1,2-DICHLOROETHANE

Data were last reviewed in IARC (1979) and the compound was classified in *IARC Monographs* Supplement 7 (1987a).

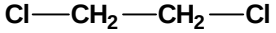
1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Serv. Reg. No.: 107-06-2
Chem. Abstr. Name: 1,2-Dichloroethane
IUPAC Systematic Name: 1,2-Dichloroethane
Synonym: Ethylene dichloride

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_2H_4Cl_2$ Relative molecular mass: 98.96

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: Colourless liquid with a pleasant odour (Budavari, 1996)
(*b*) *Boiling-point*: 83.5°C (Lide, 1995)
(*c*) *Melting-point*: –35.5°C (Lide, 1995)
(*d*) *Solubility*: Slightly soluble in water; miscible with ethanol, chloroform and diethyl ether (Lide, 1995; Budavari, 1996)
(*e*) *Vapour pressure*: 8 kPa at 20°C (Verschueren, 1996)
(*f*) *Flash-point*: 18°C, open cup (Budavari, 1996)
(*g*) *Conversion factor*: $mg/m^3 = 4.0 \times ppm$

1.2 Production and use

World production capacities in 1988 for 1,2-dichloroethane have been reported as follows (thousand tonnes): North America, 9445; western Europe, 9830; Japan, 3068; and other, 8351 (Snedecor, 1993). Production in the United States has been reported as follows (thousand tonnes): 1983, 5200; 1990, 6300; 1991, 6200; 1992, 6900; 1993, 8100 (United States National Library of Medicine, 1997). The total annual production in Canada in 1990 was estimated to be 922 thousand tonnes; more than 1000 thousand tonnes were produced in the United Kingdom in 1991 (WHO, 1995).

1,2-Dichloroethane is used primarily in the production of vinyl chloride; 99% of total demand in Canada, 90% in Japan and 88% of total production in the United States are used for this purpose. It is also used in the production of tri- and tetrachloroethylene, vinylidene chloride, ethyleneamines and trichloroethane; as a lead scavenger in antiknock fluids in gasoline; in paint, varnish and finish removers; as a component of metal-degreasing formulations; in soaps and scouring compounds, wetting and penetrating agents, organic synthesis and ore flotation; and as a solvent and fumigant. It is no longer registered for use as a fumigant on agricultural products in Canada, the United States, the United Kingdom or Belize (Lewis, 1993; WHO, 1995).

1.3 Occurrence

1.3.1 *Occupational exposure*

Current occupational exposure to 1,2-dichloroethane in North America occurs predominantly during the manufacture of other chemicals, such as vinyl chloride, where 1,2-dichloroethane is used as an intermediate. In a 1982 National Occupational Exposure Survey by the United States National Institute for Occupational Safety and Health (NIOSH), 28% of employees working with adhesives and solvents were exposed to 1,2-dichloroethane, while between 5 and 9% of workers were exposed to the substance in the medicinals and botanicals, biological products, petroleum refining and organic chemicals industries, and in museums and art galleries (United States Department of Labor, 1989).

Mean concentrations of 1,2-dichloroethane at three production plants in the United Kingdom in 1990 were 2.8, 3.2 and 6.8 mg/m^3; 95% of samples contained less than 20 mg/m^3, while maximum values at the plants were 18, 80 and 160 mg/m^3 (United Kingdom Health and Safety Executive, 1992).

1.3.2 *Environmental occurrence*

The majority of 1,2-dichloroethane released into the environment enters the atmosphere from its production and use as a chemical intermediate, solvent and lead scavenger in gasoline. It has been detected at low levels in ambient and urban air, groundwater and drinking-water samples (United States National Library of Medicine, 1997).

1.4 Regulations and guidelines

The American Conference of Governmental Industrial Hygienists (ACGIH) (1997) has recommended 40 mg/m^3 as the threshold limit value for occupational exposures to 1,2-dichloroethane in workplace air. Similar values have been used as standards or guidelines in many countries (International Labour Office, 1991).

The World Health Organization has established an international drinking water guideline for 1,2-dichloroethane of 30 μg/L (WHO, 1993).

2. Studies of Cancer in Humans

2.1 Cohort studies

Several studies have examined mortality or cancer incidence among chemical workers potentially exposed to 1,2-dichloroethane. Hogstedt *et al*. (1979) performed a cohort mortality study of 175 Swedish ethylene oxide production workers followed from 1961 through 1977. The workers had been employed for at least one year and were potentially exposed to 1,2-dichloroethane, ethylene oxide (IARC, 1994), ethylene chlorohydrin and bis(2-chloroethyl) ether. The mean exposure level to 1,2-dichloroethane among the most highly exposed workers was estimated to be 100 mg/m^3 during 1941–47 but to have decreased after that due to changes in production methods. There were 37 deaths [standardized mortality ratio (SMR), 1.4] and 12 cancer deaths [SMR, 1.8]. Excesses of stomach cancer ([SMR, 5.0], based on 4 cases) and leukaemia ([SMR, 11.1], based on 3 cases) were observed. It was not possible to link the excesses to any particular chemical exposure.

Austin and Schnatter (1983a) conducted a cohort study of 6588 white male workers employed at a petrochemical plant in the United States between 1941 and 1977. The study was conducted to investigate a cluster of brain tumours that was reported earlier in the same population (Alexander *et al*., 1980). There were 765 deaths (SMR, 0.8) and 150 cancer deaths (SMR, 0.9) observed. A greater than expected number (based on national rates) of brain cancers (SMR, 1.6; 95% confidence interval (CI), 0.8–2.8, based on 12 cases) was observed. Austin and Schnatter (1983b) also conducted a nested case–control study to examine the relationship between the risk of primary brain tumours and exposures at the facility. No significant association with 1,2-dichloroethane exposure was observed.

Sweeney *et al*. (1986) studied mortality among 2510 male chemical workers in the United States, followed from 1952 to 1977. Potential exposures included tetraethyl lead (IARC, 1987b), ethylene dibromide (see this volume), 1,2-dichloroethane, inorganic lead (IARC, 1987b) and vinyl chloride monomer (IARC, 1987c). There were 156 deaths (SMR, 0.7) and 38 cancer deaths (SMR, 1.0) observed. There were excesses of cancer of the larynx (SMR, 3.6; 90% CI, 0.7–11.5, based on 2 cases) and brain (SMR, 2.1; 90% CI, 0.7–4.9, based on 4 cases). The SMR for all lymphatic and haematopoietic cancers was 0.9 (90% CI, 0.3–1.9, based on 4 cases). Levels of exposure were not reported, but a NIOSH survey in 1980 found levels of exposure to 1,2-dichloroethane to be below the recommended NIOSH standard, while lead exposures were elevated. It was not possible to link mortality to any particular chemical exposure.

Benson and Teta (1993) studied the mortality among 278 chlorohydrin production workers who had ever been employed at a facility in the United States between 1940 and 1967. The follow-up period was from 1940 to 1988. This was a 10-year update of an earlier study conducted by Greenberg *et al*. (1990). There were 147 deaths (SMR, 1.0) and 40 cancer deaths (SMR, 1.3) observed. Excesses of pancreatic cancer (SMR, 4.9; 95% CI, 1.6–11.4; 8 cases) and lymphatic and haematopoietic cancers (SMR, 2.9; 95% CI, 1.3–5.8;

8 cases), which increased with duration of exposure, were observed. The workers were potentially exposed to 1,2-dichloroethane, ethylene chlorohydrin and bis(2-chloroethyl) ether. It was not possible to link the excesses to any particular chemical exposure and levels of exposure were not reported.

Olsen *et al*. (1997) studied mortality among 1361 men employed at two chlorohydrin production facilities in the United States similar to that studied by Benzon and Teta (1993). There were 300 deaths (SMR, 0.9) and 75 cancer deaths (SMR, 0.9) observed. The risks of pancreatic cancer (SMR, 0.3; 95% CI, 0.01–1.4; 1 case) and lymphatic and haematopoietic cancers (SMR, 1.3; 95% CI, 0.6–2.4; 10 cases) were less than those observed by Benson and Teta and no other cancers were observed in excess. It was not possible to link mortality to any particular chemical exposure and levels of exposure were not reported.

2.2 Ecological studies

Isacson *et al*. (1985) examined the association between cancer incidence and indices of water contamination in an ecological study conducted in the central United States. Cancer incidence rates in towns with populations between 1000 and 10 000 were compared by level of volatile organic compounds and metals in the drinking-water. Among men, significant associations between the level of 1,2-dichloroethane (≥ 0.1 ppm) and colon ($p = 0.009$) and rectal cancer ($p = 0.02$) were observed. The authors stated that 1,2-dichloroethane might be an indicator for other types of contamination rather than a causal agent.

3. Studies of Cancer in Experimental Animals

1,2-Dichloroethane was tested in one experiment in mice and in one in rats by oral administration. In mice, it produced benign and malignant tumours of the lung and malignant lymphomas in animals of both sexes, hepatocellular carcinomas in males and mammary and uterine adenocarcinomas in females. In rats, it produced carcinomas of the forestomach in male animals, benign and malignant mammary tumours in females and haemangiosarcomas in animals of both sexes. It was inadequately tested by intraperitoneal administration in mice (IARC, 1979).

3.1 Inhalation exposure

3.1.1 *Mouse*

Groups of 90 male and 90 female Swiss mice, 11 weeks of age, were exposed to concentrations of 5, 10, 50 or 250 ppm [20, 40, 200 or 1000 mg/m^3] 1,2-dichloroethane (purity, 99.82%; 1,1-dichloroethane, 0.02%; carbon tetrachloride, 0.02%; trichloroethylene, 0.02%; tetrachloroethylene, 0.03%; benzene, 0.09%) in air for 7 h per day on five days per week for 78 weeks. After several days of exposure to 250 ppm, the concentration was reduced to 150 ppm because of severe toxic effects. A group of 115 males and

134 females kept in a nearby room served as controls. At the end of the treatment period, the animals were kept until spontaneous death. The experiment lasted 119 weeks. A complete autopsy was carried out on all animals and histological examination was performed on almost all organs. Survival at 78 weeks of age was 42/115, 26/90, 34/90, 30/90 and 26/90 in control, 5-ppm, 10-ppm, 50-ppm and 150–250-ppm males and 76/134, 68/90, 50/90, 49/90 and 44/90 in control, 5-ppm, 10-ppm, 50-ppm and 150–250-ppm females, respectively. No specific types of tumour or changes in the incidence of tumours normally occurring in the strain of mice used were observed in the treated animals (Maltoni *et al*., 1980). [The Working Group noted the low survival rates, especially in males.]

Groups of 50 male and 50 female BDF_1 mice, six weeks of age, were exposed by whole-body inhalation to 0, 10, 30 or 90 ppm [0, 40, 120 or 360 mg/m^3] 1,2-dichloroethane (purity, > 99%) for 6 h per day on five days per week for 104 weeks. The maximum exposure concentration (90 ppm) was selected on the basis of the result of a 13-week study. In males, significantly increased incidence of liver haemangiosarcomas was observed at mid- and high-dose. In females, increased incidence of bronchiolar-alveolar adenomas and carcinomas, hepatocellular adenomas, adenocarcinomas of the mammary gland and endometrial stromal polyps occurred, with a significantly positive trend [statistics not specified] (Table 1) (Nagano *et al.*, 1998).

Table 1. Tumour incidence in mice administered 1,2-dichloroethane by inhalation exposure

Mice		Exposure concentration (ppm)			
		0	10	30	90
Males	Liver haemangiosarcoma	0/50	4/49	6/50	5/50
Females	Hepatocellular adenoma	1/49	1/50	1/50	6/50
	Bronchiolar-alveolar adenoma and carcinoma	5/49	1/50	4/50	11/50
	Mammary gland adenocarcinoma	1/49	2/50	1/50	6/50
	Endometrial stromal polyp	2/49	0/50	1/50	6/50

From Nagano *et al*. (1998)

3.1.2 *Rat*

Groups of 90 male and 90 female Sprague-Dawley rats, 12 weeks of age, were exposed to concentrations of 5, 10, 50 or 250 ppm [20, 40, 200 or 1000 mg/m^3] 1,2-dichloroethane (purity, 99.82%; 1,1-dichloroethane, 0.02%; carbon tetrachloride, 0.02%; trichloroethylene, 0.02%; tetrachloroethylene, 0.03%; benzene, 0.09%) in air for 7 h per day on five days per week for 78 weeks. After several days of exposure to 250 ppm, the concentration was reduced to 150 ppm because of severe toxic effects. A group of 90 males and 90 females kept in an exposure chamber under the same conditions for the same amount of

time as the exposed animals served as chamber controls. Another group of 90 males and 90 females kept in a nearby room served as untreated controls. At the end of the treatment period, the animals were kept until spontaneous death. The experiment lasted for 148 weeks. A complete autopsy was carried out on all animals and histological examination was performed on almost all organs. Survival at 104 weeks of age was 16/90, 12/90, 45/90, 13/90, 17/90 and 10/90 in control, chamber-control, 5-ppm, 10-ppm, 50-ppm and 150–250-ppm males and 36/90, 22/90, 48/90, 26/90, 29/90 and 21/90 in control, chamber-control, 5-ppm, 10-ppm, 50-ppm and 150–250-ppm females, respectively. The incidence of mammary fibromas and fibroadenomas in females was 47/90, 27/90, 56/90, 33/90, 49/90 and 47/90 in control, chamber-control, 5-ppm, 10-ppm, 50-ppm and 150–250-ppm groups, respectively. The increase in the incidence of these mammary tumours was significant (chi-square test) in the 150–250-ppm ($p < 0.001$), 50-ppm ($p < 0.01$) and 5 ppm ($p < 0.001$) groups, in comparison to chamber controls. The difference between the incidences in the two control groups was also significant ($p < 0.01$) (Maltoni *et al*., 1980). [The Working Group noted the low and variable survival rates.]

Groups of 50 male and 50 female Sprague-Dawley rats, 5.5–6 weeks of age, were exposed to concentrations of 0 or 50 ppm [200 mg/m^3] 1,2-dichloroethane (purity, > 99%) for 7 h per day on five days per week for 24 months. A complete autopsy was carried out on each animal and histological examination was performed on almost all organs and all gross lesions and tissue masses. Survival was 58% and 60% among the control and treated males and 54% and 64% among the control and treated females, respectively. There were no significant differences in the incidence of tumours between the control and treated groups (Cheever *et al*., 1990). [The Working Group noted the low exposure level.]

Groups of 50 male and 50 female Fischer 344 rats, six weeks of age, were exposed by whole-body inhalation to 0, 10, 40 or 160 ppm [0, 40, 160 or 640 mg/m^3] 1,2-dichloroethane (purity, > 99%) for 6 h per day on five days per week for 104 weeks. The maximum exposure concentration (160 ppm) was selected on the basis of the result of a 13-week study. In males, increased incidences of fibromas of the subcutis, fibroadenomas of the mammary gland and mesotheliomas of the peritoneum occurred, with a significantly positive trend [statistics not specified]. In females, increased incidences of fibromas of the subcutis and fibroadenomas, adenomas and adenocarcinomas of the mammary gland occurred, with a significantly positive trend (Table 2) (Nagano *et al.*, 1998).

3.2 Skin application

Mouse: A group of 30 female Ha:ICR Swiss mice, six to eight weeks of age, received skin applications of 126 mg/animal 1,2-dichloroethane [purity unspecified] in 0.2 mL acetone three times per week for life [survival and duration of treatment unspecified]. A group of 30 mice that received applications of 0.1 mL acetone alone served as controls. A complete autopsy was carried out and histological examinations were performed on the skin, liver, stomach, kidney and all abnormal-appearing tissues and organs. An increased incidence of lung tumours was observed in the high-dose treated group (26/30) compared with controls (11/30) ($p < 0.0005$, chi-square test). No skin tumours were observed in

Table 2. Tumour incidence in rats administered 1,2-dichloroethane by inhalation exposure

Rats		Exposure concentration (ppm)			
		0	10	40	160
Males	Mammary fibroadenoma	0/50	0/50	1/50	5/50
	Subcutaneous fibroma	6/50	9/50	12/50	15/50
	Peritoneal mesothelioma	1/50	1/50	1/50	5/50
Females	Mammary adenoma	3/50	5/50	5/50	11/50
	Mammary fibroadenoma	4/50	1/50	6/50	13/50
	Mammary adenocarcinoma	1/50	2/50	0/50	5/50
	Subcutaneous fibroma	0/50	0/50	1/50	5/50

From Nagano *et al.* (1998)

treated mice or controls (Van Duuren *et al.*, 1979). [The Working Group noted the inadequate reporting.]

3.3 Multistage protocols and preneoplastic lesions

3.3.1 *Mouse*

In a two-stage mouse-skin assay, a group of 30 female Ha:ICR Swiss mice, six to eight weeks of age, received a single skin application of 126 mg per animal 1,2-dichloroethane [purity unspecified] in 0.2 mL acetone, followed 14 days later by 5 µg per animal phorbol myristyl acetate in 0.2 mL acetone three times weekly for life. Survival was described as excellent, the median survival for the various groups in the study [that included some groups exposed to chemicals other than 1,2-dichloroethane and the controls] ranging from 429 to 576 days. Animals treated with phorbol myristyl acetate alone served as controls. There were no significant differences in the occurrence of skin tumours between controls (total, 7 papillomas in 6/90 mice) and treated groups (total, 3 papillomas in 3/30 mice) (Van Duuren *et al.*, 1979).

Groups of 25 male B6C3F$_1$ mice, 30 days of age, received drinking-water containing 10 mg/L *N*-nitrosodiethylamine (NDEA) for four weeks. Animals were then given drinking-water containing 0 (controls), 835 or 2500 mg/L 1,2-dichloroethane [purity unspecified] for 52 weeks. The highest concentration of 1,2-dichloroethane was that which failed to cause mortality in eight-week-old B6C3F$_1$ mice after a four-week exposure period. A complete autopsy was carried out and histological examination was performed on the liver, kidney and lung. There were no significant differences in either tumour incidence or number of tumours per mouse in any organ between the controls and 1,2-dichloroethane-treated groups. The incidences of liver tumours were 25/25, 25/25 and 23/25 in control, low-dose and high-dose mice, respectively, and the numbers of liver tumours per mouse were 29.30 ± 15.40, 34.50 ± 17.40 and 25.20 ± 16.70, respectively.

The incidences of lung tumours were 18/25, 12/25 and 23/25, respectively, and the numbers of lung tumours per mouse were 1.40 ± 1.40, 1.00 ± 1.10 and 2.60 ± 2.00, respectively (Klaunig *et al.*, 1986). [The Working Group noted that the tumour incidences in controls were too high for evaluation of a promoting effect of 1,2-dichloroethane.]

3.3.2 *Rat*

In an initiation study, one group of 10 male Osborne-Mendel rats, weighing 180–230 g, was given a two-thirds partial hepatectomy and, 24 h later, a single dose of 100 mg/kg bw 1,2-dichloroethane (purity, 97–99%) (maximum tolerated dose) in corn oil by gavage. Similar groups of animals were treated with 2 mL/kg bw corn oil alone (vehicle controls) or 30 mg/kg bw *N*-nitrosodiethylamine (NDEA; positive controls) followed by a two-thirds partial hepatectomy. Starting six days after partial hepatectomy, the rats received 500 mg/kg of diet (0.05% w/w) phenobarbital for seven weeks, then control diet for seven more days, after which time they were killed and the livers were examined histologically for γ-glutamyltranspeptidase (γ-GT)-positive foci. There was no significant increase in the number of total γ-GT-positive foci (1.02 ± 0.55 and 0.27 ± 0.19/cm^2 in the 1,2-dichloroethane group and vehicle controls, respectively). NDEA treatment increased the numbers of γ-GT-positive foci (4.04 ± 1.47/cm^2) (Milman *et al*., 1988). [The Working Group noted the small number of animals.]

In a promotion study, groups of 10 male Osborne-Mendel rats, weighing 180–230 g, were given a single intraperitoneal injection of 30 mg/kg bw NDEA 24 h after a two-thirds partial hepatectomy. Starting six days later, the rats received daily 100 mg/kg bw 1,2-dichloroethane (purity, 97–99%) (maximum tolerated dose) in corn oil by gavage on five days per week for seven weeks. Control rats received corn oil alone instead of 1,2-dichloroethane. After the promotion phase, the rats were held for seven more days, after which they were killed and the livers were examined histologically for γ-GT-positive foci. There was no significant difference in the number of total γ-GT-positive foci between the 1,2-dichloroethane group and controls (1.54 ± 0.54 and 1.62 ± 0.33/cm^2, respectively) (Milman *et al*., 1988). [The Working Group noted the small number of animals.]

A group of 50 male and 50 female Sprague-Dawley rats, 5.5–6 weeks of age, was exposed by inhalation to 50 ppm [200 mg/m^3] 1,2-dichloroethane (purity, > 99%) for 7 h per day on five days per week and to 500 mg/kg of diet (0.05%) disulfiram (purity, 98%) for 24 months. A complete autopsy was carried out on each animal and histopathological examination was performed on almost all organs and all gross lesions and tissue masses. In the liver, increased incidences of intrahepatic bile duct cholangiomas (0/50 untreated control males, 9/49 treated males, 0/50 untreated control females and 17/50 treated females), intrahepatic bile duct cysts (1/50 control males, 12/49 treated males, 1/50 treated females and 24/50 treated females) and neoplastic nodules in males (0/50 untreated controls and 6/49 treated) were observed in the treated group ($p < 0.05$; Fisher's exact test). The incidence of adenocarcinomas of the mammary gland in females (4/50 controls and 12/48 treated) and that of interstitial-cell tumours of the testis in males (2/50 controls and 11/50 treated) were increased in the treated group ($p < 0.05$) (Cheever *et al*., 1990).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Case reports of reported acute toxic effects following inhalation exposure to 1,2-dichloroethane in the workplace indicate that 1,2-dichloroethane is readily absorbed by humans (Nouchi *et al.*, 1984).

The analysis of several tissues of humans who died following acute oral poisoning with 1,2-dichloroethane showed that 1,2-dichloroethane is widely distributed throughout the human body. Concentrations ranged from 1 to 50 mg/kg in the spleen and 100 to 1000 mg/kg in the stomach; levels in the liver and kidney were approximately 10 times lower than those in the stomach (Luznikov *et al.*, 1985).

Cytochrome P450 IIE1 is a major catalyst in the oxidation of 1,2-dichloroethane in human liver microsomes (Guengerich *et al.*, 1991).

4.1.2 *Experimental animals*

In rats, absorption following ingestion of 1,2-dichloroethane is rapid and complete (Reitz *et al.*, 1982). The pharmacokinetics following oral administration of 1,2-dichloroethane are dose-dependent over the range 25–150 mg/kg bw. The plasma elimination $t_{½}$ increases from 25 min to 57 min, while the area under the curve (AUC) increases 16-fold with a six-fold increase in dose. However, C_{max} is proportional to dose up to oral doses of 150 mg/kg bw (Spreafico *et al.*, 1980). There was no significant difference in kinetic parameters following single and repeated daily administrations of 50 mg/kg bw for 10 days. Gastrointestinal absorption in rats was more rapid and efficient following administration in water, compared with corn oil (Withey *et al.*, 1983).

Absorption following inhalation by experimental animals was also rapid. In rats, levels of 1,2-dichloroethane in the blood peaked (8–10 µg/mL) within 1–2 h of continuous inhalation of 600 mg/m^3 for 6 h (Reitz *et al.*, 1982).

1,2-Dichloroethane is also rapidly absorbed through the skin in mice, rats and guinea-pigs (Tsuruta, 1975, 1977). It was rapidly absorbed when applied in aqueous solution to the skin of rats *in vivo*, giving blood levels directly related to the concentration of the solution (Jakobson *et al.*, 1982; Morgan *et al.*, 1991). 1,2-Dichloroethane is widely distributed throughout the body in rats exposed via inhalation or ingestion. After inhalation, the highest concentrations were usually found in adipose tissue, although 1,2-dichloroethane was also detected in blood, liver, kidney, brain and spleen (Spreafico *et al.*, 1980).

Reitz *et al.* (1982) reported that the relative distribution of radioactivity at 48 h (assumed to be primarily in the form of metabolites) was similar in rats given ^{14}C-labelled 1,2-dichloroethane orally (single dose of 150 mg/kg bw) or by inhalation (600 mg/m^3 for 6 h). Residual radioactivity in selected tissues was 1.5–2.0 times higher after oral exposure than following inhalation. There was also a higher residual activity in the fore-

stomach after the oral exposure. The distribution pattern for macromolecular binding was similar, as determined 4 h after oral ingestion or directly after inhalation. Oral exposure produced lower (i.e., 1.5–2 times lower) levels of total macromolecular binding but higher (3–5 times) levels of DNA alkylation than inhalation, although the absolute levels were considered low.

Arfellini *et al*. (1984) reported a greater degree of binding to DNA in organs (liver, kidneys, lung and stomach) of mice than in those of rats (1.45–2.26-fold) 22 h after intraperitoneal administration of equivalent single doses of 8.7 μmol/kg bw.

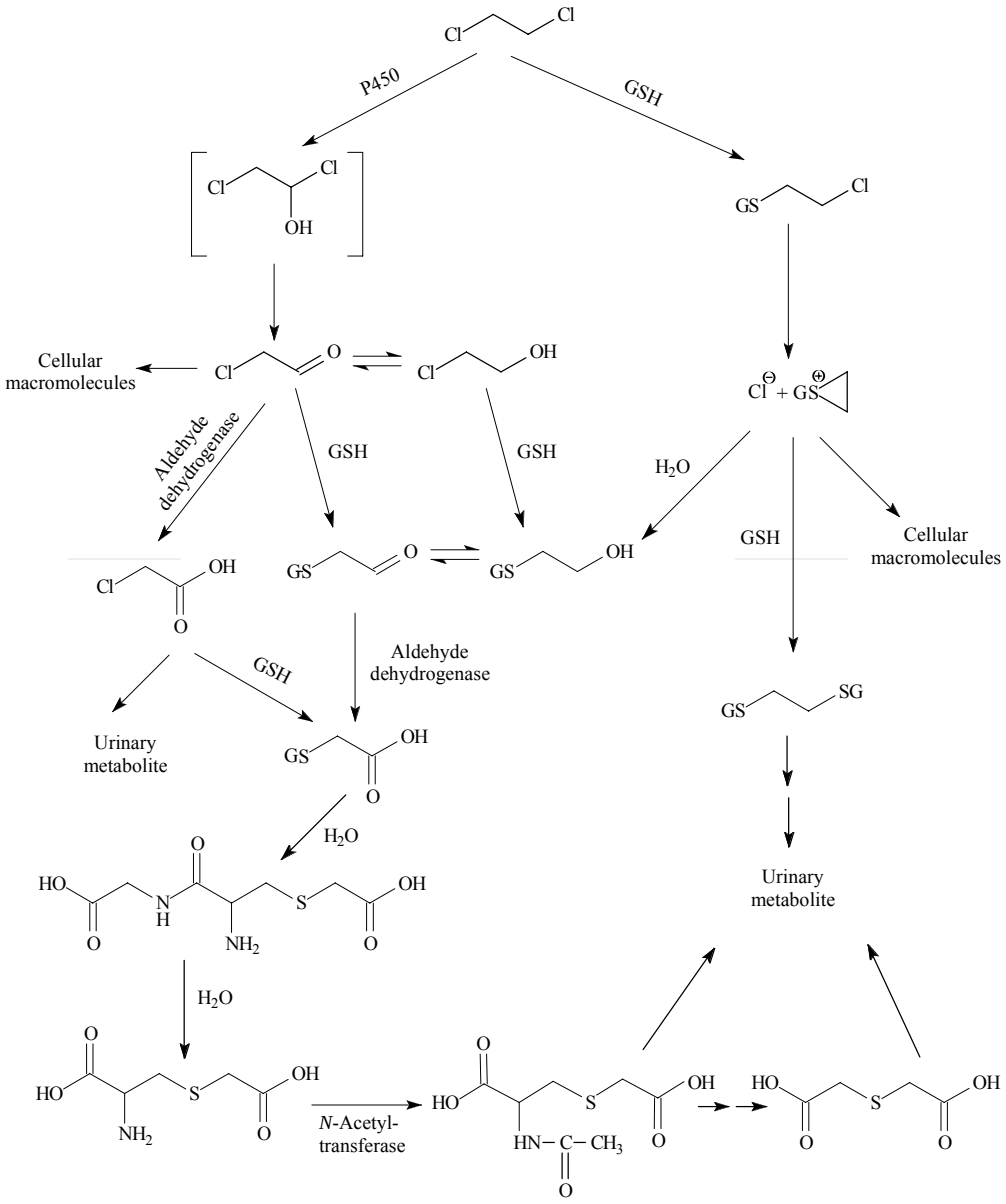
In periods from one minute to four days following intravenous administration of a single dose (0.73 mg/kg bw) of radiolabelled 1,2-dichloroethane to mice, the highest levels of radioactivity (non-volatile and bound metabolites) determined by whole-body autoradiography were present in the nasal olfactory mucosa and the tracheo-bronchial epithelium. Low levels of metabolites were also present in the epithelium of the upper alimentary tract, vagina and eyelid and in the liver and kidney. Mucosal and epithelial binding was decreased by pretreatment with metyrapone, indicating that binding might be due to oxidative metabolism. In in-vitro studies with tissues from the same strain of mice, reactive products formed from 1,2-dichloroethane were irreversibly bound to the nasal mucosa, lung and liver but not to the oesophagus, forestomach or vagina. The level of binding in the nasal mucosa was twice and in the lung 1.4 times that observed in the liver. The epithelium of the respiratory tract may be a potential target for the toxic effects of 1,2-dichloroethane due to in-situ metabolism to reactive intermediates (Brittebo *et al.*, 1989).

1,2-Dichloroethane was detected in fetal tissue of rats following maternal exposure for 5 h to airborne concentrations ranging from 612 to 8000 mg/m^3 (153–2000 ppm) on day 17 of gestation (Withey & Karpinski, 1985).

1,2-Dichloroethane is metabolized extensively in rats and mice (Mitoma *et al.*, 1985). Reitz *et al*. (1982) reported 70 and 91% transformation of 1,2-dichloroethane in the rat following oral (150 mg/kg bw) and inhalation (600 mg/m^3 for 6 h) exposures, respectively, with 85% of the metabolites appearing in the urine. The metabolism of 1,2-dichloroethane appears to be saturated or limited in rats at levels of exposure resulting in blood concentrations of 5–10 μg/mL.

Metabolism appears to occur via two principal pathways, catalysed by cytochrome P450 and by glutathione *S*-transferase (Figure 1). Cytochrome P450 enzymes catalyse oxidative transformation of 1,2-dichloroethane to 2-chloroacetaldehyde, 2-chloroacetic acid and 2-chloroethanol (Guengerich *et al.*, 1980), which are conjugated both enzymatically and non-enzymatically with glutathione (GSH). The other pathway involves direct conjugation with GSH to form *S*-(2-chloroethyl)glutathione, which is a sulfur half mustard (Schasteen & Reed, 1983; Foureman & Reed, 1987). A non-enzymatic reaction of the half mustard gives a putative alkylating agent (episulfonium ion) which may react with water to form *S*-(2-hydroxyethyl)glutathione, with thiols such as GSH to form ethene bis-glutathione, or with DNA to form adducts. With the exception of *S*-(2-chloroethyl)glutathione which forms DNA adducts, the reaction products are considered non-toxic and undergo further metabolism.

Figure 1. Proposed pathways for metabolism of 1,2-dichloroethane



Although some DNA damage has been induced via the P450 pathway *in vitro* (Banerjee *et al.*, 1980; Guengerich *et al.*, 1980; Lin *et al.*, 1985), several lines of evidence suggest that the GSH conjugation pathway is probably the major route for DNA damage (Guengerich *et al.*, 1980; Rannug, 1980; Guengerich *et al.*, 1981; Van Bladeren *et al.*, 1981; Sundheimer *et al.*, 1982; Crespi *et al.*, 1985; Storer & Conolly, 1985; Inskeep *et al.*, 1986; Koga *et al.*, 1986; Cheever *et al.*, 1990).

A single dose of 150 mg/kg bw radiolabelled 1,2-dichloroethane was administered by gavage to male and female rats 10–14 days after cessation of two years of 1,2-dichloroethane exposure via inhalation at a concentration of 50 ppm [200 mg/m^3]. The proportions of radioactivity present in the urine within 24 h were 42.5 and 33.9% in males and females, respectively, while 27.3 and 40.3% were eliminated as the unchanged parent compound in the breath. Only a very small amount of radioactivity was detected as $^{14}CO_2$ or in the faeces. In rats that had been exposed concomitantly to disulfiram during the two-year period, the proportion of unchanged 1,2-dichloroethane eliminated in the breath increased significantIy (i.e., 57.6 and 57.7%; $p < 0.05$), while the proportion eliminated in the urine decreased correspondingly (27.6 and 24.9 %). Levels of unchanged 1,2-dichloroethane in blood were significantly ($p < 0.05$) higher in rats exposed to 1,2-dichloroethane and disulfiram than in those exposed to 1,2-dichloroethane alone (Cheever *et al.*, 1990).

The pattern of elimination of metabolites was similar in rats and mice 48 h after administration of oral doses of radiolabelled 1,2-dichloroethane (100 and 150 mg/kg bw, respectively). In rats, 8.2 and 69.5% of the radiolabelled dose was recovered as CO_2 and in the excreta (principally urine), respectively, compared with 18 and 82% in mice. The overall recovery was reported to be less in rats than in mice (96 versus 110%) (Mitoma *et al.*, 1985).

In rats exposed to 600 mg/m^3 [150 ppm] 1,2-dichloroethane for 6 h or administered 150 mg/kg bw by gavage, there was no significant difference in the route of excretion of non-volatile metabolites (Reitz *et al.*, 1982). The major urinary metabolites identified following exposure of rats by either route were thiodiacetic acid (67–68%) and thiodiacetic acid sulfoxide (26–29%).

The rate of elimination following oral administration (gavage) or inhalation was rapid and 1,2-dichloroethane was no longer detected in the blood a few hours after oral or inhalation exposure and only small amounts were detected in tissues (liver, kidney, lung, spleen, forestomach, stomach and carcass) 48 h after exposure (Spreafico *et al.*, 1980; Reitz *et al.*, 1982).

The percentage of administered radioactivity excreted in the urine over a 24 h period in rats decreased with increasing single doses (0.25–8.08 mmol/kg bw 1,2-dichloroethane) administered by gavage in mineral oil (Payan *et al.*, 1993). The authors attributed these results to saturation of metabolism rather than kidney damage, as there were no variations in biochemical parameters of nephrotoxicity between the controls and groups exposed to doses up to 4.04 mmol/kg bw. Urinary levels of thiodiglycolic acid increased as a linear function of the dose of 1,2-dichloroethane until

at least 1.01 mmol/kg bw; this accounted for 63% of the total metabolites in urine at this dose.

Although 1,2-dichloroethane is eliminated more slowly from adipose tissue than from blood or other tissues (lung and liver) following exposure, it is unlikely to bioaccumulate, as no significant difference was observed between levels in blood or tissues following single or repeated (10 days) oral doses of 50 mg/kg bw in rats (Spreafico *et al.*, 1980; Cheever *et al.*, 1990).

4.2 Toxic effects

The toxicity of 1,2-dichloroethane has been reviewed (WHO, 1995).

4.2.1 *Humans*

Deaths due to ingestion or inhalation of 1,2-dichloroethane have been attributed to circulatory and respiratory failure; repeated exposures in the occupational environment have been associated with anorexia, nausea, abdominal pain, irritation of the mucous membranes, dysfunction of liver and kidney and neurological disorders (IARC, 1979).

4.2.2 *Experimental systems*

Acute exposure of rats to 1,2-dichloroethane caused disseminated haemorrhagic lesions, mainly in the liver; chronic exposure caused degeneration of the liver and tubular damage and necrosis of the kidneys (IARC, 1979). The limited organ toxicity of 1,2-dichloroethane in long-term experiments was substantiated in a long-term study (United States National Cancer Institute, 1978), in which no gross or histopathological indications of hepato- or nephrotoxicity were observed by gavage in Osborne-Mendel rats (47 or 95 mg/kg bw/day, five days per week for 78 weeks for both sexes) or B6C3F_1 mice (97 or 195 mg/kg bw/day, five days per week for 78 weeks for males; 149 or 299 mg/kg bw/day, five days per week for 78 weeks for females), although in rats of each sex and in female mice, survival was significantly reduced at the highest dose.

As a part of a long-term carcinogenicity study (Maltoni *et al.*, 1980), haematological parameters and clinical chemistry parameters reflecting liver and kidney function were studied after three, six, 12 or 18 months inhalation exposure to 5, 10, 50 or 150–250 ppm [20, 40, 200 or 600–1000 mg/m^3] 1,2-dichloroethane (Spreafico *et al.*, 1980). No consistent treatment-related effect was observed.

A single oral dose (≥ 400 mg/kg bw) of 1,2-dichloroethane to B6C3F_1 mice induced an elevation of alanine aminotransferase activity and an increase in relative liver weight, and some mortality occurred. The lowest intraperitoneal dose inducing an elevation of these enzymes was 500 mg/kg bw; intraperitoneal doses of up to 600 mg/kg bw did not kill any of the animals (n = 5). Inhalation exposure to 500 ppm [2000 mg/m^3] for 4 h was hepatotoxic to some of the mice, while at 150 ppm [600 mg/m^3] no toxicity was observed. Relative kidney weight was elevated after 300 mg/kg bw orally, 400 mg/kg bw intraperitoneally and after a 4-h exposure to 500 ppm 1,2-dichloroethane (Storer *et al.*, 1984).

In a 13-week study, using administration of 1,2-dichloroethane in the drinking-water, the highest dose used, 8000 ppm (corresponding to 515–727 mg/kg bw/day), no histological evidence of toxicity was observed in male Fischer 344/N rats or Osborne-Mendel or Sprague-Dawley rats of either sex. Minimal histological damage was observed in the kidney of female Fischer 344/N rats. Equivalent doses given by gavage to Fischer 344 rats were more toxic than those introduced in the drinking-water and caused substantial mortality. However, no histological damage to the liver or kidney was observed in the gavage experiments (Morgan *et al*., 1990) .

In a 10-day toxicity study (Daniel *et al*., 1994), Sprague-Dawley rats of each sex were given 1,2-dichloroethane at dose levels of 10, 30, 100 or 300 mg/kg bw per day by gavage. Although 8/10 males and all females in the high-dose group died, no haematological or clinical chemical changes were observed. The only histopathological effect was a slight inflammation of the forestomach in the 100-mg/kg bw group. In a 90-day study at dose levels of 37.5, 75 and 150 mg/kg bw per day, no treatment-related effect on mortality or gross histopathology was observed.

Mild forestomach hyperplastic changes and hyperkeratosis were observed in 2/8 male Fischer 344/N rats given 1,2-dichloroethane (350 or 700 mg/kg bw) by gavage (five days per week for two weeks), while no such changes were observed in 16 vehicle-treated animals (Ghanayem *et al*., 1986). The difference between treated animals and controls was not significant.

A non-significant 13% decrease in the cellular glutathione content in the absence of cell lysis was observed in freshly isolated hepatocytes from Sprague-Dawley rats upon incubation with 1.2 mmol/L 1,2-dichloroethane for 1 h (Jean & Reed, 1992).

Inhalation exposure (≤ 455 ppm [1820 mg/m^3], 7 h per day for five days per week, for 30 days) of male Sprague-Dawley rats to 1,2-dichloroethane induced no histopathological changes in the liver or testis. However, when the animals were simultaneously treated with disulfiram (0.15% in the diet), bilateral testicular atrophy and periportal necrosis and cytoplasmic swelling of hepatocytes, together with moderate bile duct proliferation and periductal mononuclear infiltration were seen at the two highest 1,2-dichloroethane dose levels. Similar interaction was also observed when 1,2-dichloroethane was given by the intraperitoneal route (Igwe *et al*., 1986). A single oral dose of 1,2-dichloroethane (6 μL/100 g) induced a slight increase in thiobarbituric-reacting substances and the activity of aspartate aminotransaminase in the serum and decreased the hepatic content of glutathione, but had no effect on alanine aminotransaminase or sorbitol dehydrogenase in male Wistar rats. Co-administration with carbon tetrachloride resulted in more than additive increases in serum thiobarbituric acid-reacting substances and all the serum enzyme activities, but did not accentuate the decrease in hepatic glutathione content (Aragno *et al*., 1992).

When CD-1 mice were given 1,2-dichloroethane by gavage for 14 days at a level of 4.9 or 49 mg/kg bw per day (0.01 and 0.1 × LD_{50}, as determined in an acute toxicity study), the number of splenic IgM antibody-forming cells in response to sheep red blood cells showed a dose-dependent suppression (Munson *et al*., 1982); no significant effect

was observed in the cell-mediated immune response to sheep erythrocytes. In a 90-day study (0.02, 0.2 or 2.0 mg/L in the drinking-water, calculated to yield 3, 24, or 189 mg/kg bw per day 1,2-dichloroethane), no effect on antibody-forming cell number, splenic response to the B-cell mitogen *Salmonella* lipopolysaccharide or to the T-cell mitogen concanavalin A, or vascular clearance of ^{51}Cr-labelled sheep erythrocytes was observed. Inhalation exposure of CD-1 mice to 5 or 10 ppm [20 or 40 mg/m^3] 1,2-dichloroethane for 3 h significantly decreased survival of the mice upon challenge of inhalation exposure to *Streptococcus zooepidemicus*; exposure to 10 ppm also decreased the bactericidal activity of the lungs toward *Klebsiella pneumoniae*. No effect was observed on the phagocytic or cytostatic activity of alveolar macrophages even at concentrations of 100 ppm [400 mg/m^3]. No immunotoxic effects were observed in rats (Sherwood *et al*., 1987).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

In a teratology study (Rao *et al*., 1980), rats and rabbits were exposed to 100 or 300 ppm [400 or 1200 mg/m^3] 1,2-dichloroethane for 7 h per day on days 6 through 15 (rats) or 6 through 18 (rabbits) of gestation. In rats, 10/16 dams died at the high dose, one exhibited implantation sites but all the implantantations were resorbed. At 100 ppm, 1,2-dichloroethane was not overtly toxic to the dam and did not induce fetotoxicity, teratogenicity or skeletal variations with the exception of a decrease in the number of bilobed thoracic centra. In rabbits, 3/19 dams died at the high dose; there were no adverse effects on fetal or embryonal development.

In a reproduction study (Rao *et al*., 1980), rats were exposed to 25, 75 or 150 ppm [100, 300 or 600 mg/m^3] 1,2-dichloroethane for 60 days before breeding (6 h per day, five days per week) and thereafter to similar concentrations for 6 h per day on seven days per week, with the exception of day 21 of gestation through day 4 postpartum. No effect on the reproductive performance or on the development (until day 21) of the F_1A or F_1B (bred 21 days after F_1A birth) litters was observed.

In a two-generation reproduction study (Lane *et al*., 1982), ICR Swiss mice were continuously administered 1,2-dichloroethane in the drinking-water (30, 90 or 290 mg/L with the aim of producing daily doses of 5, 15 or 50 mg/kg bw) starting five weeks before mating of the F_0 generation. No treatment-related effect on fertility, gestation, viability, pup survival, weight gain or teratogenicity was observed.

1,2-Dichloroethane administration (1.2, 1.6, 2.0 or 2.4 mmol/kg bw/day by gavage or inhalation of 150, 200, 250 or 300 ppm [600, 800, 1000 or 1200 mg/m^3] for 6 h per day on days 6 through 20 of gestation) induced no embryo- or fetotoxicity, changes in fetal growth or teratological effects. Maternal toxicity, as indicated by smaller weight gain, was observed at the highest inhalation dose level and two highest oral dose levels (Payan *et al*., 1995).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 3 for references)

1,2-Dichloroethane was mutagenic in most of the *Salmonella typhimurium* strains (TA100, TA98) tested with and without an exogenous metabolic activation system. In TA1535, mutagenic activity was dependent on addition of an exogenous metabolic system (not from frog) or specifically glutathione *S*-transferase. 1,2-Dichloroethane was mutagenic in *Drosophila melanogaster* for all end-points tested. In one study, 1,2-dichloroethane was not mutagenic in *Aspergillus nidulans*.

In vitro in animal cells, DNA repair and *hprt* gene mutations were induced by 1,2-dichloroethane. Cell transformation was observed in Syrian hamster embryo cells in a single study but not in two independent studies with BALB/c-3T3 cells. 1,2-Dichloroethane induced gene mutations in human lymphoblastoid cell lines.

In vivo in mouse liver, DNA strand breaks were induced by 1,2-dichloroethane after intraperitoneal injection or oral exposure but not after inhalation. DNA single strand-breaks were also observed in liver cells after gavage of rats. *In vivo* in mice, single studies with the spot test and sister chromatid exchange were inconclusive and positive, respectively; no micronuclei were found in bone marrow or peripheral blood cells of mice.

1,2-Dichloroethane binds *in vitro* and *in vivo* to DNA, RNA and proteins in mice and rats.

In a single study, 1,2-dichloroethane induced mainly micronuclei not staining for the presence of kinetochore (which is indicative of aneuploidy) in human MCL-5 cells that stably express cDNAs encoding human CYP1A2, CYP2A6, CYP3A4, CYP2E1 and epoxide hydrolase and in h2E1 cells, which contain a cDNA for CYP2E1. AHH-1 cells constitutively expressing CYP1A1 showed an increase in the frequency only of non-kinetochore-staining micronuclei.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

1,2-Dichloroethane is used mainly in the production of vinyl chloride. It is no longer registered as a fumigant. It has been detected at low levels in ambient and urban air, groundwater and drinking-water.

5.2 Human carcinogenicity data

Five cohort studies and one nested case–control study of brain tumours have examined the risk of cancer among workers with potential exposure to 1,2-dichloroethane. Excesses of lymphatic and haematopoietic cancers were observed in three studies and of stomach cancer in one study, while an excess of pancreatic cancer was observed in

Table 3. Genetic and related effects of 1,2-dichloroethane

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
PRB, SOS chromotest	–	–	NG	Quillardet *et al.* (1985)
ECD, *Escherichia coli pol* A, differential toxicity (spot test)	(+)	NT	12000	Brem *et al.* (1974)
SAF, *Salmonella typhimurium* BA13 (*Ara* test), forward mutation	–	+	74	Roldán-Arjona *et al.* (1991)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	1782	King *et al.* (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	3120	Barber *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	60000	Principe *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	3960	Van Bladeren *et al.* (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	+	+	NG	Milman *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)[c]	NT	20[d]	Simula *et al.* (1993)
SA3, *Salmonella typhimurium* TA1530, reverse mutation	(+)	NT	495	Brem *et al.* (1974)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	(+)	NT	495	Brem *et al.* (1974)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	(+)	+	740	Rannug & Ramel (1977)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	1782	King *et al.* (1979)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	990	Cheh *et al.* (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	990	Guengerich *et al.* (1980)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	1574	Barber *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	(+)	60000	Principe *et al.* (1981)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	+	1250	Moriya *et al.* (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	+	NG	Milman *et al.* (1988)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	1782	King *et al.* (1979)
SA7, *Salmonella typhimurium* TA1537, reverse mutation (spot test)	–	–	60000	Principe *et al.* (1979)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NG	Milman *et al.* (1988)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	NT	495	Brem *et al.* (1974)

Table 3 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	1782	King *et al.* (1979)
SA8, *Salmonella typhimurium* TA1538, reverse mutation (spot test)	–	–	60000	Principe *et al.* (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	1782	King *et al.* (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	11475	Barber *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	60000	Principe *et al.* (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	+	+	NG	Milman *et al.* (1988)
SAS, *Salmonella typhimurium* TA1535 + SOS/*umuC"lacZ*, *umuC* gene expression	+	NT	50	Oda *et al.* (1996)
SAS, *Salmonella typhimurium*,TA1535 + GST (NM 5004) + SOS/*umuC"lacZ*, reverse mutation	+	NT	1	Oda *et al.* (1996)
ECK, *Escherichia coli* K12, forward or reverse mutation	–	–	990	King *et al.* (1979)
ANG, *Aspergillus nidulans*, genetic crossing-over	–	NT	1.4% in air	Crebelli *et al.* (1984)
STF, *Streptomyces coelicolor*, forward mutation	–	NT	60000	Principe *et al.* (1981)
ANF, *Aspergillus nidulans*, forward mutation	–	NT	300000	Principe *et al.* (1981)
ANN, *Aspergillus nidulans*, aneuploidy	+	NT	2500	Crebelli *et al.* (1988)
DMG, *Drosophila melanogaster*, interchromosomal mitotic recombination	+		200 ppm diet	Vogel & Nivard (1993)
DMM, *Drosophila melanogaster*, somatic mutation and recombination test (SMART)	+		1200 diet	Nylander *et al.* (1978)
DMM, *Drosophila melanogaster*, somatic mutation and recombination test (SMART)	+		40 mg/m^3 96 h inh	Kramers *et al.* (1991)
DMM, *Drosophila melanogaster*, somatic wing spot test	+[e]		500 ppm inh	Romert *et al.* (1990)
DMM, *Drosophila melanogaster*, somatic mutation, eye spot test	+		100 ppm, 48 h inh	Ballering *et al.* (1993)
DMM, *Drosophila melanogaster*, *vermilion* forward mutation assay	+		250 ppm inh	Ballering *et al.* (1994)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		4950 feed	King *et al.* (1979)

Table 3 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		8 mg/m^3 96 h inh	Kramers *et al.* (1991)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	+		12 000 feed	Ballering *et al.* (1993)
DMN, *Drosophila melanogaster*, ring-X chromosome loss	(+)		1200 mg/m^3 inh	Kramers *et al.* (1991)
DMN, *Drosophila melanogaster*, ring-X chromosome loss	+		12 000 48 h feed	Ballering *et al.* (1993)
RIA, DNA repair, mouse hepatocytes *in vitro*	+	NT	NG	Milman *et al.* (1988)
URP, Unscheduled DNA synthesis, rat hepatocytes *in vitro*	+	NT	NG	Milman *et al.* (1988)
GCO, Gene mutation, Chinese hamster ovary CHO cells, *hprt* locus *in vitro*	+	+	99	Tan & Hsie (1981)
GCO, Gene mutation, Chinese hamster ovary CHO cells, *hprt* locus *in vitro*	+	NT	8[d]	Zamora *et al.* (1983)
AIA, Aneuploidy, AHH-1 cells (CYP1A1 native) *in vitro*, kinetochore staining	–	NT	495	Doherty *et al.* (1996)
AIA, Aneuploidy, MCL-5 cells (cDNAs for CYP1A2, 2A6, 3A4, 2E1 and epoxide hydrolase) *in vitro*, kinetochore staining	(+)	NT	495	Doherty *et al.* (1996)
AIA, Aneuploidy, h2E1 cells (cDNA for CYP2E1) *in vitro*, kinetochore staining	–	NT	495	Doherty *et al.* (1996)
TBM, Cell transformation, BALB/c-3T3, mouse cells	–	NT	50	Tu *et al.* (1985)
TBM, Cell transformation, BALB/c-3T3, mouse cells	–	NT	NG	Milman *et al.* (1988)
T7S, Cell transformation, SA7/Syrian hamster embryo cells	+	NT	1.3% in air	Hatch *et al.* (1983)
GIH, Gene mutation, human EUE cells *in vitro*	+	NT	99	Ferreri *et al.* (1983)
GIH, Gene mutation, human lymphoblastoid cell line AHH-1 *in vitro*	+	NT	100	Crespi *et al.* (1985)
GIH, Gene mutation, human lymphoblastoid cell line TK6 *in vitro*	+	NT	500	Crespi *et al.* (1985)
MIH, Micronucleus test, AHH-1 cells (CYP1A1 native) *in vitro*	+[f]	NT	198	Doherty *et al.* (1996)
MIH, Micronucleus test, MCL-5 cells (cDNAs for CYP1A2, 2A6, 3A4, 2E1 and epoxide hydrolase) *in vitro*	+[f]	NT	198	Doherty *et al.* (1996)

Table 3 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
MIH, Micronucleus test, h2E1 cells (cDNA for CYP2E1) *in vitro*	+[f]	NT	198	Doherty *et al.* (1996)
BFA, Bile of CBA mice, *Salmonella typhimurium* TA1535, reverse mutation	+		80 ip × 1	Rannug & Beije (1979)
HMM, Host-mediated assay, *Escherichia coli* K12 in female NMRI mouse hosts	–		198 ip × 1	King *et al.* (1979)
DVA, DNA single-strand breaks, B6C3F$_1$ mouse liver *in vivo*	+		198 ip × 1	Storer & Conolly (1983)
DVA, DNA single-strand breaks, B6C3F$_1$ mouse liver *in vivo*	+		100 po × 1	Storer *et al.* (1984)
DVA, DNA single-strand breaks, B6C3F$_1$ mouse liver *in vivo*	+		150 ip × 1	Storer *et al.* (1984)
DVA, DNA single-strand breaks, B6C3F$_1$ mouse liver *in vivo*	–		500 ppm inh 4 h	Storer *et al.* (1984)
DVA, DNA damage, CD rat liver cells *in vivo*	+		134 po × 2	Kitchin & Brown (1994)
MST, Mouse spot test, female C57BL/6J Han mice *in vivo*	?		300 ip × 1	Gocke *et al.* (1983)
SVA, Sister chromatid exchange, male Swiss albino mouse bone marrow *in vivo*	+		1 ip × 1	Giri & Que Hee (1988)
MVM, Micronucleus test, NMRI mouse bone marrow *in vivo*	–		396 ip × 2	King *et al.* (1979)
MVM, Micronucleus test, Eμ-PIM-1 transgenic mouse peripheral blood *in vivo*	–		300 po/d 41 wk	Armstrong & Galloway (1993)
DLM, Dominant lethal test, ICR Swiss mice *in vivo*	–		50 po × 7 d	Lane *et al.* (1982)
BID, Binding (covalent) to calf thymus DNA *in vitro*	–	+	99	Guengerich *et al.* (1980)
BID, Binding (covalent) to calf thymus DNA *in vitro*	+	+[g]	3.6	Arfellini *et al.* (1984)
BID, Binding (covalent) to DNA *in vitro*	–	+	6	Colacci *et al.* (1985)
BID, Binding (covalent) to DNA, mouse hepatocytes *in vitro*	+	NT	103 μg	Banerjee (1988)
BVD, Binding (covalent) to DNA, rat liver, spleen, kidney and stomach *in vivo*	+		150 po × 1	Reitz *et al.* (1982)
BVD, Binding (covalent) to DNA, Wistar rat liver, kidney, stomach and lung *in vivo*	+		0.86 ip × 1	Arfellini *et al.* (1984)

Table 3 (contd)

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
BVD, Binding (covalent) to DNA, BALB/c mouse liver, kidney, stomach and lung *in vivo*	+		0.86 ip × 1	Arfellini *et al.* (1984)
BVD, Binding (covalent) to DNA, Sprague-Dawley rat hepatocytes *in vivo*	+		150 ip × 1	Inskeep *et al.* (1986)
BVD, Binding (covalent) to DNA, Sprague-Dawley rat liver *in vivo*	+		1.38 ip × 1	Banerjee (1988)
BVD, Binding (covalent) to DNA, B6C3F$_1$ mouse liver *in vivo*	+		1.38 ip × 1	Banerjee (1988)
BVD, Binding (covalent) to DNA, Sprague-Dawley rat liver *in vivo*	+		150 po × 1	Cheever *et al.* (1990)
BVD, Binding (covalent) to DNA, Fischer 344 rat lung *in vivo*	+		34 inh 4 h	Baertsch *et al.* (1990)
BVP, Binding (covalent) to RNA and proteins, Wistar rat liver, kidney, stomach and lung *in vivo*	+		0.86 ip × 1	Arfellini *et al.* (1984)
BVP, Binding (covalent) to RNA and proteins, BALB/c mouse liver, kidney, stomach and lung *in vivo*	+		0.86 ip × 1	Arfellini *et al.* (1984)

[a] +, positive; (+), weak positive; –, negative; NT, not tested; ?, inconclusive

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL; in-vivo tests, mg/kg bw/day; NG, not given; inh, inhalation; ip, intraperitoneal; po, oral

[c] Strains transfected with plasmids expressing human α-class glutathione *S*-transferase (GST) were more sensitive than those expressing π-class GSTs or the control TA100 strain

[d] Atmospheric concentration (µg/mL)

[e] 24-h pretreatment with buthionine sulfoximine, an inhibitor of GSH synthesis, significantly decreased the mutagenic activity, while pretreatment with phenobarbital, an inducer of glutathione *S*-transferase, significantly increased the mutagenic activity of 1,2-dichloroethane.

[f] Approximately 20% of the micronucleated cells stained positive for kinetochore at the highest dose (5 mM).

[g] S9 from rat of mouse liver, stomach, lung or kidney mediated DNA binding.

one study. All the cohort studies included workers with potential exposure to multiple agents and were not able to examine the excess risk associated with 1,2-dichloroethane.

5.3 Animal carcinogenicity data

1,2-Dichloroethane was tested in one experiment in mice and in one in rats by oral administration. In mice, it produced benign and malignant tumours of the lung and malignant lymphomas in animals of each sex, hepatocellular carcinomas in males and mammary and uterine adenocarcinomas in females. In rats, it produced carcinomas of the forestomach in males, benign and malignant mammary tumours in females and haemangiosarcomas in animals of each sex. No increase in tumour incidence was found after inhalation exposure in two experiments in rats or in one experiment in mice, but these studies were considered to be inadequate. In two other inhalation studies, one in mice and one in rats, 1,2-dichloroethane increased the incidence of tumours at various sites including the liver, lung and mammary gland.

In a multistage study measuring γ-glutamyl transpeptidase (γ-GT)-positive foci in the liver of male rats, single administration of 1,2-dichloroethane by gavage after a two-thirds partial hepatectomy followed by treatment with phenobarbital (initiation study) or repeated administration of 1,2-dichloroethane by gavage after a two-thirds partial hepatectomy and initiation by *N*-nitrosodiethylamine (promotion study) did not increase the number of γ-GT-positive foci. In a two-stage mouse-skin assay, 1,2-dichloroethane was not active as an initiator of skin carcinogenicity.

5.4 Other relevant data

1,2-Dichloroethane is easily absorbed by humans and animals and is metabolized extensively by rats and mice via cytochrome P450 and glutathione *S*-transferase.

No teratogenic effect was seen in rats, rabbits or mice.

1,2-Dichloromethane is mutagenic in bacteria, *Drosophila melanogaster* and mammalian cells. It induces DNA damage in liver cells *in vivo* and binds to DNA, RNA and proteins in animals.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of 1,2-dichloroethane.

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,2-dichloroethane.

Overall evaluation

1,2-Dichloroethane is *possibly carcinogenic to humans (Group 2B)*.

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