PROPYLENE OXIDE

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

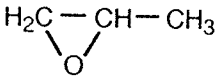
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 75-56-9
Chem. Abstr. Name: Methyloxirane
IUPAC Systematic Name: Propylene oxide
Synonyms: Epoxypropane; 1,2-epoxypropane; 2,3-epoxypropane; methyloxacyclopropane; propene oxide; propylene epoxide; 1,2-propylene oxide

1.1.2 *Structural and molecular formulae and relative molecular mass*



C_3H_6O Relative molecular mass: 58.08

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid (Kahlich *et al.*, 1993)
(*b*) *Boiling-point*: 34.3 °C (Lide, 1991)
(*c*) *Melting-point*: –112.1 °C (Beratergremium für umweltrelevante Altstoffe, 1993); –111.93 °C (Kahlich *et al.*, 1993)
(*d*) *Density*: 0.859 at 0 °C/4 °C (Lide, 1991); 1.44 g/L at 20 °C (vapour) (Kahlich *et al.*, 1993)
(*e*) *Spectroscopy data*: Infrared [prism, 387; grating, 15270], nuclear magnetic resonance, ultraviolet and mass spectral data have been reported (Weast & Astle, 1985; Sadtler Research Laboratories, 1991).
(*f*) *Solubility*: Soluble in water (40.5 wt% at 20 °C), acetone, benzene, carbon tetrachloride, diethyl ether and ethanol (American Conference of Governmental Industrial Hygienists, 1991; Lide, 1991; Kahlich *et al.*, 1993)

(*g*) *Volatility*: Vapour pressure, 58.8 kPa at 20 °C (Kahlich *et al.*, 1993)
(*h*) *Stability*: Lower explosive limit (in air), 2.3%; highly inflammable; inflammable concentrations of vapour form readily at room temperature (Kahlich *et al.*, 1993)
(*i*) *Reactivity*: May polymerize violently; very reactive, particularly with chlorine, ammonia, strong oxidants and acids (WHO, 1985; Kahlich *et al.*, 1993)
(*j*) *Octanol/water partition coefficient (P)*: log P, 0.03 (Sangster, 1989)
(*k*) *Conversion factor*: $mg/m^3 = 2.38 \times ppm$[a]

1.1.4 *Technical products and impurities*

Propylene oxide exists in two optical isomers, and commercial propylene oxide is a racemic mixture. The purity of the commercial product is > 99.9% (Kahlich *et al.*, 1993). Typical product specifications are: water, 500 mg/kg max.; aldehydes (total of acetaldehyde and propionaldehyde), 100 mg/kg max.; chlorides (as chlorine), 40 mg/kg max.; acidity (as acetic acid), 20 mg/kg max.; and specific gravity (20 °C/20 °C), 0.829–0.831 (Dow Chemical Co., 1993).

1.1.5 *Analysis*

Propylene oxide is detected and measured in workplace air by packed column gas chromatography with a flame ionization detector. The sample is adsorbed on charcoal and desorbed with carbon disulfide. This method (NIOSH Method 1612) has an estimated limit of detection of 0.01 mg per sample (Eller, 1985).

Biological monitoring of occupational exposure to propylene oxide by analysis of blood has been reported. These methods involve the determination of the haemoglobin (Hb) adducts *N*-(2-hydroxypropyl)cysteine, *N*-(2-hydroxypropyl)histidine and *N*-(2-hydroxypropyl)valine by gas chromatography–mass spectrometry or capillary gas chromatography with selective ion monitoring mass spectrometry (Osterman-Golkar *et al.*, 1984; Bailey *et al.*, 1987; Kautiainen & Törnqvist, 1991).

Residues of propylene oxide in ethoxylated surfactants and demulsifiers have been determined by headspace gas chromatography with flame ionization detection (Dahlgran & Shingleton, 1987).

1.2 Production and use

1.2.1 *Production*

The selection of a production route for propylene oxide is influenced by the application and market potential of co-products and by the availability of raw materials and possibilities for by-product management. The techniques so far developed can be divided into: chlorohydrin processes, indirect oxidation processes and direct oxidation processes. Only the chlorohydrin and indirect oxidation processes are practised currently on an industrial scale. It

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

has not been possible so far to produce propylene oxide in a technically and economically satisfactory manner by direct gas-phase oxidation (with silver catalysts), in analogy with the process used for ethylene oxide. Common to all current propylene oxide process techniques is the fact that significant amounts of co-products are always generated. In the conventional chlorohydrin process, up to 2 mol of salt (sodium or calcium chloride) in the form of dilute brine solution are generated per mole of propylene oxide. In the case of the direct oxidation methods, complex organic mixtures arise which must then be separated by distillation and either sold, further converted or incinerated. Indirect oxidation techniques also involve the formation of some by-products (Kahlich *et al.*, 1993).

Commercial production of propylene oxide began in the early 1900s, by the chlorohydrin process involving the dehydrochlorination of propylene chlorohydrin with a base. The chlorohydrin process is carried out in two steps: synthesis of propylene chlorohydrin from propylene and chlorine in water and subsequent dehydrochlorination of propylene chlorohydrin to propylene oxide (Kahlich *et al.*, 1993).

Several reaction routes and process alternatives for the production of propylene oxide by indirect oxidation have been reported, but only a few are practised on an industrial scale. Indirect oxidation is a two-step process: (i) formation of hydrogen peroxide or an organic peroxide from a suitable alkane, aldehyde or acid; and (ii) use of the peroxide as a selective oxidizing agent in the epoxidation of propylene to propylene oxide, with formation of a commercially useful co-product, the corresponding alcohol or acid (Kahlich *et al.*, 1993).

In one indirect oxidation process, ethylbenzene is reacted with oxygen to form ethylbenzene hydroperoxide. This product is subsequently used to epoxidize propylene to propylene oxide and methyl benzyl alcohol. In an alternative process, isobutane is substituted for ethylbenzene and, through analogous chemistry, *tert*-butanol is the co-product. Methyl benzyl alcohol and *tert*-butanol can then be dehydrated to styrene monomer and isobutylene, respectively (ARCO Chemical Co., 1993).

Information available in 1991 indicated that propylene oxide was produced by seven companies in Japan, six in Germany, four in China and the USA and one each in Brazil, Canada, France, Italy, the Netherlands, the Republic of Korea, Spain and the former Yugoslavia (Chemical Information Services Ltd, 1991). Production figures available for Germany, Japan and the USA are presented in Table 1; worldwide capacity for the production of propylene oxide is presented in Table 2.

1.2.2 *Use*

Propylene oxide is an important basic chemical intermediate. Nearly all of the propylene oxide produced is converted into derivatives, often for applications similar to those of ethylene oxide derivatives. Propylene oxide is used primarily to produce polyether polyols, propylene glycols and propylene glycol ethers. It is certified for use as a package fumigant for dried fruits and as a bulk fumigant for foodstuffs such as cocoa, spices, processed nutmeats, starch and gums; it may be used alone or in mixtures with carbon dioxide. Use patterns for propylene oxide in the USA, which are typical of those for the world market, are presented in Table 3 (Kirk & Dempsey, 1982; Kahlich *et al.*, 1993).

Table 1. Reported production of propylene oxide in selected countries

Country	Production (thousand tonnes)					
	1982	1984	1986	1988	1990	1992
Germany	NR	491	533	549	591	556
Japan	NR	210	225	288	336	323
USA	753	NR	NR	NR	NR	NR

From Mannsville Chemical Products Corp. (1984); Japan Chemical Week (1985); Anon. (1987a, 1989); Japan Chemical Week (1987, 1989, 1991); Anon. (1993a); Japan Petrochemical Industry Association (1993); NR, not reported

Table 2. World capacity for production of propylene oxide in 1991

Country or region	Process	Capacity (thousand tonnes/year)
Americas		1735
Brazil	Chlorohydrin, with lime	150
Canada	Chlorohydrin, with NaOH	60
USA	Styrene	270
	tert-Butyl alcohol	550
	Chlorohydrin, with NaOH	700
	Direct oxidation	5
Asia		563
China	Chlorohydrin, with lime	68
India	Chlorohydrin, with lime	24
Japan	Styrene	140
	Chlorohydrin, with lime	216
Republic of Korea	Styrene	100
Taiwan	Chlorohydrin, with lime	15
Europe		1614
Bulgaria	Chlorohydrin, with lime	12
Former Czechoslovakia	Chlorohydrin, with lime	5
France	*tert*-Butyl alcohol	200
Germany	Chlorohydrin, with NaOH	420
	Chlorohydrin, with lime	290
Italy	Chlorohydrin, with lime	60
Netherlands	*tert*-Butyl alcohol	250
	Styrene	140
Poland	Chlorohydrin, with lime	20
Romania	Chlorohydrin, with lime	72

Table 2 (contd)

Country or region	Process	Capacity (thousand tonnes/year)
Europe (contd)		
Russia	Chlorohydrin, with lime	25
	Styrene	50
Spain	Styrene	50
Former Yugoslavia	Chlorohydrin, with lime	20
Total		3912

From Kahlich *et al.* (1993)

Table 3. Use patterns (%) for propylene oxide as a chemical intermediate in the USA

Use	Year				
	1981	1984	1987	1990	1993
Urethane polyether polyols	54	59	60	60	65[a]
Propylene glycol	21	21	20	20	25
Glycol ethers	–	–	3	3	5
Dipropylene glycol	2	2	2		–
Miscellaneous[b]	13	9	6	5	5
Exports	10	9	9	12	–

From Anon. (1981, 1984, 1987b, 1990, 1993b)

[a]Flexible foams, 75%; rigid foams, 15%; non-foam uses, 10%

[b]Includes glycol ethers, industrial polyglycols, glycerine, surfactants and isopropanolamines (unless otherwise noted elsewhere)

Most of the propylene oxide produced is used as an intermediate for polyether polyols, which are used mainly in the manufacture of polyurethanes. Polyurethanes can be prepared so as to have a wide range of hardness, rigidity and density characteristics. Flexible polyurethane foams, used in furniture and automobile seating, bedding and carpet underlay, are made from polyols with relative molecular masses > 3000. Polyols with lower relative molecular masses result in rigid foams for such applications as thermal insulation. Homo- and copolymerized polyethers are used as surface-active agents in detergents, textiles, defoamers, hair-care preparations, brake fluids and lubricants (ARCO Chemical Co., 1993; Kahlich *et al.*, 1993).

Propylene glycols constitute the second largest application for propylene oxide. Monopropylene glycol is the direct reaction product of propylene oxide with water. Di-, tri- and higher propylene glycols are co-produced by the reaction of monopropylene glycol with propylene oxide. Propylene glycol is used mainly as the raw material for unsaturated polyester resins, especially in the textile and construction industries. It is also used as a humectant and as a solvent and emollient in food, drugs and cosmetics. Further uses are in coatings,

plasticizers, heat transfer and hydraulic fluids, antifreezes and aircraft deicing fluid (ARCO Chemical Co., 1993; Kahlich *et al.*, 1993).

Propylene glycol ethers are formed by the reaction of propylene oxide with alcohols, usually methanol, ethanol, propanol or butanol. Certain traditional ethylene glycol ethers and their acetates are being replaced by their propylene oxide-based analogues. The demand for propylene oxide-based glycol ethers and acetates is therefore growing rapidly and now constitutes the third largest market for propylene oxide. Typical applications are as a solvent in coatings, paints, inks, resins, cleaners, waxes and electronic circuit board lamination. Glycol ethers are also found in heat-transfer fluids and anti-icing agents for jet fuel (Kahlich *et al.*, 1993).

Various special organic compounds can be derived from propylene oxide, including allyl alcohol (used in glycerol synthesis), propylene carbonate (a special solvent for organic and some inorganic compounds), mono-, di- and tri-isopropanolamines (detergent raw materials) and hydroxypropylated cellulose (Kahlich *et al.*, 1993). Hydroxypropyl starch ethers, produced by treating starch with propylene oxide, are used as additives in salad dressings, pie fillings and other food thickening applications (Whistler & Daniel, 1983). Propylene oxide is also used as a reactive diluent in preparations for embedding tissues for transmission electron microscopy (McDowell, 1978).

1.3 Occurrence

1.3.1 *Natural occurrence*

Propylene oxide is not known to occur as a natural product.

1.3.2 *Occupational exposure*

The National Occupational Exposure Survey conducted by the National Institute for Occupational Safety and Health in the USA between 1981 and 1983 indicated that 421 000 US employees were potentially exposed to propylene oxide at work (US National Institute for Occupational Safety and Health, 1993). Of this number, 2% were estimated to be exposed to propylene oxide and 98% were estimated to be exposed to materials containing propylene oxide. The estimate is based on a survey of US companies and did not involve measurements of actual exposures.

Occupational exposure to propylene oxide has been measured in the chemical industry, during its production and the production of its derivatives, and in the starch industry where it is used to produce hydroxypropyl starch derivatives (Table 4). In the chemical industry, high exposures have been reported only during brief periods such as maintenance operations (Thiess *et al.*, 1981a; Flores, 1983). Hogstedt *et al.* (1979) reported that exposure to propylene oxide during its production by the chlorohydrin process in a Swedish plant was in the range of 10–25 mg/m^3 and occasionally 125–150 mg/m^3. Personal sampling in industrial starch production indicated that jobs such as mechanic and operator in the reaction area may entail 8-h time-weighted average (TWA) exposures above 50 mg/m^3 (McCammon *et al.*, 1990).

Table 4. Concentrations of propylene oxide in various industries and operations

Industry, operations	No. of samples	Concentration range (mg/m^3)	Year of measurement	Country	Reference
Production of propylene oxide	NR	< 0.1–6.5 (8-h TWA)	1978–81	Netherlands	de Jong *et al.* (1988)
Production of propylene oxide	NR	0.5–4.8 (8-h TWA) 24–9025 (peak)[a]	1979	USA	Flores (1983)
Production of propylene oxide derivatives	7	< 0.4–3.6 (6-h TWA)	1978	USA	Oser *et al.* (1978)
Production of propylene oxide derivatives			1979	USA	Oser *et al.* (1979)
Polymer polyol unit					
Oxide adducts unit	4	0.5–5.9 (6-h TWA)			
Flexible polyol unit	6	< 0.6–1.2 (6-h TWA)			
	4	< 0.5 (6-h TWA)			
Industrial starch production	5 workers	1.4–29 (TWA for 25–75% of working time) Up to 2400 (peak)	1981	Sweden	Pero *et al.* (1982)
Industrial starch production			1988–89	USA	Hills (1990a)
Personal samples	42	0.2–14 (8-h TWA)			
Area samples	15	< 0.2–26 (5 min–11 h)			
Industrial starch production			1989	USA	McCammon *et al.* (1990)
Personal samples	26	< 0.3–1500 (45 min–4 h TWA)			
Area samples	40	< 1–5600 (45 min–8 h TWA)			
Industrial starch production			1988	USA	Hills (1990b)
Area samples	89	0.2–14 (45 min–12 h)			
Personal samples					
Operators	15	0.2–1.7 (8-h TWA)			
Laboratory technician	11	< 0.2–1.0 (8-h TWA)			

NR, not reported; TWA, time-weighted average. Values are converted to mg/m^3, when necessary.
[a]Before implementation of engineering controls

1.3.3 *Environment*

Annual industrial emissions of propylene oxide into air in the USA, reported by industrial facilities to the US Environmental Protection Agency, decreased from 1600 tonnes in 1987 to 500 tonnes in 1991 (US National Library of Medicine, 1993).

It has been suggested that propylene oxide may also be introduced into the atmosphere from combustion exhausts of sources that burn hydrocarbons. In the atmosphere, propylene oxide reacts slowly with photochemically produced hydroxyl radicals, with an atmospheric half-life of 3–20 days (Grosjean, 1990; Kahlich *et al.*, 1993).

In water, propylene oxide is hydrolysed to propylene glycol with an estimated half-life of 11.6 days at 25 °C and pH 7. The chloride ions in salt water accelerate the chemical degradation to a half-life of 4.1 days (Kahlich *et al.*, 1993).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for propylene oxide in a number of countries are presented in Table 5.

The US Food and Drug Administration (1993) has approved the use of not more than 25% propylene oxide, by itself or in combination with various sources of active chlorine and/or oxygen, for etherification in the production of modified food starch; the residual propylene chlorohydrin should not exceed 5 ppm (21 CFR 172.892). It has also established regulations for use of propylene oxide in products in contact with food, including defoaming agents and slimicides used in the manufacture of paper and paperboard (21 CFR 176.210, 176.300); and as a reactant in the production of lubricants with incidental food contact (21 CFR 178.3570).

Residues of propylene oxide are exempt from the requirement of a tolerance when used as a stabilizer in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest or applied to animals (US Environmental Protection Agency, 1992a).

Propylene oxide, either alone or in mixtures with carbon dioxide, is permitted as a package fumigant in or on dried prunes and glacé fruit [residue tolerance, 700 ppm (as propylene glycol)] or as a bulk fumigant in or on cocoa, gums, processed spices, starch and processed nutmeats (except peanuts) [residue tolerance, 300 ppm as propylene glycol] (US Environmental Protection Agency, 1992b).

2. Studies of Cancer in Humans

2.1 Cohort studies

Several of the cohort studies described in the monograph on ethylene oxide included some workers who were also exposed to propylene oxide (Hogstedt *et al.*, 1979, 1986; Thiess *et al.*, 1981b; Hogstedt, 1988; Gardner *et al.*, 1989). No conclusion could be drawn about the risk for cancer in relation to exposure to propylene oxide specifically.

Table 5. Occupational exposure limits and guidelines for propylene oxide

Country	Year	Concentration (mg/m^3)	Interpretation
Argentina	1991	50	TWA; potential carcinogen
Australia	1983	50	TWA; probable human carcinogen
Austria	1982	120	TWA
Belgium	1984	50	TWA
Canada	1986	50	TWA
Denmark	1988	12	TWA; suspected carcinogen; skin
Finland	1993	12	TWA; suspected of having carcinogenic potential
France	1993	50	TWA
Germany	1993	None	Carcinogenic in animals
Indonesia	1978	240	TWA
Italy	1978	240	TWA
Mexico	1989	50	TWA
Netherlands	1986	240	TWA
Norway	1990	2	TWA; carcinogen
Romania	1975	100	Average
		200	Maximum
Sweden	1991	12	TWA; suspected of having carcinogenic potential; skin
		25	STEL (15 min)
Switzerland	After 1987	6	TWA; suspected carcinogen
United Kingdom	1992	50	TWA
		240	STEL (10 min)
USA			
ACGIH (TLV)	1994	48	TWA[a]
OSHA (PEL)	1992	240	TWA
NIOSH	1992	20	LOQ[b]
Venezuela	1978	240	TWA
		360	Ceiling

From Cook (1987); Direktoratet for Arbeidstilsynet (1990); ILO (1991); US National Institute for Occupational Safety and Health (NIOSH) (1992); US Occupational Safety and Health Administration (OSHA) (1992); American Conference of Governmental Industrial Hygienists (ACGIH) (1993); Deutsche Forschungsgemeinschaft (1993); Institut National de Recherche et de Sécurité (1993); Työministeriö (1993); UNEP (1993)

TWA, time-weighted average; STEL, short-term exposure limit; TLV, threshold limit value; PEL, permissible exposure level; LOQ, limit of quantification; skin, absorption through the skin may be a significant source of exposure

[a]Substance identified by other sources as a suspected or confirmed human carcinogen

[b]NIOSH has not established a specific numerical recommended exposure level for propylene oxide but has recommended reduction of worker exposures to the lowest feasible concentration and that the substance be recognized as a potential occupational carcinogen.

2.2 Case–control study

Risk estimates for exposure to propylene oxide and 20 other chemicals were derived in a nested case–control study carried out at two large chemical manufacturing facilities and a research and development centre in the USA (Ott *et al.*, 1989). The study was carried out because an earlier cohort study of the same population (Rinsky *et al.*, 1988) had shown elevated death rates from lymphatic and haematopoietic cancer. The cases (52 of non-Hodgkin's lymphoma, 20 of multiple myeloma, 39 of non-lymphatic leukaemia and 18 of lymphatic leukaemia) were identified from underlying and contributory causes of death for male members of the cohort who died during 1940–78. Controls were selected from the total cohort in a ratio of 5:1 and were matched to cases by sex, decade of first employment and survival to the start of the same five-year period. Exposures were inferred from recorded job histories up to the beginning of the survival period of the case. Odds ratios for men ever *versus* never exposed to propylene oxide (and the numbers of exposed cases) were as follows: non-Hodgkin's lymphoma, 1.5 (four); multiple myeloma, 3.4 (three); non-lymphatic leukaemia, 1.3 (three); lymphatic leukaemia, 0 (zero). None of these associations was significant. The associations between non-Hodgkin's lymphoma and exposure to propylene oxide were similar for men with less than five (odds ratio, 1.7) and at least five years' exposure (odds ratio, 1.3). [The Working Group noted that no information was given on levels of exposure to propylene oxide or on possible confounding effects of other exposures.]

3. Studies of Cancer in Experimental Animals

3.1 Oral administration

Rat: Groups of 50 female Sprague-Dawley rats, about 100 days old, were administered 0 (control), 15 or 60 mg/kg bw propylene oxide (purity, 99%) in a commercial vegetable oil [composition unspecified] by gastric intubation twice a week for 109.5 weeks (average total dose, 2714 or 10 798 mg/kg bw, respectively) and observed for life. Another untreated control group consisting of 50 females was also available. Survival rates in rats treated with propylene oxide were comparable to those of controls. Treatment with propylene oxide resulted in a dose-dependent increase in the incidence of forestomach tumours, which were mainly squamous-cell carcinomas. The incidences of squamous-cell carcinomas of the forestomach were 0/50 and 0/50 in control groups, 2/50 in the low-dose group and 19/50 in the high-dose group; one additional animal in the high-dose group had a carcinoma *in situ*, and a further animal had an adenocarcinoma of the glandular stomach. In addition, 7/50 low-dose and 17/50 high-dose animals developed papillomas, hyperplasia and hyperkeratosis of the foretomach. The incidences of tumours at other sites in treated animals were no greater than those in controls (Dunkelberg, 1982).

3.2 Inhalation

3.2.1 *Mouse*

Groups of 50 male and 50 female B6C3F1 mice, seven to nine weeks old, were exposed by inhalation to 0 (control), 200 or 400 ppm (474 or 948 mg/m^3) propylene oxide (purity,

> 99.9%) vapour for 6 h per day on five days per week for 103 weeks. Fewer treated than control animals survived to the end of the experiment: males—control, 42/50; low-dose, 34/50; high-dose, 29/50 ($p = 0.006$); females—control, 38/50; low-dose, 29/50; high-dose, 10/50 ($p < 0.001$). One squamous-cell carcinoma and one papilloma of the nasal cavity occurred in two high-dose male mice, and two high-dose female mice had adenocarcinomas of the nasal cavity. The (combined) incidences of haemangiomas and haemangiosarcomas in the nasal cavity were: males—0/50 control, 0/50 low-dose and 10/50 high-dose ($p < 0.001$, Fisher exact test); females—0/50 control, 0/50 low-dose and 5/50 high-dose ($p = 0.028$, Fisher exact test). Propylene oxide caused inflammation of the respiratory epithelium of the nasal turbinates; squamous metaplasia was observed in one low-dose male and in two high-dose female mice. Three high-dose males and three high-dose females had focal angiectasis of the submucosal turbinate vessels (US National Toxicology Program, 1985; Renne *et al.*, 1986).

3.2.2 *Rat*

Groups of 80 male weanling Fischer 344 rats were exposed by inhalation to filtered air containing 0 (control), 100 or 300 ppm (237 or 711 mg/m^3) propylene oxide (purity, 98%) vapour for about 7 h per day on five days per week for 104 weeks. Increased mortality over that in controls was observed in the two groups of rats exposed to propylene oxide, which was significant in the high-dose group ($p < 0.01$). Rats exposed to 100 or 300 ppm propylene oxide had an increased incidence of inflammatory lesions of the respiratory system and of a 'complex epithelial hyperplasia' in the nasal cavity, which was dose dependent (control, 0/76; low-dose, 2/77; high-dose, 11/78). Two rats in the high-dose group developed adenomas in the nasal cavity, which were not seen in controls. Adrenal phaeochromocytomas developed in 8/78 controls, 25/78 rats of the low-dose group and 22/80 rats of the high-dose group ($p < 0.05$, χ^2 test). A slight, nonsignificant increase in the incidence of peritoneal mesotheliomas was also found in the exposed groups (control, 3/78; low-dose, 8/78; high-dose, 9/80) (Lynch *et al.*, 1984a).

Groups of 50 male and 50 female Fischer 344/N rats, seven to eight weeks of age, were exposed by inhalation to 0 (control), 200 or 400 ppm (474 or 948 mg/m^3) propylene oxide (purity, > 99.9%) vapour for 6 h per day on five days per week for 103 weeks. Survival of rats exposed to propylene oxide was comparable to that of controls; terminal body weights were lower in high-dose males and high-dose females than in controls. Suppurative inflammation, epithelial hyperplasia and squamous metaplasia of the respiratory epithelium and underlying submucosal glands of the nasal turbinates were observed in exposed rats. Papillary adenomas of the nasal cavity occurred in 0/50 control, 0/50 low-dose and 3/50 high-dose females ($p = 0.037$, Cochran-Armitage trend test) and in 0/50 control, 0/50 low-dose and 2/50 high-dose males ($p > 0.05$). In historical controls, the incidence of nasal cavity tumours was 3/1523 in females and 1/1477 in males. In female rats, the combined incidences of C-cell adenomas and C-cell carcinomas of the thyroid were increased (control, 2/45; low-dose, 2/35; high-dose, 7/37; $p = 0.023$, Cochran-Armitage trend test). The incidence in historical controls was 122/1472 (8.3 ± 4.3% (SD) (US National Toxicology Program, 1985; Renne *et al.*, 1986).

Groups of 50 male Sprague-Dawley rats, 11–12 weeks old, were exposed by inhalation to 435 or 870 ppm (1031 or 2062 mg/m^3) propylene oxide (purity, > 95%) vapour in air for 6 h per day on five days per week for 30 days. A group of 50 rats was exposed to 1740 ppm (4124 mg/m^3) propylene oxide for only eight days because of high mortality [exact numbers unspecified]. A control group of 98 male rats was exposed to air alone. All animals were observed for life. Median lifespans were: control, 613 days; low-dose, 655 days; mid-dose, 635 days; and high-dose, 519 days. No nasal tumour was observed in any group receiving propylene oxide; two mid-dose animals had adenomas of the lung. Control animals developed no tumour in any part of the respiratory tract (Sellakumar *et al.*, 1987). [The Working Group noted the short exposure period.]

Groups of 100 male and 100 female Wistar rats, 34–38 days old, were exposed by inhalation to 0 (control), 30, 100 or 300 ppm (71.1, 237 or 711 mg/m^3) propylene oxide (purity, > 99.99%) vapour for 6 h per day on five days per week for 124 weeks (males) and 123 weeks (females). The body weights of exposed males in the high-dose group were lower than those of the controls throughout the study and lower than those of treated females only during the first year. After 12, 18 and 24 months, 10 rats of each sex from each group were killed. By week 115, mortality of male and female rats in the high-dose group was higher than that in controls; at week 119, the mortality of females in the mid-dose group was also higher than that in controls. The incidences of mammary gland tumours were significantly higher in high-dose females: fibroadenoma—control, 32/69; low-dose, 30/71; mid-dose, 39/69; high-dose, 47/70 ($p < 0.04$); tubulopapillary adenocarcinoma—control, 3/69; low-dose, 6/71; mid-dose, 5/69; high-dose, 8/70 ($p < 0.01$; Cox's test, adjusted for time of tumour appearance). The mean numbers of benign mammary tumours per tumour-bearing rat were: control, 1.3; low-dose, 2.1; mid-dose, 2.2; and high-dose, 2.4. Exposure to propylene oxide increased the incidences of degenerative and hyperplastic changes in the nasal mucosa in all of the treatment groups over that in controls. Three malignant tumours were found in the nasal cavity of treated males: one tumour described as an 'ameloblastic fibrosarcoma' in a low-dose male, one squamous-cell carcinoma in a low-dose male and one in a high-dose male. Four males in the high-dose group had a carcinoma in the larynx or pharynx, trachea or lungs; no such tumour was seen in any of the controls or low-dose males (Kuper *et al.*, 1988).

3.3 Subcutaneous administration

3.3.1 *Mouse*

Groups of 100 female NMRI mice, six to eight weeks old, received subcutaneous injections of propylene oxide (purity, 99%) in tricaprylin at 0.1, 0.3, 1.0 or 2.5 mg/mouse once a week for 95 weeks (mean total dose, 6.8, 21,7, 72.8 or 165.4 mg/mouse, respectively). Groups of 200 untreated and 200 tricaprylin-treated mice served as controls. Survival rates in the animals treated with propylene oxide were comparable to those in controls. The incidences of sarcomas at the site of injection were: untreated control, 0/200; tricaprylin control, 4/200; 0.1-mg, 3/100; 0.3-mg, 2/100; 1.0-mg, 12/100; and 2.5-mg, 15/100 [$p < 0.001$, Cochran-Armitage test for trend]. No increase in tumour incidence at other sites was found (Dunkelberg, 1981).

3.3.2 *Rat*

Of 12 rats [age, sex and strain unspecified] given a total of 1500 mg/kg bw propylene oxide [purity unspecified] in arachis oil by subcutaneous injection over a period of 325 days [dosing schedule unspecified], eight developed local sarcomas after 507–739 days. In a similar experiment, in which 1500 mg/kg bw propylene oxide in water were injected subcutaneously, 3/12 rats developed a local sarcoma after 158 days and two developed local sarcomas after 737 days (Walpole, 1958). [The Working Group noted the inadequate reporting of the experiment.]

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

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available on absorption or distribution of propylene oxide in humans.

Propylene oxide is an electrophilic compound which directly alkylates macromolecules, introducing a hydroxypropyl group at nucleophilic centres. The adducts of propylene oxide at N^{τ}-histidine (HOPrHis) and at the N-terminal valine (HOPrVal) of Hb have been used to monitor dose in humans. Workers (all smokers) exposed to propylene oxide during the production of alkylated starch had HOPrHis adduct levels of 180–10 200 pmol/g Hb; unexposed people (38% smokers) had levels of < 100–380 pmol/g Hb. A negative correlation ($r = -0.64$) was reported between HOPrHis level and DNA repair proficiency, measured as unscheduled DNA synthesis in leukocytes after a challenge with *N*-acetoxy-2-acetylaminofluorene *in vitro*. The authors suggested that the effect was due to inactivation of DNA repair enzymes or of enzymes involved in purine or pyrimidine metabolism (Pero *et al.*, 1985).

In a study in a starch alkylation factory, the concentrations of HOPrVal were determined to be below 20 pmol/g Hb in controls, including smokers and nonsmokers, and from 230 to 3500 pmol/g Hb in exposed workers. The adduct levels correlated with the mean concentrations in the breathing zones, which varied between 0.33 and 11.4 ppm [0.8 and 27.5 mg/m^3] during sampling periods of 2–4 h (Högstedt *et al.*, 1990). The steady-state background concentration of HOPrVal adducts in Hb was 2 pmol/g Hb in unexposed people (Törnqvist & Ehrenberg, 1990). The increment in workers exposed for 40 h/week to 1 ppm [2.4 mg/m^3] propylene oxide (TWA) was estimated to be about 500 pmol/g Hb (Kautiainen & Törnqvist, 1991).

Hydroxylpropyl valine adduct concentrations in Hb were found to be slightly higher in propylene oxide manufacturing and loading workers than in controls, after correction for smoking (van Sittert & van Vliet, 1994).

4.1.2 *Experimental systems*

The presence of propylene oxide did not inhibit styrene oxide metabolism catalysed by microsomal epoxide hydrolase isolated from human liver, indicating that epoxide hydrolase

has little or no affinity for propylene oxide as a substrate (Oesch, 1974). The action of glutathione *S*-transferase on 1-chloro-2,4-dinitrobenzene (1 mmol/L) in human erythrocytes was reduced to 57% of the control value by the presence of propylene oxide (3 mmol/L) in incubations containing 1 mmol/L glutathione (pH 6.5, 25 °C). This value, measured *in situ*, was similar to the I_{50} value of 3.1 mmol/L obtained with purified anionic glutathione from human erythrocytes (Ansari *et al.*, 1987). Purified human plasma α_1-proteinase inhibitor was inactivated by very high concentrations (> 100 mmol/L) of propylene oxide (Ansari *et al.*, 1988).

The inhalation pharmacokinetics of propylene oxide in male Sprague-Dawley rats was studied by gas uptake in closed exposure chambers, in which the atmospheric concentration–time course was measured after injection of a single dose into the chamber atmosphere. A single injection of propylene oxide into the atmosphere of the chambers resulted in an initial air concentration of up to 3000 ppm [7230 mg/m^3]. The uptake of propylene oxide into the body was rather high: clearance due to uptake, reflecting the transfer rate of propylene oxide from the atmosphere into the body of one rat weighing 250 g, was 75 ml/min, representing 64% of the alveolar ventilation (117 ml/min; Arms & Travis, 1988). Maximal accumulation of propylene oxide in a single rat, determined as the thermodynamic partition coefficient for whole body:air (K_{eq} = $Conc._{animal}/Conc._{air}$), was 45. In the same rat, the concentration ratio at steady-state whole body:air was only 1.2 because of rapid metabolic elimination of the inhaled propylene oxide. Most (96%) of the propylene oxide taken up by the rat was metabolized, and only a small amount (3%) was exhaled unchanged. On the basis of the pharmacokinetic parameters derived, the body burden of propylene oxide gas in rats exposed under steady-state conditions to 100 ppm was calculated by the authors to be 124 nl/ml tissue (Golka *et al.*, 1989).

In male Fischer 344/N rats exposed by nose only for 60 min to 14 ppm [33.7 mg/m^3] propylene oxide, the blood concentrations increased during the first 10 min, reaching a plateau at about 3 ng/g blood (Maples & Dahl, 1993).

As determined *in vitro*, propylene oxide is metabolized via two pathways: conjugation with glutathione and hydrolysis to 1,2-propanediol. Propylene oxide (10 mmol/L) was reacted at pH 6.5 with glutathione (10 mmol/L) in the presence of glutathione *S*-transferase isolated from livers of male Sprague-Dawley rats. Adducts were identified only indirectly with ninhydrin after thin-layer chromatography (Fjellstedt *et al.*, 1973). Propylene oxide (1 mmol/L) was hydrolysed to 1,2-propanediol by two forms of epoxide hydrolase obtained from liver microsomes of male Sprague-Dawley rats which had been pretreated with phenobarbital. Incubations were carried out at pH 8.7. The metabolic rate of propylene oxide hydrolysis was reported to be lower than that of other epoxides tested, 1 and 4 nmol/min per mg protein or 0.058–0.232 μg/min per mg protein in two fractions (Guengerich & Mason, 1980).

The inhibitory effectiveness of a series of epoxides, including propylene oxide, was compared *in vitro* with microsomal membrane-bound and purified epoxide hydrolase obtained from livers of phenobarbital-pretreated male Fischer 344 rats; styrene-7,8-oxide and benzo[*a*]pyrene-4,5-epoxide were used as substrates. The inhibition constants (IC_{50}) for propylene oxide were higher (62.5 mmol/L for styrene-7,8-oxide and 450 mmol/L for benzo[*a*]pyrene-4,5-epoxide) than those for the other epoxides. The authors concluded that

propylene oxide is a poor substrate for microsomal epoxide hydrolase (Dent & Schnell, 1981).

Non-enzymic hydrolysis of propylene oxide at pH 1 in 0.1 mol/L hydrochloric acid (37 °C) resulted in a half-life similar to that in the acidic conditions of the stomach and was reported to be about 1 min (reviewed by Ehrenberg & Hussain, 1981).

1,2-Propanediol is further metabolized to lactic and pyruvic acids and, hence, has served as a nutrient for dogs, cattle, rats and chickens (reviewed by Ruddick, 1972). 1,2-Propanediol can also be excreted in part unchanged in urine after its oral administration to dogs (Lehman & Newman, 1937).

Propylene oxide alkylated the N-terminal valine of Hb when incubated with whole blood or erythrocytes (Törnqvist *et al.*, 1986) or with Hb (Mowrer *et al.*, 1986). HOPrHis and HOPrVal have been used for tissue dosimetry of propylene oxide in animals *in vivo* (Farmer *et al.*, 1982; Bailey *et al.*, 1987; Svensson *et al.*, 1991; Segerbäck *et al.*, 1992). An HOPrHis adduct level of 10.5 ng/g globin was detected by gas chromatography–mass spectrometry (detection limit, 0.2 ng/g globin) in female Wistar rats after exposure to 1300 ppm [3130 mg/m^3] propylene oxide over 4 h (Farmer *et al.*, 1982). Concentrations of HOPrVal were measured in male CBA mice 3 and 5 h after intraperitoneal injection of uniformly labelled ^{14}C-propylene oxide (0.065–0.19 mmol/kg bw [3.8–11 mg/kg bw]). A linear relationship through the origin was found between adduct level and administered dose of propylene oxide, corresponding to about 1300 pmol/g globin per mmol propylene oxide/kg bw [22 pmol/g globin per mg propylene oxide/kg bw] (Svensson *et al.*, 1991).

Species differences in HOPrVal levels in Hb after administration of propylene oxide were investigated in mice, rats and dogs (Table 6). Male B6C3F1 mice and male Fischer 344 rats were exposed to uniformly labelled ^{14}C-propylene oxide administered intraperitoneally or via inhalation in closed exposure chambers in which the atmospheric concentration–time course was measured after injection of a single dose into the chamber atmosphere. The exposures were terminated after 5 h, when the atmospheric radioactivity had dropped to less than 5% of the initial values. The animals were killed 2 h later and blood was collected. HOPrVal levels were also measured in male and female beagle dogs exposed for about 1 h to 100 or 500 ppm [238 or 1190 mg/m^3] propylene oxide through an anaesthetic mask. Blood samples were taken before exposure, immediately after exposure and when the dogs were killed 4 h later. The mean levels of HOPrVal in mice and rats, when normalized to an uptake of propylene oxide of 1 mg/kg bw, were independent of route of administration. The extent of HOPrVal alkylation was similar in rats and dogs (70–90 pmol/g Hb per mg propylene oxide/kg bw) but about 50% lower in mice (30–40 pmol/g Hb per mg propylene oxide/kg bw) (Segerbäck *et al.*, 1992).

In a further study, the rate constants for the reaction of propylene oxide with N-terminal valine in Hb in erythrocytes from different species were determined *in vitro*. The values for rats, dogs and man ($K_{val} \times 10^4$) were similar: 0.22, 0.28 and 0.25 L/g Hb per h. The value for mice was 0.14 L/g Hb per h. The rate constant for the reaction of propylene oxide with 7-guanine in calf thymus DNA *in vitro* was 0.25 L/g DNA per h, and the value should not differ among species. On the basis of Hb adduct levels measured in workers exposed to propylene oxide and the adduct levels in Hb and DNA measured experimentally *in vivo*, tissue doses were calculated for the purposes of interspecies comparison. The dose in blood

was virtually the same in the three experimental animal species and in man, but an extrapolation based on surface area showed as approximately seven-fold difference between mice and dogs (Segerbäck *et al.*, 1994).

Table 6. Concentrations of propylene oxide–haemoglobin adducts in mice, rats and dogs after treatment with propylene oxide

Species	Dose route	Dose (mg/kg)	HOPrVal adduct concentration (pmol/g Hb)
Mouse		0	5
	Intraperitoneal	3.1	72–86
		7.6	170–210
	Inhalation	6.5	270
		18.4	590
Rat		0	15
	Intraperitoneal	3.1	110–250
		7.6	430–740
	Inhalation	3.8	260–320
		10.9	660–760
Dog		0	< 5
	Inhalation	3.8	280
		15.3	1700

From Segerbäck *et al.* (1992); HOPrVal, *N*-(2-hydroxypropyl)-valine

4.2 Toxic effects

The toxicology of propylene oxide has been reviewed (WHO, 1985; Meylan *et al.*, 1986; US Environmental Protection Agency, 1987; Beratergremium für umweltrelevante Alstoffe, 1993).

4.2.1 *Humans*

Three cases of corneal burns after exposure to propylene oxide have been described (McLaughlin, 1946).

van Ketel (1979) described the development of hand eczema in a female laboratory analyst who was working with pure propylene oxide or a concentrated solution (50%). Two cases of contact dermatitis from a disposable swab containing 70% isopropyl alcohol and 1% propylene oxide were reported by Jensen (1981).

4.2.2 *Experimental systems*

(*a*) *Acute toxicity*

No organ injury was seen in rats exposed by inhalation to calculated concentrations of 9480 mg/m^3 (4000 ppm) propylene oxide vapour for 0.5 h, to 4740 mg/m^3 (2000 ppm) for 2 h

or 2370 mg/m^3 (1000 ppm) for 7 h. Four of 10 rats died after 4 h of exposure to the highest concentration (Rowe *et al.*, 1956).

A single exposure of female CD1 mice to 20 ppm propylene oxide [48.2 mg/m^3] by inhalation for 3 h had no significant effect on lung host defenses, monitored as mortality resulting from streptococcal pneumonia or pulmonary bactericidal activity against inhaled ^{35}S-*Klebsiellae pneumoniae* (Aranyi *et al.*, 1986).

(*b*) *Subchronic toxicity*

Male Fischer 344 rats were exposed to 0, 10, 20, 50, 150 or 525 ppm [24.1, 48.2, 120.5, 361.5 or 1265 mg/m^3] propylene oxide vapour for up to four weeks followed by recovery for up to four weeks, and toxicity and cell proliferation were examined in the nasal cavity. Respiratory epithelial hyperplasia, degeneration of olfactory epithelium and cell proliferation at both sites were dose and time dependent and reversible upon cessation of exposure. No effect was observed at 50 ppm propylene oxide (Eldridge *et al.*, 1994).

Exposure of male Wistar rats to 1500 ppm [3615 mg/m^3] propylene oxide (6 h/day, five days/week, seven weeks) by inhalation caused ataxia in the hindlegs without muscular atrophy. A central–peripheral distal axonopathy was verified histologically by the observation of axonal degeneration of myelinated fibres in hindleg nerves and in the fasciculus gracilis (Ohnishi *et al.*, 1988; Ohnishi & Murai, 1993).

(*c*) *Chronic toxicity*

The chronic toxicity of inhaled propylene oxide was studied in male weanling Fischer 344 rats exposed to 100 or 300 ppm [241 and 723 mg/m^3] for 7 h/day on five days/week for 104 weeks. Body weights of rats exposed to either concentration were significantly lower than those of controls, and a significant increase in mortality was observed in both groups of exposed rats over that in controls. All groups developed *Mycoplasma pulmonis* infection about 16 months into the study, and the infection, alone and in combination with the exposures, affected the survival of rats and influenced the development of proliferative lesions in the nasal mucosa. Some changes in organ:body weight ratios were seen in treated rats after two years of the study: small increases were reported for lungs, adrenal glands and brain, and a small reduction for testes. The serum activities of aspartate aminotransferase and sorbitol dehydrogenase were increased only in the low-exposure group. Skeletal muscle atrophy with no sciatic nerve involvement was observed primarily in the high-exposure group and consisted of multifocal areas of atrophy and degeneration. Treated animals had higher incidences than controls of inflammatory lesions in the nasal cavity, trachea, lung and middle ear, which increased with dose in the nasal cavity. A dose-dependent increase, significant at the high dose, was also seen in the incidence of complex epithelial hyperplasia in the nasal mucosa, although an influence of the infection could not be ruled out (Lynch *et al.*, 1984a).

In another study, male and female Fischer 344/N rats and male and female B6C3F1 mice were exposed by inhalation to propylene oxide at concentrations of 200 and 400 ppm [482 and 964 mg/m^3] for 6 h/day on five days/week for 103 weeks. During the second year of exposure, the mean body weights of animals of both species at the high dose were lower than those of the controls; survival of rats was comparable to that of controls, but survival of exposed mice was decreased. A dose-related increase in the incidence of acute–chronic

rhinitis was seen in exposed mice (28% in each sex at 200 ppm [482 mg/m^3], 76% in males and 36% in females at 400 ppm [964 mg/m^3]), with degeneration and necrosis of mucosal epithelium in some areas of severe rhinitis. Suppurative rhinitis was observed in rats, in 18% of male and 6% of female controls, 42% of males and 10.4% of females at 200 ppm [482 mg/m^3] and 76% of males and 48% of females at 400 ppm [964 mg/m^3]. In rats exposed to the high dose of propylene oxide, there were also significant increases in the incidences of squamous metaplasia and hyperplasia of the respiratory epithelium of the nasal mucosa and the epithelium of the mucosal glands (US National Toxicology Program, 1985; Renne *et al.*, 1986).

After male and female Wistar rats were exposed chronically (6 h/day, five days/week, 28 months) to atmospheric concentrations of 30, 100 and 300 ppm [72.3, 241 and 723 mg/m^3] propylene oxide, mortality was increased in animals of each sex at the highest dose and in females also at the medium dose. Body weights were lower than those of the controls throughout the study in males exposed to 300 ppm and during the first year in females exposed to 300 ppm. Increased incidences of degenerative and hyperplastic changes of the nasal mucosa were observed in all exposed groups (Kuper *et al.*, 1988).

4.3 Reproductive and prenatal effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.1 *Experimental systems*

New Zealand white rabbits were exposed by inhalation to 0 (17 animals) or 500 ppm [1205 mg/m^3] propylene oxide (purity, 99%) vapour for 7 h per day on gestation days 7–19 (11 animals) or 1–19 (19 animals). Fetuses were examined on day 30. Food consumption, but not maternal body weight, was generally depressed in the treated groups during the periods of exposure. Fertility was low in all groups, but the overall resorption rate was not increased, and no adverse effect was observed in the fetuses in the treated groups. Sprague-Dawley rats were exposed by inhalation to 0 (46 animals) or 500 ppm propylene oxide (purity, 99%) vapour for 7 h per day either from three weeks before gestation to day 16 of gestation (43 animals) or on days 1–16 (41 animals) or 7–16 of gestation (44 animals). Fetuses were examined on day 21. Food consumption was reduced in females that received the pregestational exposure, and maternal weight gain tended to be lower in all treated groups during exposure. Fetal growth was lower in all treated groups than in controls. No major malformation related to treatment was seen, but the incidence of rib dysmorphology (primarily wavy ribs) was increased in all treated groups (Hackett *et al.*, 1982).

Hayes *et al.* (1988) exposed Fischer 344 rats to propylene oxide (> 99.7% pure) by inhalation (whole-body exposure) for two generations. Groups of 30 males and 30 females were exposed to 0, 30, 100 or 300 ppm [72.3, 241 or 723 mg/m^3] propylene oxide for 6 h per day on five days per week (seven days per week from mating to end of lactation except for four to five days during parturition) for 14 weeks, and then mated. Groups of offspring (F1) were exposed after weaning to the same levels for 17 weeks and then mated to produce F2

litters. Other than decreased body weight gain at the highest dose level, no adverse effect was seen on fertility, litter size, development or postnatal survival. Gross and histological examination of the high-dose and control pups (F1 and F2) showed no adverse effects.

A teratology study was carried out on groups of 20–23 pregnant Fischer 344 rats exposed (whole-body) to 0, 100, 300 or 500 ppm [241, 723 or 1205 mg/m^3] propylene oxide (> 99% pure) for 6 h per day from days 6 to 15 of gestation and killed on day 20. Maternal body weight gain was depressed at the highest dose level, but no adverse effect was observed on litter size, resorptions or fetal weight, and no increase in malformations was seen. The incidence of seventh cervical ribs was increased (13.6% *versus* 2.8% in controls [$p = 0.026$]) in the highest dose group only (Harris *et al.*, 1989).

4.4 Genetic and related effects (see also Table 7 and Appendices 1 and 2)

4.4.1 *Humans*

Results from the analysis of chromosomal aberrations and micronuclei in peripheral blood lymphocytes from 20 male workers exposed to propylene oxide during the production of alkylated starch were inconclusive because no data were available on controls (Högstedt *et al.*, 1990).

4.4.2 *Experimental systems*

(*a*) *DNA adducts*

Propylene oxide binds covalently to DNA. Using ^{32}P-postlabelling, Randerath *et al.* (1981) detected 15 different DNA adducts after incubation (12 h, 37 °C, pH 5.8) of propylene oxide (200 mmol/L) with calf thymus DNA (3 mmol/L).

After incubation (48 h, 37 °C, pH 7.4) of propylene oxide with calf thymus DNA (0.2 mmol propylene oxide per mg DNA), the yields of alkylated nucleosides were: deoxyguanosine (46% reacted) > deoxyadenosine (38% reacted) > deoxycytidine (24% reacted) > deoxythymidine (15% reacted) (Djuric *et al.*, 1986).

After incubation (10 h, 37 °C, pH 7.5) of propylene oxide (2 mol/L) with calf thymus DNA (3 mg/ml), the following 2-hydroxypropyl adducts were found: 7-guanine (133 nmol/mg DNA), 3-adenine (14 nmol/mg DNA), 3-uracil (13 nmol/mg DNA) and N^6-adenine (1 nmol/mg DNA). The 2-hydroxypropyl adduct at 3-uracil was formed from the corresponding cytosine adduct by hydrolytic deamination of the imino group (Solomon *et al.*, 1988).

7-(2-Hydroxypropyl)guanine was detected in DNA hydrolysates of various organs obtained from male CBA mice 3 h and 10 h after intraperitoneal injection of ^{14}C-propylene oxide (Svensson *et al.*, 1991). In mice, rats and dogs, the levels of DNA adducts in liver (in pmol/g DNA per mg propylene oxide per kg bw) were 17 in mice, 38 in rats and 17 in dogs after intraperitoneal or intravenous injection and somewhat higher after exposure by inhalation in mice (Segerbäck *et al.*, 1994). [The Working Group calculated a covalent binding index—(μmol adduct/mol DNA nucleotide)/(mmol chemical/kg bw)—of 0.3 for mouse liver DNA 6 h after an intraperitoneal injection.]

DNA-associated radiolabel was determined in the respiratory mucosa of male Fischer 344 rats on completion of exposure for 2 h by nose only to tritiated propylene oxide at concentrations ranging from 6 to 46 ppm [14.5–111 mg/m^3]. After exposure to 46 ppm, radioactivity counts were highest in nasal cavities, intermediate in trachea and lowest in lung, reaching 17, 5.8 and 3.3 adducts/10^6 base, respectively. The persistence of radiolabel in the DNA of the nasal cavities, trachea and lungs of rats exposed to 19.5 ppm [47 mg/m^3] was also investigated. Either a small or no decrease in counts was found in the mucosa of lung and trachea, while a biphasic elimination of radiolabel from nasal mucosa was observed, with half-lives of 8 h and 5.3 days (Snyder & Solomon, 1993). [The Working Group noted that the author did not attempt to differentiate between radioactivity incorporated metabolically into DNA and radiolabel covalently bound to DNA; therefore, these figures may not accurately reflect the DNA binding of propylene oxide.]

(*b*) *Mutation and allied effects*

Propylene oxide induced DNA damage and gene mutation in bacteria. It caused gene mutation in yeast and fungi, and in one study it induced mitotic gene conversion in *Saccharomyces cerevisiae*. Induction of sex-linked recessive lethal mutations in *Drosophila* was reported in a single study. Propylene oxide induced DNA damage, gene mutation, sister chromatid exchange and chromosomal aberrations in mammalian cells *in vitro*. It also induced sister chromatid exchange and chromosomal aberrations in human lymphocytes *in vitro*. Propylene oxide was shown to alkylate calf thymus DNA in one study *in vitro* at a high concentration.

One study showed no significant increase in sister chromatid exchange or chromosomal aberration frequency in peripheral blood lymphocytes of cynomolgus monkeys exposed to 300 ppm propylene oxide for 7 h per day on five days a week for two years. Micronuclei were not induced in bone-marrow cells of mice administered propylene oxide by gavage but were induced in those of mice receiving the compound by intraperitoneal injection. In single studies, chromosomal aberrations and sister chromatid exchange were induced in mouse bone-marrow cells after intraperitoneal injection. Dominant lethal mutations were not induced in mice exposed orally or in rats exposed by inhalation. Propylene oxide did not cause sperm abnormalities in mice treated by inhalation (7 h per day, five days).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Propylene oxide is produced by dehydrochlorination of propylene chlorohydrin or by indirect oxidation of propylene. It is used primarily as a chemical intermediate to produce polyether polyols, propylene glycols and propylene glycol ethers. It is used to a lesser extent in the production of hydroxypropyl starch ethers, as a food additive and as a fumigant for certain dried fruits and nuts.

Occupational exposure occurs during the production of propylene oxide and its derivatives and during production of hydroxypropyl starch ethers.

Table 7. Genetic and related effects of propylene oxide

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS functions, *Salmonella typhimurium* TA1535/pSK1002	+	+	23.0000[c]	Ong *et al.* (1987)
BRD, Bacteria (other), differential toxicity	+	0	500.0000	Bootman *et al.* (1979)
BPF, Bacteriophage, forward mutation	-	0	39000.0000	Cookson *et al.* (1971)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	0	750.0000	Wade *et al.* (1978)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	50.0000	Bootman *et al.* (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	0	58.0000	Hemminki & Falck (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	145.0000	Pfeiffer & Dunkelberg (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	239.0000[c]	Simmon (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	200.0000	Yamaguchi (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	1667.0000	Canter *et al.* (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	30.0000	Djurić *et al.* (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	+	50.0000[d]	Hughes *et al.* (1987)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	5000.0000	Zeiger *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	0	174.0000	Agurell *et al.* (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	0.2300[c]	Castelain *et al.* (1993)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	(+)	0	500.0000	Wade *et al.* (1978)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	50.0000	Bootman *et al.* (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	0	145.0000	Pfeiffer & Dunkelberg (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	0	96.0000[c]	Simmon (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	1667.0000	Canter *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	0	10.0000	Djurić *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	+	833.0000	Zeiger *et al.* (1988)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	0	174.0000	Agurell *et al.* (1991)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	0.1200[c]	Castelain *et al.* (1993)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	350.0000	Bootman *et al.* (1979)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	0	2900.0000	Pfeiffer & Dunkelberg (1980)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	?	?	0.0000	Canter *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	-	5000.0000	Zeiger *et al.* (1988)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	-	-	1000.0000	Dean *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	350.0000	Bootman *et al.* (1979)

Table 7 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	0	2900.0000	Pfeiffer & Dunkelberg (1980)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	0.0000	Canter *et al.* (1986)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	5000.0000	Zeiger *et al.* (1988)
SAS, *Salmonella typhimurium* TA97, reverse mutation	+	+	0.0000	Canter *et al.* (1986)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	5000.0000	Zeiger *et al.* (1988)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	–	0	58.0000	Hemminki & Falck (1979)
ECW, *Escherichia coli* WP2 *uvr*A, reverse mutation	+	+	20.0000	Dean *et al.* (1985)
EC2, *Escherichia coli* WP2, reverse mutation	+	+	350.0000	Bootman *et al.* (1979)
EC2, *Escherichia coli* WP2, reverse mutation	+	–	20.0000	Dean *et al.* (1985)
ECR, *Escherichia coli* B (Arg-) Hs30R, reverse mutation	+	0	58.0000	Kohda *et al.* (1987)
KPF, *Klebsiella pneumonia*, forward mutation	+	0	29.0000	Voogd *et al.* (1981)
SCG, *Saccharamyces cerevisiae*, gene conversion	+	0	1740.0000	Agurell *et al.* (1991)
SCR, *Saccharamyces cerevisiae*, reverse mutation	+	0	1740.0000	Agurell *et al.* (1991)
SZF, *Schizosaccharomyces pombe*, forward mutation	+	+	174.0000	Migliore *et al.* (1982)
NCR, *Neurospora crassa*, reverse mutation	+	0	29000.0000	Kølmark & Giles (1955)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutation	+	0	1.5000[c]	Hardin *et al.* (1983)
DIA, DNA single strand breaks, rat hepatocytes *in vitro*	+	0	1.7000	Sina *et al.* (1983)
GCO, Gene mutation, Chinese hamster ovary cells, *hprt* locus	+	0	16.0000[c]	Zamora *et al.* (1983)
G5T, Gene mutation, mouse L5178Y cells, *tk* locus	+	0	1.0000[c]	McGregor *et al.* (1991)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	+	5.0000	Gulati *et al.* (1989)
SIC, Sister chromatid exchange, Chinese hamster V79 cells *in vitro*	+	0	290.0000	von der Hude *et al.* (1992)
SIR, Sister chromatid exchange, rat liver cells *in vitro*	+	0	50.0000	Dean & Hodson-Walker (1979)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	(+)	+	160.0000	Gulati *et al.* (1989)
CIR, Chromosomal aberrations, rat liver cells *in vitro*	+	0	25.0000	Dean & Hodson-Walker (1979)
CIR, Chromosomal aberrations, rat liver cells *in vitro*	+	0	25.0000	Dean *et al.* (1985)

Table 7 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	58.0000[c]	Tucker *et al.* (1986)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	145.0000	Agurell *et al.* (1991)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	+	0	1.9000	Bootman *et al.* (1979)
SVA, Sister chromatid exchange, monkey lymphocytes *in vivo*	-		110.0000, inhal. 7 h/d[e]	Lynch *et al.* (1984b)
SVA, Sister chromatid exchange, mouse bone-marrow cells *in vivo*	+		100.0000×1 ip	Farooqi *et al.* (1993)
MVM, Micronucleus formation, mouse bone-marrow cells *in vivo*	+		300.0000×2 ip	Bootman *et al.* (1979)
MVM, Micronucleus formation, mouse bone-marrow cells *in vivo*	-		500.0000×2 po	Bootman *et al.* (1979)
MVM, Micronucleus formation, mouse bone-marrow *in vivo*	+		100.0000×1 ip	Farooqi *et al.* (1993)
CLA, Chromosomal aberrations, monkey lymphocytes *in vivo*	-		110.0000, inhal. 7 h/d[e]	Lynch *et al.* (1984b)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	+		100.0000, ip×1	Farooqi *et al.* (1993)
DLM, Dominant lethal mutation, mouse *in vivo*	-		250.0000×14 po	Bootman *et al.* (1979)
DLR, Dominant lethal mutation, rat *in vivo*	-		29.0000, inhal. 7 h/d×5	Hardin *et al.* (1983)
MVH, Micronucleus formation, human lymphocytes *in vivo*	?		0.0000[f]	Högstedt *et al.* (1990)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	?		0.0000[f]	Högstedt *et al.* (1990)
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	0	11600.0000	Randerath *et al.* (1981)
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	0	40.0000	Djurić *et al.* (1986)
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	0	116000.0000	Solomon *et al.* (1988)
BVD, Binding (covalent) to mouse DNA *in vivo*	+		6.0000×1 ip	Svensson *et al.* (1991)
BVD, Binding (covalent) to rat DNA *in vivo*	+		3.0000 inhal. 2 h	Snyder & Solomon (1993)
BVD, Binding (covalent) to mouse, rat and dog DNA *in vivo*	+		3.0000×1, ip, iv or inhal. 5 h	Segerbäck *et al.* (1994)
SPM, Sperm morphology, mouse *in vivo*	-		290.0000, inhal. 7 h/d×5	Hardin *et al.* (1983)

Table 7 (contd)

Test system	Result[a]		Dose[b] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Protein binding				
BVP, Binding (covalent) to mouse protein *in vivo*	+		4.0000×1 ip	Svensson *et al.* (1991)
BVP, Binding (covalent) to mouse, rat and dog haemoglobin *in vivo*	+		3.0000×1 ip, iv or inhal. 5 h	Segerbäck *et al.* (1994)
BHP, Binding (covalent) to human haemoglobin *in vivo*	+		0.0000	Pero *et al.* (1985)

[a] +, positive; (+), weak positive; –, negative; 0, not tested; ?, inconclusive (variable response within several experiments within an adequate study)
[b] In-vitro tests, μg/ml; in-vivo tests, mg/kg bw
[c] Atmospheric concentration in exposure chamber
[d] Incubated in Tedlar bags
[e] Five days/week; two years
[f] No controls (not on profile)

5.2 Human carcinogenicity data

One case–control study provides information about cancer risk in relation to exposure to propylene oxide specifically but does not allow any firm conclusion regarding carcinogenicity.

5.3 Animal carcinogenicity data

Propylene oxide was tested by oral gavage in one study in rats, by inhalation in one study in mice and in three adequate studies in rats and by subcutaneous administration in one study in mice and in one study in rats. Propylene oxide administered by oral gavage to rats produced tumours of the forestomach, which were mainly squamous-cell carcinomas. In mice exposed by inhalation, propylene oxide produced haemangiomas and haemangiosarcomas of the nasal cavity and a few malignant nasal epithelial tumours. In a study in rats of each sex exposed by inhalation, papillary adenomas of the nasal cavity were observed in males and females and thyroid adenomas and carcinomas were found in females; in the second study, in males, papillary adenomas of the nasal cavity and an increased incidence of adrenal phaeochromocytomas were observed; in the third study, in females, increased incidences of mammary fibroadenomas and adenocarcinomas were observed. Subcutaneous administration of propylene oxide to mice produced local sarcomas; the study in rats was inadequate for evaluation.

5.4 Other relevant data

In rats exposed by inhalation, there is strong uptake of propylene oxide, which is then metabolized extensively and eliminated rapidly. Metabolism occurs predominantly by conjugation with glutathione. Propylene oxide can also be hydrolysed by epoxide hydrolase to 1,2-propanediol, which is subsequently metabolized to lactic and pyruvic acids. Propylene oxide forms adducts with proteins, including haemoglobin, in man, dog, rat and mouse. In mice, the concentration of the N-terminal valine adduct of propylene oxide in haemoglobin is linearly related to the administered dose. The alkylation efficiency in mice exposed by inhalation is about one-half that observed in rats and dogs.

In a seven-week study of rats exposed by inhalation, ataxia in the absence of muscular atrophy was observed, which was due to distal axonopathy in the central and peripheral nervous systems. Chronic and subchronic exposure of rats to propylene oxide by inhalation induced proliferative lesions, irritation and toxicity in the nasal mucosa and respiratory epithelium.

Other than occasional reductions in fetal weight, no adverse effects on reproduction were observed in rats or rabbits exposed to propylene oxide at up to 500 ppm.

DNA adducts of propylene oxide are formed in various organs of mice, rats and dogs. Binding in mouse liver DNA was about one-twentieth that of ethylene oxide.

Dominant lethal mutations were not induced in rats or mice, and sperm abnormalities were not observed in mice exposed to propylene oxide *in vivo*. Micronuclei and, in single studies, chromosomal aberrations and sister chromatid exchange were induced in mouse

bone marrow after intraperitoneal injection of propylene oxide. Neither sister chromatid exchange nor chromosomal aberrations were induced in monkeys exposed by inhalation to 300 ppm. Propylene oxide induced chromosomal aberrations and sister chromatid exchange in human lymphocytes and DNA damage, gene mutation, chromosomal aberrations and sister chromatid exchange in mammalian cells *in vitro*. It caused dominant lethal mutation in *Drosophila* and was mutagenic to yeast, fungi and bacteria.

5.5 Evaluation[1]

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

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

Overall evaluation

Propylene oxide *is possibly carcinogenic to humans (Group 2B).*

6. References

Agurell, E., Cederberg, H., Ehrenberg, L., Lindahl-Kiessling, K., Rannug, U. & Törnqvist, M. (1991) Genotoxic effects of ethylene oxide and propylene oxide: a comparative study. *Mutat. Res.*, **250**, 229–237

American Conference of Governmental Industrial Hygienists (1991) *Documentation of the Threshold Limit Values and Biological Exposure Indices*, 6th Ed., Cincinnati, OH, pp. 1316–1321

American Conference of Governmental Industrial Hygienists (1993) *1993–1994 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*, Cincinnati, OH, p. 30

Anon. (1981) Chemical profile: propylene oxide. *Chem. Mark. Rep.*, **220**, 50

Anon. (1984) Chemical profile: propylene oxide. *Chem. Mark. Rep.*, **225**, 54

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

Anon. (1987b) Chemical profile: propylene oxide. *Chem. Mark. Rep.*, **231**

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

Anon. (1990) Chemical profile: propylene oxide. *Chem. Mark. Rep.*, **237**, 46

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

Anon. (1993b) Chemical profile: propylene oxide. *Chem. Mark. Rep.*, **243**, 45

Ansari, G.A.S., Singh, S.V., Gan, J.C. & Awasthi, Y.C. (1987) Human erythrocyte glutathione *S*-transferase: a possible marker of chemical exposure. *Toxicol. Lett.*, **37**, 57–62

Ansari, G.A.S., Gan, J.C. & Barton, B.K. (1988) In vitro inactivation of plasma α_1-proteinase inhibitor by epoxides and 1,2-dihaloethanes. *Arch. environ. Contam. Toxicol.*, **17**, 537–542

Aranyi, C., O'Shea, W.J., Graham, J.A. & Miller, F.J. (1986) The effects of inhalation of organic chemical air contaminants on murine lung host defenses. *Fundam. appl. Toxicol.*, **6**, 713–720

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

ARCO Chemical Co. (1993) *Product Safety Bulletin: Propylene Oxide*, Newton Square, PA

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

Bailey, E., Farmer, P.B. & Shuker, D.E.G. (1987) Estimation of exposure to alkylating carcinogens by the GC–MS determination of adducts to hemoglobin and nucleic acid bases in urine. *Arch. Toxicol.*, **60**, 187–191

Beratergremium für umweltrelevante Altstoffe [Advisory Committee on Existing Chemicals of Environmental Relevance] (1993) *Propylene Oxide* (Report No. 94, Gesellschaft Deutscher Chemiker [Society of German Chemists]), Weinheim, VCH Verlagsgesellschaft

Bootman, J., Lodge, D.C. & Whalley, H.E. (1979) Mutagenic activity of propylene oxide in bacterial and mammalian systems. *Mutat. Res.*, **67**, 101–112

Canter, D.A., Zeiger, E., Haworth, S., Lawlor, T., Mortelmans, K. & Speck, W. (1986) Comparative mutagenicity of aliphatic epoxides in *Salmonella*. *Mutat. Res.*, **172**, 105–138

Castelain, P., Criado, B., Cornet, M., Laib, R., Rogiers, V. & Kirsch-Volders, M. (1993) Comparative mutagenicity of structurally related aliphatic epoxides in a modified *Salmonella*/microsome assay. *Mutagenesis*, **8**, 387–393

Chemical Information Services Ltd (1991) *Directory of World Chemical Producers 1992/93 Edition*, Dallas, TX, p. 500

Cook, W.A., ed. (1987) *Occupational Exposure Limits—Worldwide*, Akron, OH, American Industrial Hygiene Association, pp. 151, 211

Cookson, M.J., Sims, P. & Grover, P.L. (1971) Mutagenicity of epoxides of polycylic hydrocarbons correlates with carcinogenicity of parent hydrocarbons. *Nature*, **234**, 186–187

Dahlgran, J.R. & Shingleton, C.R. (1987) Determination of ethylene oxide in ethoxylated surfactants and demulsifiers by headspace gas chromatography. *J. Assoc. off. anal. Chem.*, **70**, 796–798

Dean, B.J. & Hodson-Walker, G. (1979) An in vitro chromosome assay using cultured rat-liver cells. *Mutat. Res.*, **64**, 329–337

Dean, B.J., Brooks, T.M., Hodson-Walker, G. & Hutson, D.H. (1985) Genetic toxicology testing of 41 industrial chemicals. *Mutat. Res.*, **153**, 57–77

Dent, J.G., & Schnell, S.R. (1981) Inhibition of microsomal-membrane bound and purified epoxide hydrolase by C_2–C_8 1,2-alkene oxides. *Biochem. Pharmacol.*, **30**, 1712–1714

Deutsche Forschungsgemeinschaft (1993) *MAK and BAT Values 1993* (Report No. 29), Weinheim, VCH Verlagsgesellschaft, p. 45

Direktoratet for Arbeidstilsynet [Directorate of Labour Inspection] (1990) *Administrative Normer for Forurensning i Arbeidsatmosfaere* [Administrative Norms for Pollution in Work Atmosphere], Oslo, p. 18

Djurić, Z., Hooberman, B.H., Rosman, L. & Sinsheimer, J.E. (1986) Reactivity of mutagenic propylene oxides with deoxynucleosides and DNA. *Environ. Mutag.*, **8**, 369-383

Dow Chemical Co. (1993) *Sales Specification: Propylene Oxide (Product No. 70557)*, Midland, MI

Dunkelberg, H. (1981) Carcinogenic activity of ethylene oxide and its reaction products 2-chloroethanol, 2-bromoethanol, ethylene glycol and diethylene glycol. I. Carcinogenicity of ethylene oxide in comparison with 1,2-propylene oxide after subcutaneous administration in mice. *Zbl. Bakt. Hyg. I. Abt. Orig. B*, **174**, 383–404 (in German)

Dunkelberg, H. (1982) Carcinogenicity of ethylene oxide and 1,2-propylene oxide upon intragastric administration to rats. *Br. J. Cancer*, **46**, 924–933

Ehrenberg, L. & Hussain, S. (1981) Genetic toxicity of some important epoxides. *Mutat. Res.*, **86**, 1–113

Eldridge, S.R., Bogdanffy, M.S., Jokinen, M.P., Ledbetter, A., Adkins, B. & Andrews, L.S. (1994) Effects of propylene oxide on nasal epithelial cell proliferation in F344 rats: implications for risk assessment (Abstract No. 536). *Toxicologist*, **14**, 151

Eller, P.M., ed. (1985) *NIOSH Manual of Analytical Methods*, 3rd ed., Suppl. 1 (DHHS (NIOSH) Publ. No. 84-100), Washington DC, US Government Printing Office, pp. 1612-1–1612-3

Farmer, P.B., Gorf, S.M. & Bailey, E. (1982) Determination of hydroxypropylhistidine in haemoglobin as a measure of exposure to propylene oxide using high resolution gas chromatography mass spectrometry. *Biomed. mass Spectrom.*, **9**, 69–71

Farooqi, Z., Törnqvist, M., Ehrenberg, L. & Natarajan, A.T. (1993) Genotoxic effects of ethylene oxide and propylene oxide in mouse bone marrow cells. *Mutat. Res.*, **288**, 223–228

Fjellstedt, T.A., Allen, R.H., Duncan, B.K. & Jakoby, W.B. (1973) Enzymatic conjugation of epoxides with glutathione. *J. biol. Chem.*, **248**, 3702–3707

Flores, G.H. (1983) Controlling exposure to alkylene oxides. *Chem. Eng. News*, **79**, 39–43

Gardner, M.J., Coggon, D., Pannett, B. & Harris, E.C. (1989) Workers exposed to ethylene oxide: a follow-up study. *Br. J. ind. Med.*, **46**, 860–865

Golka, K., Peter, H., Denk, B. & Filser, J.G. (1989) Pharmacokinetics of propylene and its reactive metabolite propylene oxide in Sprague-Dawley rats. *Arch. Toxicol., Suppl. 13*, 240–242

Grosjean, D. (1990) Atmospheric chemistry of toxic contaminants. 2. Saturated aliphatics: acetaldehyde, dioxane, ethylene glycol ethers, propylene oxide. *J. Air Waste Manag. Assoc.*, **40**, 1522–1531

Guengerich, F.P. & Mason, P.S. (1980) Alcohol dehydrogenase-coupled spectrophotometric assay of epoxide hydratase activity. *Anal. Biochem.*, **104**, 445–451

Gulati, D.K., Witt, K., Anderson, B., Zeiger, E. & Shelby, M.D. (1989) Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells *in vitro*. III. Results with 27 chemicals. *Environ. mol. Mutag.*, **13**, 133–193

Hackett, P.L., Brown, M.G., Buschbom, R.L., Clark, M.L., Miller, R.A., Music, R.L., Rowe, S.E., Schirmer, R.E. & Sikov, M.R. (1982) *Teratogenic Study of Ethylene and Propylene Oxide and n-Butyl Acetate* (NIOSH Contract No. 210-80-0013), Richland, WA, Battelle Pacific Northwest Laboratories

Hardin, B.D., Schuler, R.L., McGinnis, P.M., Niemeier, R.W. & Smith, R.J. (1983) Evaluation of propylene oxide for mutagenic activity in 3 in vivo test systems. *Mutat. Res.*, **117**, 337–344

Harris, S.B., Schardein, J.L., Ulrich, C.E. & Ridlon, S.A. (1989) Inhalation developmental toxicity study of propylene oxide in Fischer 344 rats. *Fundam. appl. Toxicol.*, **13**, 323–331

Hayes, W.C., Kirk, H.D., Gushow, T.S. & Young, J.T. (1988) Effect of inhaled propylene oxide on reproductive parameters in Fischer 344 rats. *Fundam. appl. Toxicol.*, **10**, 82–88

Hemminki, K. & Falck, K. (1979) Correlation of mutagenicity and 4-(*p*-nitrobenzyl)pyridine alkylation by epoxides. *Toxicol. Lett.*, **4**, 103–106

Hills, B. (1990a) *Health Hazard Determination Report, National Starch and Chemical Co., Island Falls, ME* (Report No. 88-340-2048), Cincinnati, OH, US National Institute for Occupational Safety and Health

Hills, B. (1990b) *Health Hazard Evaluation Report, A.E. Staley Manufacturing Co., Houlton, ME* (Report No. HETA 88-336-2038), Cincinnati, OH, US National Institute for Occupational Safety and Health

Hogstedt, L.C. (1988) Epidemiological studies on ethylene oxide and cancer: an updating. In: Bartsch, H., Hemminki, K. & O'Neill, I.K., eds, *Methods for Detecting DNA Damaging Agents in Humans: Applications in Cancer Epidemiology and Prevention* (IARC Scientific Publications No. 89), Lyon, IARC, pp. 265–270

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

Hogstedt, C., Aringer, L. & Gustavsson, A. (1986) Epidemiologic support for ethylene oxide as a cancer-causing agent. *J. Am. med. Assoc.*, **255**, 1575–1578

Högstedt, B., Bergmark, E., Törnqvist, M. & Osterman-Golkar, S. (1990) Chromosomal aberrations and micronuclei in lymphocytes in relation to alkylation of hemoglobin in workers exposed to ethylene oxide and propylene oxide. *Hereditas*, **113**, 133–138

von der Hude, W., Carstensen, S., Gürtler, R. & Obe, G. (1992) Structure-activity relationships of epoxides: induction of sister-chromatid exchanges in V79 cells by enantiomeric epoxides. *Mutat. Res.*, **278**, 289–297

Hughes, T.J., Simmons, D.M., Monteith, L.G. & Claxton, L.D. (1987) Vaporization technique to measure mutagenic activity of volatile organic chemicals in the Ames/*Salmonella* assay. *Environ. Mutag.*, **9**, 421–441

IARC (1976) *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*, Vol. 11, *Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics*, Lyon, pp. 191–199

IARC (1985) *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans*, Vol. 36, *Allyl Compounds, Aldehydes, Epoxides and Peroxides*, Lyon, pp. 227–243

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Suppl. 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, pp. 328–329

ILO (1991) *Occupational Exposure Limits for Airborne Toxic Substances: Values of Selected Countries* (Occupational Safety and Health Series No. 37), 3rd Ed., Geneva, pp. 188–189 (Substance No. 932)

Institut National de Recherche et de Sécurité (1993) *Limit Values for the Concentrations of Dangerous Substances in the Air of Work Places*, Paris

Japan Chemical Week, ed. (1985) *Japan Chemical Annual 1985: Japan's Chemical Industry and Engineering*, Tokyo, The Chemical Daily Co. Ltd, pp. 36–43

Japan Chemical Week, ed. (1987) *Japan Chemical Annual 1987/1988: Japan's Chemical Industry and Engineering*, Tokyo, The Chemical Daily Co. Ltd, pp. 34–41

Japan Chemical Week, ed. (1989) *Japan Chemical Annual 1989: Japan's Chemical Industry*, Tokyo, The Chemical Daily Co., Ltd., pp. 22–26

Japan Chemical Week, ed. (1991) *Japan Chemical Annual 1991: Japan's Chemical Industry*, Tokyo, The Chemical Daily Co., Ltd., pp. 28–32

Japan Petrochemical Industry Association (1993) *Petrochemical Industry of Japan*, Tokyo, p. 3

Jensen, O. (1981) Contact allergy to propylene oxide and isopropyl alcohol in a skin disinfectant swab. *Contact Derm.*, **7**, 148–150

de Jong, G., van Sittert, N.J. & Natarajan, A.T. (1988) Cytogenetic monitoring of industrial populations potentially exposed to genotoxic chemicals and of control populations. *Mutat. Res.*, **204**, 451–464

Kahlich, D., Wiechern, U. & Lindner, J. (1993) Propylene oxide. In: Elvers, B., Hawkins, S., Russey, W. & Schulz, G., eds, *Ullmann's Encyclopedia of Industrial Chemistry*, 5th rev. Ed., Vol. A22, New York, VCH Publishers, pp. 239–260

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

van Ketel, W.G. (1979) Contact dermatitis from propylene oxide. *Contact Derm.*, **5**, 191–192

Kirk, R.O. & Dempsey, T.J. (1982) Propylene oxide. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd Ed., Vol. 19, New York, John Wiley & Sons, pp. 246–274

Kohda, K.H., Ninomiya, S.-I., Washizu, K., Shiraki, K., Ebie, M. & Kawazoe, Y. (1987) Mutagenicity of a series of *N*-alkyl-, *N*-hydroxyalkyl-, *N*-haloalkyl- and *N*-carboxyalkyl-*N*-nitrosoureas in *Escherichia coli* tester strains: dependence on the *uvr*A DNA-repair system. *Mutat. Res.*, **177**, 219–228

Kølmark, G. & Giles, N.H. (1955) Comparative studies of monoepoxides as inducers of reverse mutations in *Neurospora*. *Genetics*, **40**, 890–902

Kuper, C.F., Reuzel, P.G.J., Feron, V.J. & Verschuuren, H. (1988) Chronic inhalation toxicity and carcinogenicity study of propylene oxide in Wistar rats. *Food chem. Toxicol.*, **26**, 159–167

Lehman, A.J. & Newman, H.W. (1937) Propylene glycol: rates of metabolism, absorption and excretion, with a method for estimation in body fluids. *J. Pharmacol. exp. Ther.*, **60**, 312–322

Lide, D.R., ed. (1991) *CRC Handbook of Chemistry and Physics*, 72nd Ed., Boca Raton, FL, CRC Press, pp. 3–427, 6–70

Lynch, D.W., Lewis, T.R., Moorman, W.J., Burg, J.R., Groth, D.H., Khan, A., Ackerman, L.J. & Cockrell, B.Y. (1984a) Carcinogenic and toxicologic effects of inhaled ethylene oxide and propylene oxide in F344 rats. *Toxicol. appl. Pharmacol.*, **76**, 69–84

Lynch, D.W., Lewis, T.R., Moorman, W.J., Burg, J.R., Gulati, D.K., Kaur, P. & Sabharwal, P.S. (1984b) Sister-chromatid exchanges and chromosomal aberrations in lymphocytes from monkeys exposed to ethylene oxide and propylene oxide by inhalation. *Toxicol. appl. Pharmacol.*, **76**, 85–95

Mannsville Chemical Products Corp. (1984) *Chemical Products Synopsis: Propylene Oxide*, Cortland, NY

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

McCammon, J., Orgel, D. & Hills, B. (1990) *Health Hazard Evaluation Report, A.E. Staley Manufacturing Co., Decatur, IL* (Report No. HETA 88-348-2081), Cincinnati, OH, US National Institute for Occupational Safety and Health

McDowell, E.M. (1978) Fixation and processing. In: Trump, B.F. & Jones, R.T., eds, *Diagnostic Electron Microscopy*, Vol. 1, New York, John Wiley & Sons, p. 135

McGregor, D., Brown, A.G., Cattanach, P., Edwards, I., McBride, D., Riach, C., Shepherd, W. & Caspary, W.J. (1991) Responses of the L5178Y mouse lymphoma forward mutation assay: V. Gases and vapors. *Environ. mol. Mutag.*, **17**, 122–129

McLaughlin, R.S. (1946) Chemical burns of the human cornea. *Am. J. Ophthalmol.*, **29**, 1355–1362

Meylan, W., Papa, L., De Rosa, C.T. & Stara, J.F. (1986) Chemical of current interest. Propylene oxide: health and environmental effects profile. *Toxicol. ind. Health*, **2**, 219–260

Migliore, L., Rossi, A.M. & Loprieno, N. (1982) Mutagenic action of structurally related alkene oxides on *Schizosaccharomyces pombe*: the influence, *'in vitro'*, of mouse-liver metabolizing system. *Mutat. Res.*, **102**, 425–437

Mowrer, J., Törnqvist, M., Jensen, S. & Ehrenberg, L. (1986) Modified Edman degradation applied to hemoglobin for monitoring occupational exposure to alkylating agents. *Toxicol. environ. Chem.*, **11**, 215–231

Oesch, F. (1974) Purification and specificity of a human microsomal epoxide hydratase. *Biochem. J.*, **139**, 77–88

Ohnishi, A. & Murai, Y. (1993) Polyneuropathy due to ethylene oxide, propylene oxide and butylene oxide. *Environ. Res.*, **60**, 242-247

Ohnishi, A., Yamamoto, T., Murai, Y., Hayashida, Y., Hori, H. & Tanaka, I. (1988) Propylene oxide causes central–peripheral distal axonopathy in rats. *Arch. environ. Health*, **43**, 353–356

Ong, T.-M., Stewart, J., Wen, Y.-F. & Whong, W.-Z. (1987) Application of SOS *umu*-test for the detection of genotoxic volatile chemicals and air pollutants. *Environ. Mutag.*, **9**, 171–176

Oser, J., Crandall, M., Phillips, R. & Marlow, D. (1978) *Indepth Industrial Hygiene Report of Ethylene Oxide Exposure at Union Carbide Corp., Institute, WV* (US NTIS PB82-114786), Cincinnati, OH, US National Institute for Occupational Safety and Health, pp. 14–15, 22

Oser, J., Young, M., Boyle, T. & Marlow, D. (1979) *Indepth Industrial Hygiene Report of Ethylene Oxide Exposure at Union Carbide Corp., South Charleston, WV* (US NTIS PB82-110024), Cincinnati, OH, US National Institute for Occupational Safety and Health, pp. 6, 13

Osterman-Golkar, S., Bailey, E., Farmer, P.B., Gorf, S.M. & Lamb, J.H. (1984) Monitoring exposure to propylene oxide through the determination of hemoglobin alkylation. *Scand. J. Work Environ. Health*, **10**, 99–102

Ott, M.G., Teta, M.J. & Greenberg, H.L. (1989) Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. *Am. J. ind. Med.*, **16**, 631–643

Pero, R.W., Bryngelsson, T., Widegren, B., Högstedt, B. & Welinder H. (1982) A reduced capacity for unscheduled DNA synthesis in lymphocytes from individuals exposed to propylene oxide and ethylene oxide. *Mutat. Res.*, **104**, 193–200

Pero, R.W., Osterman-Golkar, S. & Högstedt, B. (1985) Unscheduled DNA synthesis correlated to alkylation of hemoglobin in individuals occupationally exposed to propylene oxide. *Cell Biol. Toxicol.*, **1**, 309–314

Pfeiffer, E.H. & Dunkelberg, H. (1980) Mutagenicity of ethylene oxide and propylene oxide and of the glycols and halohydrins formed from them during the fumigation of foodstuffs. *Food Cosmet. Toxicol.*, **18**, 115–118

Randerath, K., Reddy, M.V. & Gupta, R.C. (1981) ^{32}P-Labeling test for DNA damage. *Proc. natl Acad. Sci. USA*, **78**, 6126–6129

Renne, R.A., Giddens, W.E., Boorman, G.A., Kovatch, R., Haseman. J.E. & Clarke, W.J. (1986) Nasal cavity neoplasia in F344/N rats and (C57BL/6×C3H)F_1 mice inhaling propylene oxide for up to two years. *J. natl Cancer Inst.*, **77**, 573–582

Rinsky, R.A., Ott, G., Ward, E., Greenberg, H., Halperin, W. & Leet, T. (1988) Study of mortality among chemical workers in the Kanawha Valley of West Virginia. *Am. J. ind. Med.*, **13**, 429–448

Rowe, V.K., Hollingsworth, R.L., Oyen, F., McCollister, D.D. & Spencer, H.C. (1956) Toxicity of propylene oxide determined on experimental animals. *Arch. ind. Health*, **13**, 228–236

Ruddick, J.A. (1972) Toxicology, metabolism, and biochemistry of 1,2-propanediol. *Toxicol. appl. Pharmacol.*, **21**, 102–111

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

Sangster, J. (1989) Octanol–water partition coefficients of simple organic compounds. *J. phys. chem. Ref. Data*, **18**, 1111–1229

Segerbäck, D., Nilsson, R., Osterman-Golkar, S. & Molholt, B. (1992) Human cancer risk assessment of propylene oxide based on determination of tissue dose in experimental animals. *Fresenius environ. Bull.*, **1**, 143–150

Segerbäck, D., Osterman-Golkar, S., Molholt, B. & Nilsson, R. (1994) In vivo tissue dosimetry as a basis for cross-species extrapolation in cancer risk assessment of propylene oxide. *Regul. Toxicol. Pharmacol.* (in press)

Sellakumar, A.R., Snyder, C.A. & Albert, R.E. (1987) Inhalation carcinogenesis of various alkylating agents. *J. natl Cancer Inst.*, **79**, 285–289

Simmon, V.F. (1981) Applications of the *Salmonella*/microsome assay. In: Stich, H.F. & San, R.H.C., eds, *Short-term Tests for Chemical Carcinogens*, New York, Springer-Verlag, pp. 120–126

Sina, J.F., Bean, C.L., Dysart, G.R., Taylor, V.I. & Bradley, M.O. (1983) Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. *Mutat. Res.*, **113**, 357–391

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

Snyder, C.A. & Solomon, J.J. (1993) The extent and persistence of binding to respiratory mucosal DNA by inhaled tritiated propylene oxide. *Cancer Lett.*, **72**, 157–161

Solomon, J.J., Mukai, F., Fedyk, J. & Segal, A. (1988) Reactions of propylene oxide with 2′-deoxynucleosides and *in vitro* with calf thymus DNA. *Chem.-biol. Interactions*, **67**, 275–294

Svensson, K., Olofsson, K. & Osterman-Golkar, S. (1991) Alkylation of DNA and hemoglobin in the mouse following exposure to propene and propylene oxide. *Chem.-biol. Interactions*, **78**, 55–66

Thiess, A.M., Schwegler, H., Fleig, I. & Stocker, W.G. (1981a) Mutagenicity study of workers exposed to alkylene oxides (ethylene oxide/propylene oxide) and derivatives. *J. occup. Med.*, **23**, 343–347

Thiess, A.M., Frentzel-Beyme R., Link, R. & Stocker, W.G. (1981b) Mortality study on employees exposed to alkylene oxides (ethylene oxide/propylene oxide) and their derivatives. In: *Prevention of Occupational Cancer. International Symposium* (Occup. Saf. Health Ser. 46), Geneva, ILO, pp. 249–259

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

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

Tucker, J.D., Xu, J., Stewart, J., Baciu, P.C. & Ong, T.-M. (1986) Detection of sister chromatid exchanges induced by volatile genotoxicants. *Teratog. Carcinog. Mutag.*, **6**, 15–21

Työministeriö [Ministry of Labour] (1993) *Limit Values 1993*, Helsinki, p. 17

UNEP (1993) *IRPTC Data Profile on Propylene Oxide*, Geneva

US Environmental Protection Agency (1987) *Summary Review of the Health Effects Associated with Propylene Oxide. Health Issue Assessment* (EPA/600/8-86/007F; PB87-216438), Research Triangle Park, NC

US Environmental Protection Agency (1992a) Exemptions from the requirement of a tolerance. *US Code fed. Regul.*, **Title 40**, Part 180.1001, pp. 406–428

US Environmental Protection Agency (1992b) Propylene oxide. *US Code fed. Regul.*, **Title 40**, Part 185.5150, pp. 465–466

US Food and Drug Administration (1993) Food and drugs. *US Code fed. Regul.*, **Title 21**, Parts 172.892, 176.210, 176.300, 178.3570, pp. 101–102, 202–206, 356–358

US National Institute for Occupational Safety and Health (1992) *NIOSH Recommendations for Occupational Safety and Health. Compendium of Policy Documents and Statements* (DHHS (NIOSH) Publ. No. 92-100), Cincinnati, OH, Division of Standards Development and Technology Transfer, p. 116

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

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

US National Toxicology Program (1985) *Toxicology and Carcinogenesis Studies of Propylene Oxide (CAS No. 75-56-9) in F344/N Rats and B6C3F$_1$ Mice (Inhalation Studies)* (Technical Report Series No. 267; NTP-83-020; NIH Publ. No. 85-2527), Research Triangle Park, NC

US Occupational Safety and Health Administration (1992) *Air Contaminants* (29 CFR 1910.1000), Washington DC, US Government Printing Office, pp. 6–34

Voogd, C.E., van der Stel, J.J. & Jacobs, J.J.J.A.A. (1981) The mutagenic action of aliphatic epoxides. *Mutat. Res.*, **89**, 269–282

Wade, D.R., Airy, S.C. & Sinsheimer, J.E. (1978) Mutagenicity of aliphatic epoxides. *Mutat. Res.*, **58**, 217–223

Walpole, A.L. (1958) Carcinogenic action of alkylating agents. *Ann. N.Y. Acad. Sci.*, **68**, 750–761

Weast, R.C. & Astle, M.J. (1985) *CRC Handbook of Data on Organic Compounds*, Vol. II, Boca Raton, FL, CRC Press, pp. 146, 183

Whistler, R.L. & Daniel, J.R. (1983) Starch. In: Mark, H.F., Othmer, D.F., Overberger, C.G., Seaborg, G.T. & Grayson, M., eds, *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed., Vol. 21, New York, John Wiley & Sons, pp. 492–507

WHO (1985) *Propylene Oxide* (Environmental Health Criteria 56), Geneva

Yamaguchi, T. (1982) Mutagenicity of trioses and methyl glyoxal on *Salmonella typhimurium*. *Agric. Biol. Chem.*, **46**, 849–851

Zamora, P.O., Benson, J.M., Li, A.P. & Brooks, A.L. (1983) Evaluation of an exposure system using cells grown on collagen gels for detecting highly volatile mutagens in the CHO/HGPRT mutation assay. *Environ. Mutag.*, **5**, 795–801

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T. & Mortelmans, K. (1988) *Salmonella* mutagenicity tests: IV. Results from the testing of 300 chemicals. *Environ. mol. Mutag.*, **11** (Suppl. 12), 1–158