at 173 mg/m^3. This effect on the liver could not be related to increases in the activities of serum alkaline phosphatase, aspartate aminotransferase, or alanine aminotransferase found

mainly at the 2 highest exposures during interim sacrifices. Relative spleen weights were increased in rats that developed leukaemia.

Non-neoplastic histopathological changes observed included an elevated frequency of focal fatty metamorphosis of the adrenal cortices in both sexes and bone marrow hyperplasia in females at 173 mg/m^3. Although no effect was observed on the hind-quarter lift reflex (examined monthly), mild skeletal muscular atrophy was observed after 2 years of exposure to 173 mg/m^3.

Neoplastic findings included increased incidences of leukaemia, peritoneal mesotheliomas, brain tumours and fibroma and the earlier appearance of pituitary tumours. A dose-related increased incidence of mononuclear cell leukaemia was found in both sexes, significant at the 2 highest exposures in females from the 18th or 19th month onwards. Trend test revealed a treatment-related response in both sexes. In males, an increased incidence of peritoneal mesotheliomas originating from the testicular mesothelium occurred at 58 and 173 mg/m^3 from the 23rd month onwards. An increased incidence of subcutaneous fibroma was seen in male rats exposed to 173 mg/m^3 that had survived for 24 months. Trend analysis showed that there was a treatment-related increase in peritoneal mesothelioma. There was no increased incidence of pituitary tumours but they appeared earlier in the 173 mg/m^3 group.

Following an increased incidence of brain tumours in Fischer 344 rats exposed to ethylene oxide (Lynch *et al*, 1984a), the brain tissue from this study was re-examined both macro- and microscopically. A dose-related incidence of primary brain tumours was observed at 58 and 173 mg/m^3 that appeared to be treatment related in the trend test but was not statistically significant. The tumours were mainly diagnosed as gliomas and malignant reticular tumours. The percentage of rats with multiple neoplasms was greater than in controls at all exposure levels in females and at 173 mg/m^3 in males. At 58 and 173 mg/m^3, the percentage of female rats with at least one malignancy was increased. It was considered that a contribution of the viral outbreak to the toxicity of ethylene oxide was unlikely.

(Snellings *et al*, 1981 & 1984b/WHO, 1985)

b) In a combined toxicity-carcinogenicity study, groups of 80 male Fischer 344 rats were exposed to ethylene oxide at concentrations of 92 mg/m^3 (51 ppm) and 182 mg/m^3 (101 ppm), for 7 hours/day on 5 days per week for 2 years. The control group also comprised 80 rats. There was an exposure-free period of 2 weeks in month 16 because of a pulmonary infection, which contributed to the mortality rate.

The mortality rate increased at both exposure levels, the increase being significant at 182 mg/m^3. At 182 mg/m^3, only 19% of the rats survived 2 years of exposure compared with 49% in the unexposed group. Body weights were reduced from the 3rd or 4th month onwards.

Serum aspartate aminotransferase activity was increased in rats exposed to 92 and 182 mg/m^3. No other changes were found in the haematological or clinical chemistry parameters.

Relative weights of the adrenal and brain were increased at both exposure levels and the relative weights of lung and kidney were increased at 92 mg/m^3.

Non-neoplastic histopathological changes included an elevated incidence of vacuolisation and hyperplasia or hypertrophy in the adrenals at both exposure levels and of atrophy and degeneration of skeletal muscle fibres at 182 mg/m^3. There were also increased incidences of inflammatory lesions of the lungs, nasal cavities, trachea and internal ear at both exposure levels. Eye cataracts developed in 2/77 (2.6%), 3/79 (3.8%) and (11.5%) at 0, 92 and 182 mg/m^3, respectively.

Neoplastic findings included increased incidences of leukaemia, peritoneal mesotheliomas and brain tumours. An increased incidence of mononuclear cell leukaemia was found which was significant at the lower exposure level. The absence of a dose-relationship was attributed to the increased mortality rate at 182 mg/m^3. Dose-related increased incidences of peritoneal mesotheliomas (originating from the testicular mesothelium) and of mixed-cell gliomas in the brain were found. The increases in both tumours were significant at 182 mg/m^3.

(Lynch *et al*, 1984a/WHO, 1985)

B.6.8.1.5.3 Inhalation studies in mice

a) B6C3F1 mice (50/sex) were exposed to ethylene oxide at concentrations of 0, 50 (92 mg/m^3) or 100 ppm (183 mg/m^3) for 6 hours/day, five days/week for 102 weeks.

No treatment-related clinical signs were reported. However, there were significant dose-related increases in the incidences of tumours. There was a dose-related increase in the incidence of alveolar/bronchiolar carcinoma [6/50, 10/50, and 16/50 in males (0/49, 1/48 and 7/49 in females) at 0, 50 and 100 ppm, respectively]. The incidences of cystadenoma in the Harderian gland were increased 1/43, 9/44, and 8/42 in males (1/46, 6/46 and 8/47 in females) at 0, 50 and 100 ppm, respectively]. In females, there were dose-related increases in the incidence of malignant lymphomas of the haematopoietic system (9/49, 6/48 and 22/49 at 0, 50 and 100 ppm, respectively) and uterine adenocarcinoma (0/49, 1/47 and 5/49 at 0, 50 and 100 ppm, respectively). The incidence of mammary adenocarcinoma and adenosquamous carcinoma combined was (1/49, 8/48 and 6/49 at 0, 50 and 100 ppm, respectively.

(US National Toxicology Program, 1987/IARC 1994 & ECHC 2001)

b) Female A/J mice (considered to be highly susceptible to lung tumours) were exposed to ethylene oxide at concentrations of 128 and 366 mg/m^3 for 6 hours/day, 5 days/week, for 6 months. A dose-related increase in pulmonary adenomas was observed (only lungs examined).

(Adkins *et al*, 1986/ECHC 2001)

B.6.8.1.5.4 Other studies in mice

a) Subcutaneous exposure

Groups of 100 female NMRI mice were injected once a week with a tricaprylin solution containing 0.1, 0.3, or 1.0 mg ethylene oxide per animal, for 106 weeks. There were 200 vehicle controls and 200 untreated controls. From week 35 to week 85, the mortality rate increased by a maximum of 10% at a dose of 1.0 mg per mouse. The mean length of survival in this group was 75 weeks. An elevated incidence of tumours was only observed at the injection site, the first tumour appearing in week 79. There was a dose-related increased incidence of sarcomas, mainly fibro sarcomas, which was significant at 0.3 and 1.0 mg per mouse. The tumour incidence was 11% at the highest dose compared with 2% in vehicle controls.

(Dunkelberg, 1981/WHO, 1985)

b) Dermal exposure

Each of a group of 30 female Swiss Millerton mice received, for their lifetime, approximately 100 mg of a 10% solution of ethylene oxide (purity 99.7%) in acetone, brushed on the clipped dorsal uncovered skin, 3 times a week. A group of 60 mice did not receive any treatment and a group of 60 mice received the vehicle only. Skin tumours were not found, nor were there any sign of skin irritation. The median length of survival was 493 days for treated mice and 445 days for controls. It is assumed that ethylene oxide, applied in this manner, evaporated rapidly from the skin.

(Van Duuren *et al*, 1965/WHO, 1985)

B.6.8.1.5.5 Summary of chronic toxicity/carcinogenicity

Chronic toxicity

The main emphasis of the available chronic investigations was focussed on the carcinogenic activity of ethylene oxide. There are limited information/data on the non-neoplastic effects of ethylene oxide.

In rats, the mortality rate and the incidences of hyperplasia and hyperkeratosis in the forestomach was increased following oral exposure. Following inhalation exposure, the mortality rate was increased, body weights decreased, inflammatory lesions of the lungs, nasal cavities, trachea and internal ear were increased and the development of eye cataracts. The haematological changes included elevated leukocyte counts in both sexes. In addition, bone marrow hyperplasia, depressed red blood cell counts and haemoglobin values were seen in females. Serum aspartate aminotransferase activity was increased. The relative weight of several organs was increased (brain, liver, lung, kidneys and adrenals). The microscope changes in the adrenals included an increased frequency of focal fatty metamorphosis, vacuolisation and hyperplasia or hypertrophy in the adrenals and atrophy and degeneration of skeletal muscle.

Chronic non-neoplastic investigations in mice are not reported.

Carcinogenicity

Following oral exposure, a dose-related increase in the incidence squamous cell carcinomas in the forestomach was reported in rats at 7.5 & 30 mg/kg bw/day (invasive growth and metastases were also reported at the high dose).

Following inhalation exposure, there were significant dose-related increases in several tumour types of tumours in rats (leukaemia, peritoneal mesotheliomas, brain tumours and subcutaneous fibroma) and mice (alveolar/bronchiolar carcinoma, malignant lymphomas of the haematopoietic system, uterine adenocarcinoma and mammary adenocarcinoma and adenosquamous carcinoma). It is also noteworthy that pituitary tumours appeared earlier in rats and that an increase in lung tumours was reported in mice after only 6 months of exposure.

Following subcutaneous injections to mice, there was a dose-related increased incidence of sarcomas, mainly fibro sarcomas, at the injection sites. No skin tumours (or skin irritation) were found in mice after long-term dermal exposure but it was assumed that ethylene oxide evaporated rapidly from the skin.

Overall conclusions

The extensive evidence of genotoxicity (*in vitro* and *in vivo* effects) and carcinogenicity (a variety of tumours in rats and mice and the evidence of the early appearance of certain tumours in rats and mice) indicates that ethylene oxide is a potent genotoxic carcinogen in experimental animals. A NOAEL for ethylene oxide-induced tumours cannot be established for oral or inhalation exposure. The non-neoplastic effects of ethylene have not been fully investigated but appear to occur at dose levels above tumour induction.

B6.8.1.6 Reproductive toxicity

No reproductive studies using oral administration were submitted (or cited from the published literature). The following studies used inhalation exposure.

B.6.8.1.6.1 Multigeneration studies in rats (IIA 5.6.1)

a) Fischer 344 rats (30/sex) were exposed to ethylene oxide at concentrations of 18, 58 or 173 mg/m^3, for 6 hours/day, 5days per week, over 12 weeks. Two control groups of 30 rats per sex each exposed to air only. After mating, females were further exposed for 7 days/week for up to three weeks after delivery with the exception of the first 5 days of lactation. The percentages of pregnant females and fertile males were not affected by ethylene oxide exposure. The number of pups per litter, the number of implantation sites per female and the number of foetuses born per implantation site were decreased at 173 mg/m^3. In addition, the number of females with a gestation period longer than 22 days was also increased at this concentration but no effects were noted on the average length of the gestation period. Neither parents nor pups showed signs of toxicity from ethylene oxide.

(Snellings *et al*, 1982a/WHO, 1985)

B.6.8.1.6.2 Developmental toxicity studies (IIA 5.6.2)

Developmental studies in rats

a) Groups of Sprague Dawley rats (32-45 females) were exposed to ethylene oxide at concentrations of 0 or 270 mg/m^3 for 7 hours/day. They were exposed on days 7-16 of gestation (Group 1) or on days 1- 16 of gestation (Group 2) or during 3 weeks before mating (5 per week) and on days 1 - 16 of gestation (Group 3).

No dams died during the study but body weights were decreased in Group 3. In all exposed groups, the relative and absolute weights of kidney and spleen were increased. The results of histopathological examination did not show any abnormalities. There was a significant increase in resorptions per litter and per implantation site in Group 3 but no significant effects on the number of implants, live foetuses or pregnancies. In all exposed groups, the weights and the lengths of the foetuses were decreased. Reduced ossification of sternebrae and skull was observed.

(Hackett *et al*, 1982/WHO, 1985)

b) Groups of Fischer 344 rats (22 females) were exposed to ethylene oxide at concentrations of 18, 58, or 173 mg/m^3, for 6 hours/day on days 6-15 of gestation. Two control groups comprising 22 rats each were exposed to air only. The numbers of pregnant dams ranged from 17 to 22. Maternal behaviour was normal, and there were no deaths. The only effect on the foetuses was a 5-8% decrease in weight at 180 mg/m^3.

(Snellings *et al*, 1982b/WHO, 1985)

Developmental studies in mice

a) Groups of CD-1 mice (24-37 females) each received intravenous injections of ethylene oxide at doses of 0, 75 or 150 mg/kg bw in an aqueous dextrose solution on days 4-6, 6-8, 8-10 or 10-12 of pregnancy.

Dams exposed on days 6-8 of pregnancy did not show toxic signs but there was a 20% decrease in foetal weight. In all the other groups at the top dose, clinical signs of toxicity were observed and included increased mortality (19-48%), weakness, laboured respiration and tremor. Foetal malformations were shown in 19.3% of foetuses in exposed litters compared with 2% in control groups. These malformations were mainly fused cervical arches. In addition, fused thoracic arches, scrambled and fused sternebrae and fused, branched, or missing thoracic ribs were observed.

(Laborde & Kimmel, 1980/WHO, 1985)

b) Exposure of F1 female mice (C3H x C57B1 or SEC x C57B1) mated with F1 males (C3H x C57B1) to ethylene oxide at a concentration of 2196 mg/m^3 for 1.5 hours could produce different results depending on the timing of exposure. Females were exposed at 1, 6, 9 or 25 hours after timed 30 minute matings. These time intervals correspond to time of sperm penetration, early pronuclear stage (before DNA synthesis), pronuclear DNA synthesis and early two-cell stage, respectively. It was noted that maternal toxicity was not reported despite the high concentrations used.

Exposure at 1 or 6 hours increased the number of mid-gestational and late foetal deaths but few effects were seen after 9 hours and none were seen after 25 hours. A large proportion of the foetuses that survived after exposure at 6 hours had a range of congenital malformations including omphalocoele, hydropia, open thorax, and limb and tail defects (37% *versus* 2% in controls). Malformations were also seen in foetuses exposed at 1 hour but not those exposed at 9 or 25 hours. In a later study, with identical exposure protocols but more detailed foetal examination, an increased incidence of malformations was found after exposure at 1, 6, 9 and 25 hours. Other females exposed to ethylene oxide for up to 14 days before mating had mainly an increase in early embryonic death around the time of implantation, probably as a result of dominant lethal mutations.

(Generoso *et al*, 1987; Rutledge and Generoso, 1989/IARC 1994)

Developmental studies in rabbits

New Zealand rabbits were exposed to ethylene oxide at a concentration of 270 mg/m^3 from days 1-19 or from days 7-19 of gestation. There was no evidence of toxicity in the mothers, embryos, or foetuses, or of any developmental defects.

(Hackett *et al*, 1982/WHO, 1985)

B.6.8.1.6.3 Effects on sperm and reproductive tissues/organs

a) Wistar rats (12 or 6 males/dose) were exposed to ethylene oxide at concentrations of 0, 91.5, 183, or 457.5 mg/m^3 for 6 hours/day on fine days/week for 13 weeks. At 457.5 mg/m^3, epididymal but not testicular weight was reduced, there was slight degeneration in some seminiferous tubules, a reduced sperm count in the body and tail but not the head of the epididymus and an increase in sperm head abnormalities due mainly to the presence of immature sperm. An increase in malformed sperm heads unrelated to dose was observed in all treated groups over that in control (15% *versus* 2%).

(Mori *et al*, 1991/IARC 1994)

b) Male Cynomolgus monkeys were exposed to ethylene oxide at concentrations of 0, 90 or 180 mg/m^3 for 7 hours/day on 5 days/week for 2 years. A decline in sperm count and mobility was observed at both dose levels but the incidence of abnormal sperm heads did not change.

(Lynch *et al*, 1984c/WHO)

B.6.8.1.6.4 Summary of reproductive toxicity

No data/information has been submitted (or cited from the literature) on the reproductive toxicity of ethylene oxide via the oral exposure route. However, there are sufficient data/information generated by studies using inhalation exposure to establish that ethylene oxide is a reproductive toxin that affects fertility and development in experimental animals (some effects are evident in the absence of maternal toxicity). In mice, there is clear evidence of teratogenic activity after intravenous injections and evidence that mutagens can induce foetal malformations and death when administered around the time of fertilisation. Sperm abnormalities have been reported in rats and monkeys following inhalations exposure to ethylene oxide.

B.6.8.1.7 Neurotoxicity studies

No specific neurotoxicity studies have been submitted (or cited from the literature). All the reported effects of ethylene oxide on the nervous system in experimental animals have been observed and reported in standard repeat-dose inhalation studies.

B.6.8.1.7.1 Repeat dose neurotoxicity studies

a) In a limited, poorly reported study in rabbits and monkeys, paralysis of the hind limbs was observed in both species accompanied by atrophy of the leg muscles, following exposure to $\geq$ 370 mg/m^3 for periods ranging from 7 to 32 weeks (exact exposure periods were not clearly specified).

(Hollingsworth *et al*, 1956/ECHC, 2001)

b) In sub chronic or chronic studies, in rats exposed to ethylene oxide a concentrations between 458-915 mg/m^3 there was a range of neurological effects including awkward or ataxic gait, paralysis and atrophy of the muscles of the hind limbs, accompanied in some cases by pathological evidence of axonal degeneration of myelinated fibers in nerves of the hind legs.

(Hollingsworth *et al*, 1956 & Other workers/ECHC, 2001)

c) Poor coordination of the hind quarters was observed in rats and mice following exposure to ethylene oxide at 810 mg/m^3 for 7-8 weeks.

(Snellings *et al* 1982/ECHC, 2001)

d) Abnormal posture during gait and reduced locomotor activity were also observed in mice after exposure to ethylene oxide at concentrations ranging from 86 to 425 mg/m^3, for 6 hours/day on 5 days/week for 10 or 11 weeks. Effects on various reflexes (righting, tail pinch, toe pinch) were also noted at the highest concentration examined.

(Snellings *et al* 1984a/ECHC, 2001)

e) In two studies of male cynomolgus monkeys exposed to ethylene oxide at concentrations of 92 or 183 mg/m^3 for 2 years, histological alterations in the axons within the nucleus gracilis of the medulla oblongata and demyleination of the fasciculus gracilis within the medulla were observed.

(Sprinz *et al*, 1982/Lynch *et al*, 1984b/ECHC, 2001)

B.6.8.1.7.2 Summary of the neurotoxicity studies

There is no data/information on the neurotoxicity of ethylene oxide via the oral exposure route. There is sufficient data/information generated by studies using inhalation exposure to establish that ethylene oxide is a neurotoxin in experimental animals.

B.6.8.1.8 Other toxicological data/information

B.6.8.1.8.1 Mode of action

Ethylene oxide is an electrophilic agent that alkylates nucleophilic groups in biological macromolecules, i.e. including DNA and protein (e.g. haemoglobin & albumin). It is considered likely that the toxicological effects of ethylene oxide arise primarily from the direct alkylation of macromolecules.

Since ethylene oxide is formed during the metabolism of ethylene (a natural body constituent) both endogenous and exogenous sources of ethylene and ethylene oxide will contribute to the background alkylation of macromolecules.

(CICADS 54, 2003 & IARC 1994)

B.6.8.1.8.2 Ethylene oxide detected in food stuffs and cosmetics and on medical devices

a) Ethylene oxide was detected in 96 of 204 (47%) samples of food products taken from retail stores in Denmark in 1995 (Jensen, 1988). The reported concentrations reflect the total amount of ethylene chlorohydrin and ethylene oxide present at the time of analysis. These concentrations ranged from <0.05 to 1800 mg/kg in the individual samples without correction for recoveries. Ethylene oxide was detected frequently among 24 samples of spices at a mean concentration of 84 µg/g and a maximum concentration of 580 µg/g.

(Jensen, 1988/ECHC 2001)

b) Ethylene oxide was detected, but not quantified, in 1 of 2372 samples of eggs and in 1 sample of 3262 samples of fish collected in the United States in 19975 as part of the Food and Drug Administration Monitoring Program (1970-1976).

(Duggan *et al*, 1983/ECHC 2001)

c) Ethylene oxide may be present as a contaminant of skin care products. Current commercial preparations of polyglycol ethers may contain residues of ethylene monomer up to approximately 1 µg/g.

(Filser *et al*, 1994/ECHC 2001)

d) Ethylene oxide monomer in skin care products have been reported at 1.9 to 34 $nmol/cm^3$ (0.08 to 1.5 mg/l) and a range of maximum skin penetration of ethylene oxide of 1-14% in various product formulations.

(Kreuzer, 1992/ECHC 2001)

e) Ethylene oxide may be absorbed by medical equipment during sterilization and may remain there as unchanged compound or as one of its reaction products (WHO, 1985). Studies show that residual concentrations of ethylene oxide in medical equipment immediately following their sterilization have ranged up to 1 or 2%. These concentrations generally declined rapidly after a few days aeration, although levels exceeding 100 ppm (183 mg/m^3) were sometimes measured following aeration.

(Gillespie *et al*, 1979 & 1980/ECHC 2001)

B.6.8.1.9 Human data/information

B.6.8.1.9.1 Absorption, distribution, metabolism and excretion

a) Ethylene oxide is very soluble in blood and readily taken up by the lungs; approximately 20-25% of inhaled ethylene oxide reaching the alveolar space is exhaled as unchanged compound and 75-80% is taken up by the body and metabolised. The half-life in the body has been estimated to be less than 1 hour.

(Brugnone *et al*, 1986; 1988; Filser *et al*, 1992/IARC 1994)

b) Pharmacokinetic data obtained form experimental animals to calculate the internal dose of ethylene oxide in man obtained from daily exposure. For a man exposed for 8 hours to ethylene oxide at 1 ppm (1.8 µg/litre), the area under the concentration-time curve in blood plasma was estimated to be 18.8 µg/hour/ml on the basis of data for rats and 14.3 µg/hour/ml on the basis of dog data.

(Beliles and Parker, 1987/IARC 1994)

c) The blood concentrations of ethylene glycol were in sterilisation personnel exposed to ethylene oxide. The mean concentrations of ethylene glycol in blood in exposed worker (90 mg/litre) were twice that in unexposed workers (45 mg/ml).

(Wolfs *et al*, 1983; Brown *et al*, 1996 & Other workers/IARC 1994)

d) The concentration of thioesters excreted in urine collected from sterilisation workers at the end of sterilisation processes was twice that in non-smoking personnel.

(Burgaz *et al*, 1992/IARC 1994)

e) *In vitro* investigations suggest that the human population can be divided into conjugators (75%) and non-conjugators (25%) based on enzymic conjugation of ethylene oxide with glutathione in erythrocytes.

(Hallier *et al*, 1993/IARC 1994)

f) Ethylene oxide is an electrophilic agent that alkylates nucleophilic groups in biological macromolecules, e.g. DNA and haemoglobin. There are numerous published studies that have investigated the formation nitrogen adducts (hydroxethyl adducts of valine, cysteine and histidine) in the haemoglobin of workers occupationally exposed to ethylene oxide. Ethylene oxide binding to DNA primarily results in the formation 7-(2-hydroxethyl) guanine adducts but other adducts have been identified at lower levels. DNA extracted from lymphocytes of unexposed individuals had mean background levels of 7-(2-hydroxethyl) guanine that ranged between 2-8.5 pmol/mg DNA. It has been reported that human tissue contains 10- to 15-fold higher levels of endogenous 7-(2-hydroxethyl) guanine adducts than rodents.

(Bolt, 1996; Bolt *et al*, 1997; Wu et al, 1999a/CICADS 2003)

g) Ethylene oxide is metabolised by hydrolysis to ethylene glycol and conjugation with glutathione (both are considered to be detoxification pathways). The hydrolysis pathway predominates in larger species such as the rabbit and dog while the conjugation pathway predominates in rodents. A physiologically based pharmacokinetic (PBPK) model for the dosimetry of inhaled ethylene oxide has calculated that 80%, 60% and 20% would be metabolized via glutathione conjugation in mice, rats and humans, respectively. This appears to be consistent with the levels of glutathione S-transferase enzyme (GSTT1) activity (mice>rats>humans); ethylene oxide is a substrate for the human GSTT1 enzyme. Higher levels of haemoglobin adducts have been reported in exposed individuals (workers and smokers) with the GSTT1 'null genotype' (homozygous deletion of the GSTT1 gene) than among those with a GSTT1 'positive genotype' (at least one copy of the GSTT1 gene).

(Yong *et al*, 2001; Fennell and Brown, 2001; Pemble *et al*, 1994/CICADS 2003)

h) Reports on two PBPK models for ethylene oxide in rodents and humans indicate that ethylene oxide is a direct acting alkylating agent in humans and rodents via the same mode of action (i.e. the quantitative differences between humans and rodents result from differences in basic physiology rather than mode of action).

(Csandy *et al*, 2000; Fennel and Brown 2001; Pemble *et al*, 1994/CICADS 2003)

B.6.8.1.9.2 Acute toxicity, skin and eye irritation and sensitisation

a) Five sterilizer operators were exposed accidentally to ethylene oxide at concentrations high enough to be smelt (odour threshold 1280 mg/m^3) for periods up to 0.5 hours. Two operators suffered headache and diarrhoea which resolved after about 70 hours. Three operators suffered irritation of the eyes and throat, mouth dryness, pruritus, headache, vertigo, myasthenia, indigestion and haemolysis which had resolved within 21 days of the exposure. Haemolysis diagnosed on days 9-11 lasted until day 16.

(Deleixhe *et al*, 1986/IARC 1994)

b) Acute effects on the nervous system in nearly all inhalation cases were marked by nausea, recurrent vomiting, and headache. Less frequently reported effects included decreased consciousness (one case of coma), excitement, sleeplessness, muscular weakness, diarrhoea, and abdominal discomfort.

(Capellini and Ghezzi, 1965 and Other workers/WHO, 1985)

c) Accidental skin exposure to a 1% aqueous solution, from the waist down, was reported to result in effects on the nervous system (nausea and repeated vomiting).

(Sexton and Henson, 1949/WHO 1985)

d) Burns on the hands were attributed to gloves containing residual traces of ethylene oxide used for sterilization. Mild skin irritation has been reported after exposure to 1% aqueous solutions of ethylene oxide. Dermal irritation is characterised by erythema, oedema and the formation of vesicles and has been observed after contact with ethylene oxide-sterilized materials and clothing.

(Fisher, 1988/IARC 1994)

e) Skin and eye irritation in sterilizer operators were associated with exposures to ethylene oxide at concentrations up to 19.6 mg/m^3.

(Bryant *et al*, 1989/IARC 1994)

f) Exposure to ethylene oxide can cause irritation of the mucous membranes of the respiratory passages.

(Thiess, 1963/ECHC 2001)

g) Ethylene oxide is a sensitising agent. Type I (mild to severe anaphylactic reactions) and Type IV (contact dermatitis) hypersensitivity reactions have been observed in patients who received dialysis treatment with equipment that had been sterilized with ethylene oxide.

(Bommer and Ritz, 1987/IARC)

h) Severe respiratory problems due to inflammatory reactions in the trachea and larynx were reported inpatients who had received endotracheal intubation with tubes sterilised with ethylene oxide.

(Mantz *et al*, 1972 and Other workers/WHO 1985)

B.6.8.1.9.3 Genetic effects

Numerous studies have shown that ethylene oxide induces chromosome aberrations, micronuclei and sister chromatid exchanges in humans and the extent of the damage is related to the level and duration of exposure.

a) Increased incidences of sister chromatid exchange have been reported in peripheral blood lymphocytes of hospital sterilisation workers exposed to 1 ppm ethylene oxide (8 hour TWA) and concentrations between 0.5-25 ppm for various durations.

(Yager *at al*, 1983; Stolly *et al*, 1984; Tates *et al*, 1991a/IARC 1994)

b) Increased incidences of chromosome aberrations have been reported in lymphocytes of sterilisation workers. It has been stated that ethylene oxide exposures above 9 mg/m^3 are required to induce chromosome aberrations.

(Galloway *at al*, 1986/IARC 1994)

c) Increased incidences of micronuclei have been reported in factory workers, i.e. in lymphocytes at concentrations of 25-720 9 mg/m^3, in erythroblasts and polychromatic erythrocytes in bone marrow samples at a concentration of 1 ppm for 0.5 to 8 years and in exfoliated nasal mucosa cells following accidental exposures.

(Tates *at al*, 1991a; Hodstedt *et al*, 1983; Sarto *et al*, 1990/IARC 1994)

d) Mutations at the HPRT locus in circulating lymphocytes of factory workers have been reported in one study.

(Tates *at al*, 1991b/IARC 1994)

B.6.8.1.9.4 Neurological effects

a) Several studies in sterilizer operators have associated ethylene exposure with symptoms of peripheral and central neurotoxicity. In cases of peripheral neuropathy, the symptoms included numbness in feet and fingers, muscular weakness in the lower limbs, a reduction in sural nerve velocity, nerve fibre degeneration, and demyelination. Central nervous system effects were implied on the basis of personality dysfunction and cognitive impairment.

(Schroder *et al*, 1985 and Other workers/IARC)

b) Because of a leaking sterilizer, 4 young men were exposed intermittently, for 2-8 weeks, to ethylene oxide at levels of approximately 1000 mg/m^3. Three of the men developed a reversible peripheral neuropathy showing abnormal nerve conduction and, in 2 cases, headache, weakness and decreased reflexes in the extremities, incoordination, and a wide-based gait. The fourth man developed a reversible acute encephalopathy with headache, nausea, vomiting, lethargy, recurrent motor seizures, agitation and a diffusely slow electroencephalogram. Following this, 6 more cases were reported concerning sterilizer operators, suffering from reversible peripheral neuropathy following ethylene oxide exposure for 0.5-1.5 years.

(Gross *et al*, 1979/WHO 1985)

c) Three people exhibited subacute polyneuropathy with bilateral foot-drop, slowing of nerve conduction velocity and enervation potential on electromyography as the main findings. All 3 people had noticed the smell of ethylene oxide regularly at work while 2 persons experienced eye irritation.

(Finelli *et al*, 1983/WHO 1985)

d) Polyneuropathy was also reported in 3 sterilizer operators. Two of these cases were described in detail. Sural nerve biopsies revealed axonal degeneration with mild changes in the myelin sheath and unmyelinated fibres were also involved. Muscle biopsies showed typical denervation atrophy.

(Kuzuhara *et al*, 1983/WHO 1985)

B.6.8.1.9.5 Reproductive effects

a) The rate of spontaneous abortions was significantly higher ($P<0.05$) in Finish hospital workers associated with ethylene oxide exposure (20.4%) than in controls (11.3%). Randomly selected Californian dental assistants (aged 18-39) examined for the occurrence of spontaneous abortion and pre- (27-37 weeks) and post-term births ($\geq$ 42 weeks) in relation to ethylene oxide exposure. Ethylene exposed women were stated to be 2.7 times more likely to have any of the three adverse effects after adjusting for age.

(Hemminki *et al*, 1982; Rowland *et al*, 1996/CICADS 2003)

b) One paper reported an increased risk of spontaneous abortion in Finish women whose partners had been exposed to ethylene oxide. Paternal exposure was based upon the job and industry in which the men were employed (no quantitative exposure data). The number of spontaneous abortions (n=3) and pregnancies (n=10) in the paternal group was small and confounding factors, such as previous abortions, alcohol and tobacco consumption were not considered in the analysis.

(Lindbolm *et al*, 1991/CICADS 2003)

B.6.8.1.9.6 Occupational exposure

a) The health status of 37 male operators from an ethylene oxide-producing plant in the USA during the period 1953-62 was compared with that of age-matched operators from other production units. The average employment period was 11 years for exposed workers and 12 years for controls. The usual average exposure level was between 9 and 18 mg/m^3 with occasional peaks up to 230 mg/m^3 for one particular job (collecting a sample of the product). According to the medical records, the health of the exposed workers was somewhat better than that of the controls. A physical examination and extensive clinical tests did not reveal any exposure-related effects with the exception of a slightly increased white blood cell count.

(Joyner, 1964/WHO 1985)

b) Chromosomal damage was found in a group of 12 workers from a hospital sterilization facility in the USA. The maximum exposure concentration measured during sterilization was 65 mg/m^3. Another group of 12 persons, who worked in the adjacent operating room area, volunteered as representatives of an unexposed or accidentally exposed group. To ensure adequate control throughout the study, unexposed laboratory staff members served as a third group. Frequently-reported subjective complaints indicated irritation of the mouth, throat, and eyes, and effects on the nervous system, such as headache, nausea, speech difficulty, memory loss, dizziness and incoordination.

(Garry *et al*., 1979/WHO 1985)

c) In Belgium, a group of 18 workers, using or distributing the sterilant ethylene oxide, were compared with a well-matched control group by means of a questionnaire, and by analyses for urinary retinol-binding protein and albumin, beta-microglobulin, and chromosomal damage in lymphocytes. The overall mean exposure level was 7.6 mg/m^3 and the time-weighted average exposure, over a working day, ranged between 0.2 and 95 mg/m^3. A significant increase in the incidence of sleeplessness and leg

cramps was recorded, but not irritation or allergy. These studies did not reveal any abnormalities with the exception of an increase in sister chromatid exchanges in lymphocytes.

(Wolfs *et al*, 1983; Laurent *et al*, 1984/WHO, 1985)

d) In a plant in Bulgaria, 196 workers engaged in the production of ethylene and ethylene oxides were examined. About 73% of all concentrations of ethylene oxide measured were 1 mg/m^3 or less while 27% were between 1 mg/m^3 and 3.5 mg/m^3. Significant increases were found in deviations of the autonomous nervous system and in neurosis-like manifestations, especially in female workers but woman may be more prone to neuroses. Because of a mixed exposure was difficult to evaluate the findings.

(Spasovski *et al*, 1980/WHO, 1985)

e) Haematological changes were reported in a group of 27 workers in an ethylene oxide manufacturing and processing plant, in Sweden, in 1967. The exposure period varied from 2 to 20 years, the average length being 15 years. Controls worked with ethylene oxide in other departments where no leakages were likely. No exposure data were reported. When 2 cases of anaemia were excluded, there was still a significantly decreased haemoglobin value in exposed workers. There was a 30% increase in the number of lymphocytes, and one case of chronic lymphatic leukaemia was noted in the exposed workers.

(Ehrenberg & Hallstrom, 1967/WHO, 1985)

f) In the Federal Republic of Germany, 279 employees from 8 plants in which alkene oxides were produced or processed, were examined for morbidity during 1978. They were employed for an average of 10.8 years. Of these workers, 21 had been involved in accidents with ethylene oxide. Taking into account age and length of exposure, they were compared with groups of industrial and clerical workers within the same company. No abnormalities were found that could be related to ethylene oxide or propylene oxide. Lymphocytosis and increases in haemoglobin and erythrocyte volume were attributed to age or smoking. The exposure concentrations were not reported. The workers were also exposed to many other chemicals, some of which may be carcinogenic for man.

(Stoker & Thiess, 1979/WHO, 1985)

g) Haematological effects were observed among a group of 59 women exposed to ethylene oxide released from sterilizers while employed in nine hospitals in the USA and one hospital in Mexico. Compared with unexposed controls, US workers (exposed to a mean 8-hour TWA exposure of 0.31 mg/m^3 with a range of 0.24-0.55 mg/m^3) exhibited a statistically significant increase in the percentage of lymphocytes and a reduction in the percentage of neutrophils in the blood). No statistically significant effects were found in Mexican workers.

(Schulte *et al*, 1995/CICADS 2003)

h) Haematological effects were not observed in a group of 84 male workers involved in the manufacture of ethylene oxide and exposed to estimated concentrations of <1.83 mg/m^3.

(Currier *et al*, 1984/CICADS 2003)

i) Haematological effects were not observed in a group of 36 male workers involved in the manufacture of ethylene oxide with estimated 8-hour TWA exposures below 0.09 mg/m^3.

(van Sittert *et al*, 1985/CICADS 2003)

j) A study in 46 Israeli hospital workers exposed (at three locations with a mean period of employment of 6.6 years) to 145- to 210 minutes TWA concentrations of <0.02-0.1 mg/m^3 found statistically significant haematological effects compared to 88 non-occupational exposed controls (matched for age, sex and smoking habits). There were increases in the absolute mean numbers of erythrocytes, monocytes and eosinophils, increases in the haematocrit and reductions in the absolute mean numbers of lymphocytes and platelets.

(Shaham *et al*, 2000/CICADS 2003)

k) Lens opacities and cataracts were assessed in French hospital workers exposed to ethylene oxide at concentrations of 0.11 mg/m^3 during a 97-minute exposure to 71 mg/m^3 during a 2.5 minute exposure. There were no differences between the exposed and control groups in the case of lens opacities. However, cataracts were observed in six exposed people compared to none in the controls (lens opacities have been reported in monkeys exposed to 100 ppm for up to 24 months).

(Deschamps *et al*, 1990/CICADS 2003)

l) Following accidental exposure (4 hours/day for 4 days), to concentrations of ethylene oxide high enough to be smelt, one worker out of five developed persistent non-immunological asthma, probably induced by extensive epithelial injury which lead finally to fibrosis (no further information on the outcome).

(Deschamps *et al*, 1992/IARC 1994)

B.6.8.1.9.7 Case and epidemiological studies

Numerous summaries of case and epidemiological studies are presented in the submitted publications (IARC 1994, ECHC 2001 & CICADS 2003).

In epidemiological studies, the most frequently reported association in workers exposed to ethylene oxide has been with lymphatic and haematopoietic cancer. The workers studied fell mainly into two groups: i) people using ethylene oxide as a sterilant, ii) chemical workers manufacturing (either by the chlorohydrin process or more recently by the catalytic oxidation of ethylene) or using the compound in other processes. In general, people involved in sterilization are less likely to have occupational exposure to other chemicals.

B.6.8.1.10 Summary and conclusions

Ethylene oxide is an electrophilic agent. It is considered likely that the toxicological effects of ethylene oxide arise primarily from the direct alkylation of macromolecules (e.g. DNA and proteins).

The majority of data for ethylene oxide has been primarily generated using the inhalation exposure route. Only limited data are available for ethylene oxide administered via the oral route.

Oral exposure

The acute oral LD50 values for ethylene oxide were stated to be 330 mg/kg bw for male rats and 365 and 280 mg/kg bw for male and female mice, respectively. In a subacute rat study, the findings included loss of body weight, gastric irritation and slight liver damage. The only long-term rat study (gavage dosing) reported a dose-related increase in the incidence of squamous cell carcinomas in the forestomach at all dose levels tested.

Other routes of exposure (primarily inhalation exposure)

Ethylene oxide is very soluble in blood and the pulmonary absorption is expected to be rapid and extensive. Excretion is also rapid and occurs mainly via urine while minor amounts of unchanged parent and labelled carbon dioxide are excreted via the lungs. Distribution is widespread based on the protein and DNA adducts in various organs and tissues. Two metabolic pathways have been identified, the hydrolysis of ethylene oxide to 1,2-ethanediol and conjugation with glutathione to produce S-(2-hydroxyethyl)cysteine and N-acetyl- S-(2-hydroxyethyl)cysteine.

Following acute exposure to ethylene oxide, the respiratory system, the nervous system and the liver and kidneys were identified as target organs. Ethylene oxide is a potent eye, skin and respiratory irritant and a sensitiser.

In the short-term studies, mortalities and effects on respiratory system, the haematological system (including bone marrow), the nervous system, ocular lens, liver and kidneys, thymus and spleen and the testes were reported. A dose-related in crease in pulmonary adenoma was also seen in mice after 6 mounts of exposure.

Ethylene oxide is an alkylating agent and is considered to be a mutagen in experimental animals and humans. It forms DNA adducts and induces gene mutations, chromosome aberrations, cell transformation, unscheduled DNA synthesis, DNA strand breaks, sister chromatid exchanges, dominant lethal mutations and heritable translocations.

The chronic findings in rats included deaths, reduced body weight, inflammatory lesions of the lungs, nasal cavities, trachea and internal ear and the development of eye cataracts. There were several reports of haematological changes (including bone marrow changes) and changes in some serum enzyme activities. Organ weight changes were also reported. The microscopic findings included lesions in the adrenals

and atrophy and degeneration of skeletal muscle. No chronic non-neoplastic findings in mice were reported.

Dose related neoplastic changes were evident in rats and mice following long-term inhalation exposure. There were significant dose-related increases in several tumour types of tumours in rats (leukaemia, peritoneal mesotheliomas, brain tumours and subcutaneous fibroma) and mice (alveolar/bronchiolar carcinoma, malignant lymphomas of the haematopoietic system, uterine adenocarcinoma and mammary adenocarcinoma and adenosquamous carcinoma). It is also noteworthy that pituitary tumours appeared earlier in rats and that an increase in lung tumours was reported in mice after only 6 months of exposure.

Following subcutaneous injections to mice, there was a dose-related increased incidence of sarcomas at the injection sites. No skin tumours (or skin irritation) were found in mice after long-term dermal exposure but it was assumed that ethylene oxide evaporated rapidly from the skin.

The extensive evidence of genotoxicity (*in vitro* and *in vivo* effects) and carcinogenicity (a variety of tumours in rats and mice and the evidence of the early appearance of certain tumours in rats and mice) indicates that ethylene oxide is a potent genotoxic carcinogen in experimental animals.

In the rat multigeneration study, there were reductions in the number of pups per litter, the number of implantation sites per female and the number of foetuses born per implantation site and an increase in the length of the gestation period. An increase in resorptions per litter and per implantation site were also noted in the rat developmental study together with reduced foetal weight and length and reduced ossification of sternebrae and skull was observed. In mice, there is clear evidence of teratogenic activity (severe skeletal malformations) after intravenous injections and evidence that mutagens can induce foetal malformations and death when administered around the time of fertilisation. Effects on sperm and reproductive tissues have been reported in rats and monkeys. There are sufficient data/information to establish that ethylene oxide is a reproductive toxin that affects fertility and development in experimental animals (some effects are evident in the absence of maternal toxicity).

There are numerous reports of adverse neurotoxicity in a range of experimental animals that include effects on reflexes, reduced locomotor activity, ataxia, limb paralysis, muscle atrophy, axonal degeneration in the limbs and histological alterations of the medulla oblongata of primates.

The data base for ethylene oxide in rodents and humans indicate that ethylene oxide is a direct acting alkylating agent in humans and rodents via the same mode of action (i.e. the quantitative differences between humans and rodents result from differences in basic physiology rather than mode of action).

There are numerous reports of ethylene oxide-induced effects in humans/workers and include irritation of the eyes, skin and throat, mouth dryness, pruritus, headache, vomiting, vertigo, myasthenia, indigestion, diarrhoea and haemolysis. Less frequently reported effects included decreased consciousness (one case of coma), excitement, sleeplessness, muscular weakness, diarrhoea, and abdominal discomfort. Ethylene

oxide is also a sensitising agent and induces Type I (mild to severe anaphylactic reactions) and Type IV (contact dermatitis) hypersensitivity reactions and inflammatory reactions in the trachea and larynx.

Occupational exposures to ethylene oxide have resulted in reports of a wide range of serious adverse effects that include haematological effects, a possible increase in ocular lens cataracts, symptoms of peripheral and central neurotoxicity, increases in chromosome aberrations, micronuclei and sister chromatid exchanges and spontaneous abortions. In addition, ethylene oxide exposure of workers has frequently been associated with lymphatic and haematopoietic cancer.

In 1994, IARC concluded that there was limited evidence in humans for the carcinogenicity but there was sufficient evidence in experimental animals for the carcinogenicity of ethylene oxide. The overall conclusion of IARC 1994 was that ethylene oxide is carcinogenic to humans (Group 1) when the following evidence was taken into consideration.

Ethylene oxide is a directly acting alkylating agent that:

i) persistently induces dose-related increases in the frequency of chromosome aberrations and sister chromatid exchange in lymphocytes and micronuclei in bone marrow cells of workers;

ii) has been associated with malignancies of the lymphatic and haematopoietic system in humans and experimental animals;

iii) induces dose-related increases in the frequency of haemoglobin adducts in humans and dose related increases in the number of adducts in DNA and haemoglobin in exposed rodents;

iv) induces gene mutations and heritable translocations in germ cells in exposed rodents;

v) is a powerful mutagen and clastogen at all phylogenetic levels.

B.6.8.2 Adduct formation in experimental animals

a) The ethylene metabolite, ethylene oxide, reacts with nucleophilic centres in protein and DNA. The haemoglobin adducts N-(2-hydroxyethyl)histidine and N-(2-hydroxyethyl)valine have been used as internal dose monitors for the formation of ethylene oxide from ethylene. In male CBA mice, it has been reported that 7-8% of inhaled ethylene is metabolised to ethylene oxide. These mice were exposed to ethylene at concentrations below 23 mg/m^3 (20 ppm) 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. The levels of the haemoglobin-hydroxyethyl valine adduct was determined in Fischer rats and Syrian hamsters exposed for six months to gasoline and diesel exhausts. In hamsters, the levels of haemoglobin-hydroxyethyl valine adduct increased almost linearly with dose. At the highest dose, the levels were similar in male rats and hamsters and in

female rats and hamsters. The values were about 50-90% of those predicted from data on mice and indicated that ethylene behaves similarly in these species.

(Ehrenberg *et al*, 1977; Segerback, 1983/IARC 1994)

b) Ethylene oxide is present in cigarette smoke and smokers have higher haemoglobin adduct levels (average of 170 pmol/g of globin) than non-smokers (average of 20 pmol/g of globin). The adduct levels in non-smokers indicate widespread background exposures. Ethylene formed endogenously may contribute to this background. The highest adduct levels have been found in ethylene production workers (up to 16000 pmol/g of globin). Patients treated with cytostatic drugs that transfer hydroxyethyl groups also show elevated adduct levels (e.g. 330 pmol/g of globin for nimustine a chloroethyl nitroso urea derivative). Based on the hydroxyethyl valine adduct levels for smokers (10 cigarettes/day; 120 pmol/g of globin), non-smokers (50 pmol/g of globin) and steriliser operators (0.2-8.5 ppm; median value of 16.2 pmol/g of globin with a range of 5.2-32.7 pmol/g of globin) were reported.

(B-G-G 2003)

B.6.8.3 Human data (Ethylene exposure)

B.6.8.3.1 Volunteer studies (ADME)

a) The inhalation pharmacokinetics of ethylene was investigated in human volunteers at atmospheric concentrations of up to 50 ppm (0.1575 mg/l) by gas uptake in human volunteers in a closed spirometer system. The uptake, exhalation and metabolism, can be described by first-order kinetics. Uptake of ethylene into the body was low. Clearance due to uptake, which reflected the transfer rate of ethylene from the atmosphere into the body, was 25 litres per hour for a man of 70 kg. This value represented only 5.6% of the experimentally obtained alveolar ventilation rate of 150 litres per hour. The majority (94.4%) of ethylene inhaled into the lungs was 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 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 litres per hour for a man of 70 kg. This indicates that at steady state about 36% of systematically available ethylene was eliminated metabolically and 64% was eliminated by exhalation as the unchanged substance, as could be calculated from the values of clearance of uptake and of clearance of metabolism. The biological half-life was 0.65 hr. The alveolar retention of ethylene at steady state was calculated to be 2-3%. From theoretical considerations of the lung uptake of gases and vapours, it could be deduced that the low uptake rate of ethylene was due to its low solubility in blood (Ostwald`s solubility coefficient for human blood at 37°C: 0.15). This summary stated that ethylene gives rise to minute levels of ethylene oxide and that the maximum conversion of ethylene to ethylene oxide in humans was estimated to be 4 %.

(Filser *et al*, 1992/OECD:SIDS)

B.6.8.3.2 Occupational exposure

a) 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 0.02-3.85 mg/m^3 (0.02-3.35 ppm) with an estimated average concentration of 0.35 mg/m^3 (0.3 ppm).

(Tornqvist *et al* , 1989a/IARC)

b) Exposure to fire-fighters during the 'knockdown' phase of a fire showed a concentration of 53 mg/m^3 (46 ppm) ethylene; none was detected during the 'overhaul, phase. In laboratory studies, ethylene has been detected as a thermal degradation product of polyethylene and polypropylene.

(Hoff *et al*, 1982; Jankovic *et al*, 1991/IARC)

c) In a preliminary study, the miscarriage rate (6/15 pregnancies) in Swedish workers in five local petrochemical plants was higher than 1549 woman from outside the industry. Ethylene was the main product in four 4/5 of the petrochemical plants. No data were provided on occupational levels but measurements made in areas surrounding the plants indicated that ethylene was present in concentrations up to 10-fold higher that the other main pollutants (propylene, ethane, propane and phenol).

(Axelsson and Molin, 1988/BIBRA Toxicity Profile 1993)

d) A brief abstract notes that there was a higher than expected rate of miscarriage and gynaecological disease among female operatives of a polyethylene plant who were exposed to ethylene concentrations in the range of about 40-60 ppm and high levels of noise.

(Yakubova *et al*, 1976/BIBRA Toxicity Profile 1993)

B.6.8.3.3 Environmental exposure

a) Ethylene concentrations in ambient air and remote rural sites worldwide are generally in the range of <1-5 µg/m^3. In urban and indoor air contaminated with combustion products, ethylene concentrations range up to 1000 µg/m^3.

(Seinfeld, 1989; Colbeck & Harrison, 1985; Sawada & Totsuka, 1986/IARC)

b) Vehicle exhaust emissions make a significant contribution to urban air concentrations of ethylene. Several authors have monitored traffic emissions which ranged from 93-212 mg/km and 9.8-405 5 µg/m^3 depending on the site sampled (e.g. urban intersection or tunnel).

(Bailey *et al*, 1990a & b; Barrefors & Petersson, 1992/IARC)

c) Smoking is also a significant source of exposure to ethylene (1-2 mg ethylene are released per cigarette). The exposure of the average smoker is roughly 10 times that from urban air pollution. In two studies, the ethylene levels in tavern air were 56 and 110 µg/m^3 while the corresponding outdoor air concentrations at the time were 16 and 12 µg/m^3.

(Person *et al*, 1988; Lofroth *et al*, 1989/IARC)

d) Plants that normally produce ethylene at 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.

(Dorffling, 1982; Tille *et al* 1985/IARC).

B.6.8.3.4 Endogenous formation

Endogenous production of ethylene can be deduced from its exhalation by unexposed subjects. For a man of 70 kg, a mean production rate of 32 nmol/hour (0.9 µg/hour) 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. 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.

(Filser *et al*, 1992; Harrison, 1981/IARC)

B.6.8.3.5 Adduct formation

a) The haemoglobin adducts N-(2-hydroxyethyl)histidine and N-(2-hydroxyethyl)valine have been used as internal dose monitors for the formation of ethylene oxide from ethylene in humans. Higher levels of adducts were found in cigarette smokers than in non-smokers and ethylene and ethylene oxide were considered to be major causes of the elevated adduct levels.

(Tornqvist *et al*, 1986b & 1989a/IARC 1994)

b) Non-smoking fruit store workers exposed occupationally to atmospheric ethylene at 0.023-3.85 mg/m^3 (0.02-3.35 ppm) while ripening bananas had levels of 22-65 pmol/g haemoglobin-(hydroxyethyl valine) whereas non-smoking controls had 12-27 pmol/g haemoglobin-(hydroxyethyl valine). On the basis of a mean exposure concentration of 0.345 mg/m^3 (0.3 ppm), it was estimated that about 3% (range 1-10%) of inhaled ethylene as metabolized to ethylene oxide. This percentage is in agreement with the alveolar retention at steady state calculated from pharmacokenitics. An increment of 100-120 pmol/g haemoglobin-(hydroxyethyl valine) was estimated for a time-weighted average exposure (40 hours/week) to 1.15 mg/m^3 (1 ppm) ethylene. On the basis of the relationship between haemoglobin-(hydroxyethyl valine) levels and exposure levels of ethylene and ethylene oxide, the amount of ethylene metabolised to ethylene oxide can be calculated; 1 mg ethylene/kg bw is equivalent to a tissue dose of ethylene oxide of 0.7 x 10^{-6} mol x h/l (0.03 mg x h/kg bw). This value is in agreement with the value of 0.5 x 10^{-6} mol x h/l that can be calculated from the pharmacokinetic data for ethylene and ethylene oxide published by Filser *et al*, 1992.

(Tornqvist *et al*, 1988 & 1989a; Kautiainen & Tornqvist, 1991; Filser *et al*, 1992/IARC 1994)

c) The following tabulated exposure data was presented in an article reviewing the current position with respect to some biomarkers and volatile organic chemicals (mainly 1,3-butadiene).

Table B.6.5 Haemoglobin adduct levels (N-terminal hydroxyethyl valine) in smokers and non-smokers and in subjects with occupational exposure.

[a]Controls	Exposure groups		
	Type of exposure	Exposure concentration	Adduct level (average, range)
Ethylene (pmol/g globulin)			
[b]Non-smokers 20 (12-27)	Occupational	0.3 (0.1-1) ppm	43 (22-65)
Non-smokers 16.1 ± 2.1	Tobacco smoking	1-25 cigarettes/day	146 (50-335)
Non smokers 63 ± 2.1	Tobacco smoking	>15 cigarettes/day	Maternal blood 361 ± 105
Newborn babies blood 42 ± 18			New born babies blood) 147 ± 105
Ethylene oxide (pmol/g globulin)			
14-26	Occupational	Low: 28 ppm/week	84-2070

Key a) Background levels (average, range or mean ± SD). b) See B.6.8.3.5 b above.

The accumulation of stable haemoglobin adducts during prolonged exposure is the result of daily increments to the adduct level and daily losses due to the removal of the oldest fraction of the erythrocytes from the circulation. After exposure for a period of time exceeding 126 days in humans, a steady-state adduct level is attained. Thus, the measurement of stable adducts gives information on exposure during the months before blood sampling. Tates *et al* (1995) studied hydroxyethylvaline adducts in haemoglobin of four workers accidentally exposed to high concentrations of ethylene oxide. The adduct levels decreased linearly over time and reached background levels after approximately 110 days. Contrary to protein adducts, DNA adducts are subjected to repair and their stability varies considerably between cell type. In the absence of information on adduct stability, DNA adduct measurements give only qualitative information on exposure.

(http://www.ehponline.org/members/1996/Suppl-5/osterman-golkar-full.html)

~~**B.6.8.3.6 Residue data for ethylene and its metabolites in potatoes**~~

~~a) Endogenous concentrations of ethylene range between 0.0007-0.15 ppm for non-sprouting potato tubers and 0.1-3ppm for sprouted tubers. It was also stated that ethylene and its potential metabolites were not identified in treated potatoes at levels exceeding those found in control potatoes. Residue data for potatoes treated with 4 ppm ethylene for 150 days of storage. The residues, chloroethanol, dichloroethane, bromoethanol, ethylene oxide and ethylene glycol (including its glucoside) residues were in total less than 0.1 ppm. Residues of ethylene oxide were stated to be <2 ppm (the lower limit of quantitation of the analytical method employed). In addition, the processing or cooking of tubers is expected to result in a reduction of volatile residues (e.g. ethylene oxide) by up to 90% (no actual data included in the report).~~

~~(HC 2001)~~

b) The internal levels of dissolved and absorbed ethylene in Anjou pears during ripening have been determined. No exogenous ethylene was applied in order to establish the endogenous level in the natural ripening process. In pears, the reported internal ethylene concentrations ranged from 0.02-44.66 µl/l.

(Wang and Mellenthin, 1972)

B.6.9 Medical data and information (IIA 5.9)

The following medical data and information for ethylene was provided. The data/information in this section has not been assessed by the RMS.

B.6.9.1 Medical surveillance of manufacturing plant personnel (AII 5.9.1)

Personal and stationary monitoring of ethylene in a company where ethylene was used for controlling the ripening of bananas showed air concentrations to be in the range of 0.02 - 3.35 ppm (0.02 - 3.85mg/m^3). 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. A study was carried out among workers at a Swedish petrochemical plant in order to assess the amounts and effects of ethylene exposure. The study was carried out in two parts, part one in 1989 and part two in 1993. Eight workers exposed to high levels of ethylene (4 mg/m^3) and 3 workers exposed to lower levels (0.1 - 0.3 mg/m^3) were compared to nine controls exposed to 0.01 mg/m^3. All exposed workers showed elevated levels of haemoglobin adducts and adduct formation was dose-related. The results indicated that about 1% of the inhaled ethylene was metabolized to ethylene oxide. Part two of the study, which included four workers, was designed to more accurately determine exposure level, which had a mean of 4.5 mg/m^3. The results confirmed part one, showing that about 1% of inhaled ethylene was metabolised to ethylene oxide and the maximum fraction to be converted was estimated to be 4%.

There have been two preliminary but independent reports of increased miscarriage rates among women working in the petrochemical industry. Elevated ethylene concentrations were mentioned as a possible reason, but this has not been confirmed. No firm conclusions can be drawn from these reports. A preliminary study found no increase in lung cancer incidence in 31 workers exposed to ethylene (at unspecified levels) at a US petrochemical factory. However, due to the limited number of exposed workers in this study no conclusions regarding ethylene not causing cancer can be

drawn. A study of workers at an US petrochemical plant found that an increased risk of developing brain cancer was associated with exposure to (unspecified levels of) a number of chemicals including ethylene. However, the investigators were unconvinced that the association reflected a causal relationship (OECD SIDS).

According to Toxnet (Databases in toxicology and environmental health) HSDB, 2003, it is estimated that 12,280 workers are potentially exposed to ethylene in the U.S.A.

B.6.9.2 Clinical cases and poisoning incidents (IIA 5.9.2)

Symptoms: dizziness, headache, nausea, and loss of co-coordination.

The following are clinical effects of acute exposure to ethylene, reported in the OECD SIDS assessment profile for ethylene:

ACUTE EXPOSURE: Simple asphyxiants displace oxygen from the breathing atmosphere primarily in enclosed spaces and result in hypoxia. Four stages are described, depending on the arterial oxygen saturation:

1) INDIFFERENT STAGE (% O_2 Saturation: 90%):

Night vision: decreased

2) COMPENSATORY STAGE (% O_2 Saturation: 82 to 90%)

1 Respiratory rate: compensatory increase
2. Pulse: compensatory increase
3. Night vision: decreased further
4. Performance ability: somewhat reduced
5. Alertness: somewhat reduced

Symptoms may begin in those with significant pre-existing cardiac, pulmonary, or haematological diseases

3) DISTURBANCE STAGE (% O_2 Saturation: 64 to 82%)

1. Compensatory mechanisms become inadequate
2. Air hunger
3. Fatigue
4. Tunnel Vision
5. Dizziness
6. Headache
7. Belligerence
8. Euphoria
9. Visual acuity: reduced
10. Numbness and tingling of extremities
11. Hyperventilation
12. Poor judgement
13. Memory loss
14. Cyanosis

Decreased ability for escape from toxic environment

4) CRITICAL STAGE (%O_2 Saturation: 60 to 70% or less):

1. Deterioration in judgement and coordination may occur in 3 to 5 minutes or less
2. Total incapacitation and unconsciousness follow rapidly

- All early effects may decrease ability for self-rescue from the toxic environment.
- Some agents causing asphyxia are stored and transported in compressed or liquid form and can cause frostbite on direct skin contact.

CARDIOVASCULAR EFFECTS

1) An increased pulse rate may occur.
2) Cardiac manifestations of prolonged or severe hypoxia may include atrial or ventricular dysrhythmias, hypotension, myocardial ischemia, myocardial infarction, and eventual aystole.
3) "Sudden sniffing death", or cardiac arrest, is reported following intentional inhalation of hydrocarbons.

RESPIRATORY EFFECTS

1) Hyperventilation may develop.
2) Cyanosis may occur.
3) Bronchoconstriction and respiratory depression may be seen.
4) Pulmonary oedema and lung congestion may occur.

NEUROLOGIC EFFECTS

1) Various disturbances including headache, dizziness, mood disturbances, numbness of the extremities, sleepiness, mental confusion, poor judgement and coordination, and memory loss may occur.
2) Prolonged or severe hypoxia results in unconsciousness.
3) Prolonged asphyxia may produce CNS injury.
4) Hemiparesis has been reported with volatile substance abuse.
5) Cerebral oedema with brainstem herniation may occur.
6) Seizures have been reported following intentional inhalation.

GASTROINTESTINAL EFFECTS: Nausea, vomiting, and gastrointestinal haemorrhage may develop

MUSCULOSKELETAL EFFECTS: Rhabdomyolysis and seizures have been reported.

REPRODUCTIVE HAZARDS**:** Possible consequence of oxygen deprivation in the unborn is controversial. Cerebral palsy, previously thought to be due to acute hypoxia during labour and/or childbirth, remains poorly understood.

There are also some acute hazard of dermal and ocular frost burns. Toxnet (Databases in toxicology and environmental health) HSDB, 2003, states that acute dermal exposure may cause frostbite injury. Severe tissue burns have been reported

B.6.9.3 Exposure of the general population and epidemiological studies (IIA 5.9.3)

Ethylene is ubiquitous in the environment, arising from both natural and man made sources. Major natural sources are emissions from vegetation of all types, where it functions as a plant hormone. The main anthropogenic sources are combustion of gas, fuel, coal and biomass. The highest exposure to humans is due to ethylene from car motors. Ethylene had been in general use as an anaesthetic for many years. It has been replaced by more modern anaesthetics, mostly due to the high explosion risk. Today, elevated exposure of humans is limited to a low number of workers at ethylene protection plants, and these involved in transport of ethylene. The total global emission has been estimated to be 18-45 x 10^6 t/y, of which approximately 74% is released from natural sources and 26% from anthropogenic sources. Emission from fuel oil combustion is equal to approximately 4% of total global emissions (OECD SIDS).

In an epidemiological study, following exposure to ethylene, no increase in risk of developing myelomas was noted.

B.6.9.4 Clinical signs, symptoms of poisoning and details of clinical tests (IIA 5.9.4)

Symptoms included dizziness, headache, nausea, and loss of co-coordination. Please refer to sections B.6.9.2 and B.6.9.3.

B.6.9.5 First aid measures (IIA 5.9.5)

Move the victim to fresh air and call the medical emergencies services. Give artificial respiration if the victim is not breathing or administer oxygen if breathing is difficult. Remove and isolate contaminated clothing and shoes. In case of contact with liquefied gas, thaw frosted parts with lukewarm water. In case of burns, immediately cool affected skin for as long as possible with cold water. Do not remove clothing if adhering to the skin. Keep the victim warm and quiet. Ensure that medical personnel are aware of the material involved and take precautions to protect themselves (US Department of Transport, 2004).

Inhalation: Move to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention immediately.

Skin Contact: Wash affected area extremely thoroughly with soap and water. Seek medical attention if irritation persists. Remove all contaminated clothing.

Eye Contact: Rinse immediately with copious amounts of tepid water for at least 15 minutes and obtain medical aid.

Ingestion: Not applicable Ethylene is a gas at normal temperature and pressure.

B.6.9.6 Expected effects and duration of poisoning as a function of the type, level and duration of exposure or ingestion (IIA 5.9.6)

Under environmental conditions, ethylene is a gas; therefore the most probable route of human exposure is via inhalation. There is no evidence to suggest ethylene is an eye or skin irritant.

Concentrations of less than 20% ethylene in air (25000 ppm) do not cause harmful effects and are not irritating to the nose, throat or lungs. High concentrations of ethylene can displace oxygen in air and cause life-threatening asphyxiation. When ethylene is used as a compressed gas, high concentrations can be generated quickly if a leak occurs.

The normal oxygen concentration in air is 20.9%. At 15-16% oxygen, symptoms of sleepiness, fatigue, loss of concentration, errors in judgement and confusion are masked by a state of euphoria, giving a false sense of security and well-being. An oxygen concentration of 12% or lower can cause unconsciousness quickly and without warning. In some cases disturbed respiration, abnormal fatigue. Emotional upsets, nausea, vomiting and inability to move freely may occur. Concentrations below 6% can result in respiratory collapse and death. If the victim survives, some or all organs, including the central nervous system and brain, may show damage due to oxygen deprivation.

Marked memory disturbances have also been reported following exposure to 37.5% (37500 ppm) of ethylene for 15 minutes (this effect may have been due to oxygen deprivation) (CCOHS, 2000).

Animal toxicity information suggests that ethylene will not cause significant health effects following long-term exposure.

B.6.10 Summary of mammalian toxicology and proposed ADI, AOEL, ARfD and MAC (drinking water limit) (IIA 5.10)

No oral ADME studies have been submitted or cited; the available data has been generated using inhalation exposure. A metabolic pathway has not been proposed for ethylene in mammals.

Following inhalation of radiolabelled parent, absorption appeared to be rapid (within minutes) but the systemic uptake from the lungs was low. It has been estimated that approximately 83% of the ethylene that reaches the lungs is exhaled unchanged while 17% is absorbed. Distribution is widespread throughout the body. In rats, about 24-29% of systemically available ethylene is eliminated by metabolism and the remainder by exhalation of the unchanged substance. Elimination appears to be rapid. Most of the inhaled ethylene was exhaled unchanged with smaller amounts excreted in urine and faeces and as exhaled carbon dioxide. Apart from ethylene oxide and its metabolites [and the urinary metabolite 5-(2-hydroxyethyl)cysteine in mice], there appears to be little or no information or investigations into other potential metabolites of ethylene.

Ethylene is not classifiable via the acute inhalation route according to EC criteria (based on cited data). There are insufficient data to classify ethylene via the acute oral and dermal routes or for skin and eye irritancy and skin sensitisation using the normal EC criteria. However, based on industrial use and its use as an anaesthetic,

ethylene gas dose not appear to be classifiable as a skin or eye irritant or a skin sensitiser. It should be noted that liquefied or pressurized ethylene gas can cause frostbite damage.

No data were submitted for the oral or dermal routes for short-term exposure (or cited from the published literature). The available short term repeat dose inhalation studies reported effects on blood parameters and the nervous system. A 90-day study did not report any effects at dose levels up to 11.5 mg/l of air, the highest dose tested (this study may have been conducted by IBT under contract to the CIIT (see comments on carcinogenicity study).

There was no evidence genotoxicity in the *in vitro* bacterial and chromosome aberration assays or the *in vivo* the bone marrow micronucleus assays in rats or mice.

No long-term studies were submitted for the oral route of exposure (or data cited from the published literature). Summaries of a single long-term rat inhalation study are available in the literature. Generally, the authors of these summaries have concluded that there no evidence of chronic toxicity in this study and no evidence of compound-induced carcinogenicity. However, some authors have expressed doubts over the quality and reporting of the study (conducted by the discredited contract laboratory IBT), the interpretation of the findings in this study (e.g. mononuclear cell leukaemia) and their relationship to the toxicological effects induced by the metabolite ethylene oxide. The background to IBT can be found at section 3.1.8 of http://www.oecd.org/dataoecd/13/15/36045203.pdf]. IARC (1994) concluded that the evidence of carcinogenicity in experimental animals and humans was inadequate, however, several workers have stated that the possible carcinogenic risk from inhaling ethylene should be reconsidered/re-evaluated based on the potential exposure to ethylene (very high tonnage), the limited database and the metabolism of ethylene to ethylene oxide.

The available reproduction data are limited and the quality is equivocal. A reproductive screen test concluded there was no compound induced parental or foetal toxicity or developmental toxicity over a single generation (i.e. up to 4 days post partum) at concentrations up to 5.75 mg/l or 5000 ppm (approximately equivalent to a systemic exposure of 0.575 mg/l or 500 ppm). However, some published data (of unknown quality) appears to indicate that post-natal development could be adversely affected at a dose level of 2.62 ppm.

No specific neurotoxicity studies have been submitted for evaluation but there are some indications of treatment-related effects on the nervous system.

Ethylene is metabolised to ethylene oxide in experimental animals. Two metabolic pathways have been identified in experimental animals and humans, the hydrolysis of ethylene oxide to 1,2-ethanediol and conjugation with glutathione to produce S-(2-hydroxyethyl)cysteine and N-acetyl- S-(2-hydroxyethyl)cysteine (Fig B.6.3). Since ethylene oxide can react with chloride ions, and this reaction is acid catalysed, 2-chloroethanol might be expected to be a metabolite, especially after oral administration.

Ethylene oxide is currently classified by the ECB as a Cat: 2 for carcinogenicity (R45) and Cat: 2 for mutagenicity (R46). In addition, the literature indicates that ethylene oxide induces reproductive effects in experimental animals (foetal toxicity in the presence and absence of maternal toxicity, teratogenicity in mice, sperm effects) and there is some limited evidence of spontaneous abortions in humans. Ethylene oxide has also been associated with neurotoxicity and cataracts in the ocular lens. It is also currently classified by the ECB as Toxic by inhalation (R23) and as an irritant (R36/37/38) and the literature also indicates that it can also induce sensitisation responses. Chloroethanol, a possible reaction product with chloride in food, is also currently classified by the ECB as a Cat:2 carcinogen.

Ethylene oxide is an electrophilic agent that alkylates nucleophilic groups in biological macromolecules, i.e. including DNA and protein (e.g. haemoglobin & albumin). It is considered likely that the toxicological effects of ethylene oxide arise primarily from the direct alkylation of macromolecules. Since ethylene oxide is formed during the metabolism of ethylene (a natural body constituent) both endogenous and exogenous sources of ethylene and ethylene oxide will contribute to the background alkylation of macromolecules. There is extensive evidence of genotoxicity (*in vitro* and *in vivo* effects) and carcinogenicity indicating that ethylene oxide is a potent genotoxic carcinogen in experimental animals (via oral and inhalation routes).

Endogenous, environmental and man-made sources of ethylene exposure are well documented in the literature. Ethylene is a natural product of many plants and it is released into the atmosphere at various stages of their life cycle. Other major sources contributing to background levels of ethylene are industrial and volcanic emissions, natural gas, the burning of vegetation, smoking cigarettes, the combustion of fossil fuels (including vehicle exhaust emissions) and in food materials. Endogenous but unidentified sources of ethylene exist in man and experimental animals.

Although ethylene is classified as a “simple asphyxiant” and results in asphyxia due to oxygen displacement in enclosed spaces, the extensive list of adverse effects in humans (B.6.9) indicates that this is an oversimplification and requires further consideration. Ethylene is metabolised to ethylene oxide, a known genotoxic carcinogen, and forms adducts with DNA, haemoglobin and other proteins. The U.S. Department of Labor (Occupational Safety & Health Administration) web site states that the health effects of long-term or repeated exposure to ethylene are not known (www.osha.gov). Occupational exposure has been associated with an increased incidence of reproductive effects and brain tumours in workers in the petrochemical industry but the quality of these epidemiological studies was questioned and it was concluded that there was no convincing evidence of any causal links. However, non-smoking fruit store workers exposed occupationally to atmospheric ethylene had higher levels of haemoglobin adducts compared to non-smoking controls.

No specific occupation exposure limits have been recommended in the UK or in most developed countries but Switzerland has established a time-weighted average occupational limit of 11500 mg/m^3 (OECD: SIDS). In Germany, no exposure limit is given for ethylene because it is ‘justifiably suspected of having carcinogenic potential’ (Deutsche Forschungsgemeinschaft, 1993/IARC 1994).

B.6.10.1 Acceptable Daily Intake (ADI)

Although ethylene is an important industrial chemical, there appears to be only a limited number of standard toxicity studies and human epidemiology studies in the public domain. No oral toxicity studies are available for ethylene. The majority of the available data have been generated using inhalation exposure and the various international regulatory authorities appear to have relied upon the 2-year rat inhalation study to conclude that ethylene is not a carcinogen. In addition, the cited regulatory authorities have relied upon metabolism data generated from acute/short-term inhalation studies to estimate the predicted conversion of ethylene to ethylene oxide.

Since there are insufficient data to set an ADI for ethylene, any approvals for the use of ethylene as a growth regulator used to ripen bananas must be dependant on the residue levels of ethylene and its metabolites after treatment being no greater than the normal background rates in potatoes and bananas~~. The Health Canada (2001) document states that analytical data for ethylene and its potential metabolites in ethylene treated potatoes were either non-detectable or were at similar levels to any measurable residues found in controls (no actual exposure levels or analytical results were included in the document).~~

No analytical data was submitted for ethylene treated bananas which would substantiate that the residue levels were equal to or similar to untreated bananas. Without these relevant residue data, it is not possible to conclude that the use of ethylene for the requested uses would not present an unacceptable risk to human health.

As indicated by the Health Protection Branch of Health Canada in the "Health and Safety Status Report" for ethylene (May 1994), an acceptable daily intake (ADI) is not required for ethylene, since it is a naturally occurring chemical produced by fruits and vegetables, including potatoes, during senescence. Ethylene is also a naturally occurring endogenous chemical in humans and laboratory animals and has been identified in the air exhaled by unexposed rats and humans. Potential ethylene metabolites have also been shown to occur naturally. Analytical data for these metabolites in treated potatoes showed that residue levels were either non-detectable or were at levels similar to any measurable residues found in controls (Health Canada, 2001).

B.6.10.2 Acute Reference Dose (ARfD)

There are insufficient data to set an ARfD. Apart from the formation of adducts, there are no clear obvious effects of acute exposure presented in the literature and the relevant data for oral exposure is sparse or non-existent. Approval is therefore dependant on the residue levels of ethylene and its metabolites after treatment being no greater than the normal background rates in bananas.

The following was proposed:

An acute reference dose (ARfD) was not established, since ethylene was considered unlikely to present an acute hazard. The available literature suggests that there are no significant treatment-related findings to indicate a concern in acute dietary risk

assessment. The potential risks to humans from exposure to ethylene are considered negligible due to low toxicity concerns and the widespread use of ethylene as an anaesthetic with little concomitant toxicity (Health Canada, 2001).

B.6.10.3 Admissible Operator Exposure Level (AOEL)

There is insufficient data to set an AOEL. However, the current occupational exposure levels and application methods suggest that the use of ethylene is acceptable. However due to some reports of increased levels of haemoglobin adducts in fruit plant workers, it is recommended that exposures be kept as low as reasonably achievable e.g. use of RPE or engineering controls.

B.6.10.4 Maximum Allowable Concentration (MAC: drinking water limit)

There are insufficient data to set a health based limit. The EU limit for the concentration of any pesticide in drinking water is 0.1 μg/l.

B.6.10.5 Classification and labelling

B.6.10.5.1 Ethylene

a) Current ECB classification

R67	Vapours may cause drowsiness and dizziness.
S2	Keep out of the reach of children
S46	If swallowed, seek medical advice immediately and show this container or label.

b) Proposed classification

Ethylene is converted into ethylene oxide in rats (5-10%) and humans (estimated values of <4%). The data base is inadequate to conclude a robust proposal for the classification of ethylene for carcinogenicity and reproductive toxicity. However, assuming that humans metabolise ethylene to ethylene oxide, in the absence of data on ethylene, the classification could take account of the potential ethylene oxide exposure.

c) Classification of liquefied or pressurised ethylene

Liquefied or pressurized ethylene gas can cause frostbite damage (this may trigger part of the risk phrase RSh Directive 2003/82/EC).

B.6.10.5.2 Ethylene oxide

Current ECB classification

CAT: 2 carcinogenicity & CAT: 2 mutagenicity

R23	Toxic by inhalation
R36/37/38	Irritating to eyes, respiratory system and skin
R45	May cause cancer
R46	May cause heritable genetic damage
S45	If swallowed or if you feel unwell, seek medical advice immediately (show the label where possible).
S53	Avoid exposure-Obtain special instructions before use.

B.6.10.5.3 1,2-ethanediol (ethylene glycol)

Current ECB classification

R22	Harmful if swallowed
S2	Keep out of reach of children

B.6.10.5.4 1,2-dichloroethane (ethylene dichloride)

Current ECB classification

CAT: 2 carcinogenicity

R22	Harmful if swallowed
R36/37/38	Irritating to eyes, respiratory system and skin
R45	May cause cancer
S45	In the case of accidents or if you feel unwell seek medical advice immediately (show the label where possible).
S53	Avoid exposure-Obtain special instructions before use.

B.6.11a Acute toxicity, irritancy and skin sensitisation of the 'Ethylene' (IIIA 7.1)

'Ethylene' in cylinders contains 60 g/kg ethylene (99.9% purity) and 940 g/kg nitrogen. A single source is used by all five notifiers (i.e. Air Liquide, Air Products, Coleacp, Linde Ag and Praxair).

B.6.11.1a Acute oral toxicity in rats (AIII 7.1.1)

No studies submitted.

B.6.11.2a Acute dermal toxicity (AIII 7.1.2)

No studies submitted.

B.6 11.3 Acute inhalation toxicity (AIII 7.1.3)

No studies submitted.

B.6.11.4a Skin irritancy (AIII 7.1.4)

No studies submitted

B.6.11.5a Eye irritancy (AIII 7.1.5)

No studies submitted.

B.6.11.6a Skin sensitisation (AIII 7.1.6)

No studies submitted.

B.6.11.7a Summary of the toxicity of ethylene

Apart from the dangers of asphyxiation in confined spaces and potential frost bite injury, the potential acute toxicity, irritation and skin sensitisation effects of this product are likely to be limited to those induced by ethylene gas.

B.6.11.8a Toxicological data on non active substances (IIIA 7.4)

The nitrogen may cause asphyxiation at high concentrations in enclosed spaces due to oxygen deficiency. The symptoms of oxygen deficiency include respiratory difficulty, ringing in ears, headaches, shortness of breath, wheezing, headache, dizziness, indigestion, nausea, and at high concentrations, unconsciousness or death may occur.

B.6.11.9a Proposal for classification and labelling

Apart for the observation that liquefied or pressurized ethylene gas can cause frostbite damage (this may trigger part of the risk phrase RSh Directive 2003/82/EC), no classification is proposed for the acute toxicity, irritation or skin sensitisation of 'Ethylene' (a mixture of ethylene and nitrogen).

B.6.12a Dermal absorption studies (IIIA 7.3)

Not applicable.

B.6.13a Toxicological data on non active substances (IIIA 7.4)

There are no hazard warnings on the MSDS that give rise to toxicological concerns with respect to the classification of 'Ethylene Gas' (a mixture of ethylene and nitrogen).

B.6.11b Acute toxicity, irritancy and skin sensitisation of 'Restrain Generator Fuel' (IIIA 7.1)

The notifier of 'Restrain Generator Fuel' states that it contains 96% ethanol (i.e. food grade ethanol without any denaturant); the product is used to generate ethylene using a catalytic generator.

B.6.11.1b Acute oral toxicity in rats (AIII 7.1.1)

No studies submitted.

B.6.11.2b Acute dermal toxicity (AIII 7.1.2)

No studies submitted.

B.6 11.3b Acute inhalation toxicity (AIII 7.1.3)

No studies submitted.

B.6.11.4b Skin irritancy (AIII 7.1.4)

No studies submitted.

B.6.11.5b Eye irritancy (AIII 7.1.5)

No studies submitted.

B.6.11.6b Skin sensitisation (AIII 7.1.6)

No studies submitted.

B.6.11.7b Summary of the toxicity of 'Restrain Generator Fuel'

The acute toxicity, irritation and skin sensitisation effects of 'Restrain Generator Fuel' are driven by the ethanol content of the product. For a full evaluation of ethanol, please refer to the Ethanol Draft Assessment Report.

Ethanol is considered to be of low toxicity via the acute oral, dermal and inhalational routes. It is not a skin irritant or a skin sensitiser but there is some evidence that ethanol is an eye irritant and a respiratory irritant. Therefore, 'Restrain Generator Fuel' is classifiable as an eye irritant and a respiratory irritant based on the ethanol content.

B.6.11.8b Toxicological data on non active substances (IIIA 7.4)

The available data and information on denatured ethanol do not give rise to toxicological concerns with respect to the classification of 'Restrain Generator Fuel'.

B.6.11.9b Proposal for classification and labelling

Based on the ethanol content, 'Restrain Generator Fuel' is classifiable as given below in subsection (a). This level of classification for the carcinogenicity, mutagenicity and reproductive toxicity of ethanol is supported by publicly available animal and human data. Further discussion is presented in the Ethanol Draft Assessment Report. The current ECB classification is presented below in subsection (b).

a) Classification currently being considered by the ECB

Hazard symbol(s) T

Indication of danger: Toxic

Risk phrases:

R36/37	Irritating to eyes and respiratory system.
R45 (CAT 1or 2: Carcinogen)	May cause cancer
R46 (CAT 2: Mutagen)	May cause heritable damage
R60 (CAT 1: Reproductive toxin)	May impair fertility
R61 (CAT 1: Reproductive toxin)	May cause harm to the unborn child
R64 (CAT 1: Reproductive toxin)	May cause harm to breast-fed babies

Safety phrases:

S2: Keep out of the reach of children.
S53: Avoid exposure-Obtain special instructions before use.
S45: In case of accident or if you feel unwell seek medical advice immediately (show the label where possible).

b) Current ECB classification of ethanol

According to the ECB web site, ethanol is currently unclassified for health effects

Note: The RMS is aware that the International Agency for Research on Cancer (IARC) is currently preparing an up-dated monograph on the carcinogenic effects of alcohol which is expected to be published in the near future.

B.6.12b Dermal absorption studies (IIIA 7.3)

In the absence of data, a dermal absorption value of 100% is proposed for the operator exposure calculations.

B.6.13b Toxicological data on non active substances (IIIA 7.4)

The notifier of 'Restrain Generator Fuel' states that this product contains 96% ethanol (i.e. food grade alcohol without a denaturant); therefore, any other minor constituents are unlikely to give rise to toxicological concerns with respect to classification.

B.6.14 Exposure data (IIIA 7.2)

Ethylene

The supported use of ethylene is as a plant growth regulator, intended for use in degreening and ripening of bananas. It is applied via compressed gas cylinders containing ethylene and nitrogen or by a catalytic generator. This produces ethylene by converting liquid fuel (ethanol) to ethylene gas and water vapour. Ethylene is applied in hermetic ripening rooms. The target concentrations for the two methods of generation are sufficiently similar to allow the major conclusions drawn vis-à-vis the scenario involving ethylene introduced from gas cylinders to apply to ethylene produced from ethanol. Exposure to ethanol from handling the product and preparing the generator equipment is considered in the Draft Assessment Report for ethanol.

	Target concentration	Source of information
Cylinders (ethylene gas)	600 – 1000 ppm	GAP table
Generator (ethanol)	4 – 1200 ppm	Label for 'Ethygen II'

Table 6.14.1 – Comparison of target concentrations achieved with two forms of ethylene generation

Ethylene is not classifiable via the acute inhalation route according to EC criteria (based on cited data). There are insufficient data to classify ethylene via the acute oral and dermal routes or for skin and eye irritancy and skin sensitisation using the normal EC criteria. However, based on industrial use and its use as an anaesthetic, ethylene gas dose not appear to be classifiable as a skin or eye irritant or a skin sensitiser. Liquefied or pressurized ethylene gas can cause frostbite damage (B.6.10).

There is insufficient data available to set an AOEL for ethylene (B.6.10.3).

Ethylene oxide

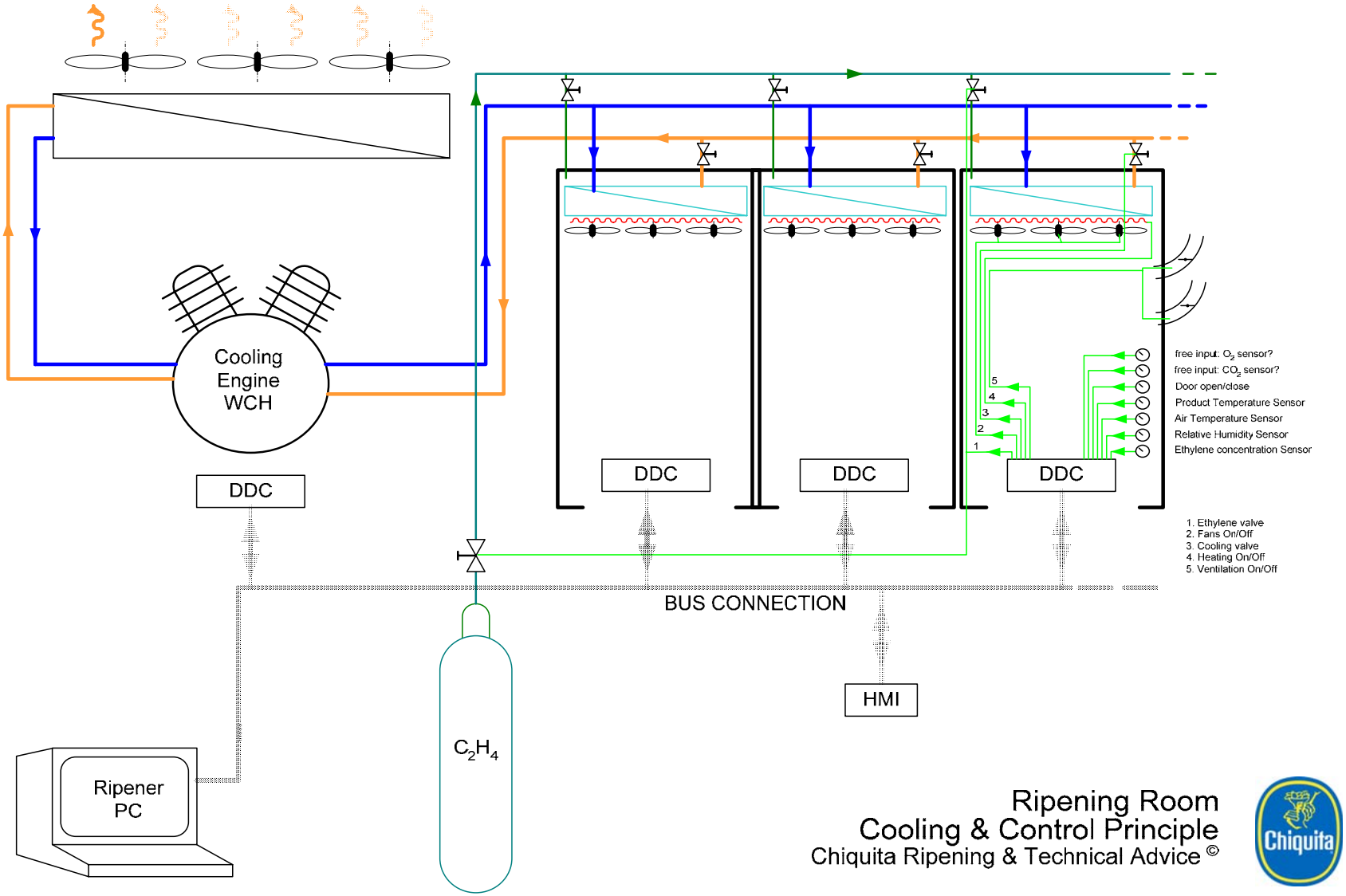
Ethylene oxide has been identified as a metabolite of ethylene (B.6.13). Ethylene is converted into ethylene oxide in rats (5-10%) and humans (estimated values of <4%) This metabolite is of toxicological concern and is therefore considered as part of this exposure assessment.

Ethylene oxide is currently classified by the ECB as a Cat: 2 for carcinogenicity (R45) and Cat: 2 for mutagenicity (R46). It is also currently classified by the ECB as Toxic by inhalation (R23) and as an irritant (R36/37/38) and the literature also indicates that it can also induce sensitisation responses.

Supported use

A summary of the treatment process is given below ;

Fig. 6.14.1.1 – A typical banana ripening installation



The gas is released from a number of cylinders and flow controlled by solenoid valves, one in the supply line after the cylinders and one in the line leading into each room in the store.

Fig. 6.14.1.2 – Ethylene station and cylinders

Fig. 6.14.1.3 Secondary solenoid valve controlling entry to a store room

(Note the cut-off valve which can be used if the secondary solenoid valve is broken.)

The valves are opened by direct digital controllers (DDCs). As the default position of both primary and secondary valves is 'closed' it is unlikely that ethylene will be accidentally released. Equipment is also incorporated which reduces the gas pressure from 200 bar in the supply tanks to 5 bar in the pipes and will alert the operator when the ethylene mixture is depleted.

The concentration of ethylene in the application room is monitored continuously and remotely by trained operators, to ensure the concentration remains near the target level throughout the application period. Typically, these are fully automated (computer controlled) systems which include automated door-locking mechanisms, which do not allow the doors to be opened when the treatment process is ongoing. Consequently, persons will not be present during the treatment process.

B.6.14.1 Operator exposure (IIIA 7.2.1)

Potential occupational exposure to ethylene may occur when entering the application room or its ventilation ductwork (e.g., for repair) after application of ethylene or when standing near the ventilation exhaust. This exposure scenario is considered under Worker exposure (B.6.14.3).

It is also possible that exposure could occur when handling the cylinders, for instance during changeover. The primary route of exposure would be via inhalation. Potential exposure to high concentrations of ethylene may occur in the event of a leak into an enclosed space. The proposed label includes precautionary statements regarding proper handling of the cylinders and gas release system to avoid leaks. Respiratory protection for entry into an area of unknown ethylene concentration is recommended on the draft label.

Although the primary route of exposure would be through inhalation, liquefied or pressurized ethylene gas can cause frostbite damage. In industry, however, PPE is normally worn to mitigate the risk of physical injury which could be caused by the heavy cylinders; gloves and safety footwear are typical. Gas leakages are considered accidental occurrences and not a risk encountered during normal procedures. However, eye protection as a precaution is a simple and prudent measure. Taking these factors and the low acute toxicity of ethylene gas into account, it is therefore recommended that for handling the gas cylinders the following PPE should be worn:

- Eye protection and suitable protective gloves.

B.6.14.2 Bystander exposure (IIIA 7.2.2)

As the treatment is made indoors in sealed rooms members of the public will not be present at the site of application. However, workers, who may not be not directly involved in the treatment operation, may be working close to areas where a treatment is taking place and could be exposed via leakages from stores via door seals (the label states the ripening room should be reasonably air-tight). Bystander exposure could also occur during the venting of the gas into the atmosphere after treatment.

No information is available to quantify these potential sources of exposure for bystanders.

B.6.14.3 Worker exposure (IIIA 7.2.3)

The automated nature of the treatment process means entry into treatment rooms is prevented until treatment has been completed and the room ventilated. Workers may then enter the rooms for inspection tasks or maintenance purposes. The exposure levels experienced by these workers will be largely dependent on the efficient functioning of the ventilation system.

Personal and stationary monitoring of ethylene in a company where this gas was used for controlling the ripening of bananas showed air concentrations (after ventilation of the treatment room) to be in the range of 0.02-3.85 mg/m^3 (0.02-3.35 ppm) with an estimated average concentration of 0.35 mg/m^3 (0.3 ppm).

(Tornqvist *et al* , 1989a/IARC)

B.6.14.4 Conclusions

In the absence of appropriate data it is not possible to quantify the exposure to ethylene which might be experienced by operators handling and changing cylinders, but due to the design of the systems involved, this is expected to be minimal under normal circumstances. It is prudent to mitigate any risk of physical injury and from an accidental release by the use of appropriate PPE (gloves and eye protection). RPE may be identified as necessary in some circumstances, for example when entering areas with unknown concentrations of ethylene.

There is uncertainty with regards to the levels of exposure which might be experienced by bystanders either due to leakages during treatment or during ventilation of the treatment room and by workers re-entering treated stores after ventilation as only limited exposure data are available. In a Swedish petrochemical plant (B.6.9.1) eleven workers exposed to levels of ethylene between 0.1 and 4 mg/m^3 showed dose-related increases in haemoglobin adduct formation. A study of fruit store workers (B.6.8.3.5) exposed to ethylene concentrations of 0.02-3.35 ppm showed similar increases in adjunct levels in relation to the control subjects. The concentrations which appear to have produced these effects are similar to the atmospheric concentrations of ethylene measured in fruit stores where ethylene has been used in the manner proposed (B.6.14.3). The presence of the haemoglobin adducts is evidence that some exposure to ethylene (and subsequently the oxide) has occurred. The significance of this exposure is unclear. However, there is some evidence that adduct levels occurring in fruit store workers are similar to the background levels measured in other sections of the population (refer to Table B.6.5). There is also evidence that dietary intake of ethylene may involve acute exposure to much higher concentrations than those encountered in fruit stores after venting; for instance, fully ripe pears may produce internal concentrations of the order of 40 ppm (Wang and Mellenthin, 1972).

In conclusion, the supported use for fruit ripening involves practical steps to minimise exposure to ethylene. The actual levels of exposure for fruit store workers are uncertain. Whilst treatment is essentially an automated, closed, operation, exposure levels for workers are expected to vary between fruit stores, i.e. some stores will be more airtight than others and some will be fitted with better ventilation systems. Member States may wish to investigate these exposure levels further.