# CHLOROPRENE

This substance was considered by previous Working Groups, in February 1978 (IARC, 1979) and March 1987 (IARC, 1987a). 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

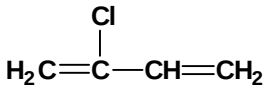
1.1.1 *Nomenclature*

*Chem. Abstr. Serv. Reg. No.*: 126-99-8

*Chem. Abstr. Name*: 2-Chloro-1,3-butadiene

*Synonyms*: 2-Chlorobutadiene; β-chloroprene

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_4H_5Cl$ Relative molecular mass: 88.54

1.1.3 *Chemical and physical properties of the pure substance*

From Lide (1995), unless otherwise specified

(*a*) *Description*: Colourless, flammable liquid (Lewis, 1993)

(*b*) *Boiling-point*: 59.4°C

(*c*) *Melting-point*: –130°C

(*d*) *Density*: $d_4^{20}$ 0.956

(*e*) *Solubility*: Slightly soluble in water; miscible in acetone, benzene and diethyl ether

(*f*) *Volatility*: Vapour pressure, 26.6 kPa at 20°C; relative vapour density (air = 1), 3.06 (Verschueren, 1996)

(*g*) *Stability*: Flash-point, –20°C (Lewis, 1993)

(*h*) *Reactivity*: Readily forms dimers and oxidizes at room temperature (American Conference of Governmental Industrial Hygienists, 1991)

(*i*) *Octanol/water partition coefficient (P):* log *P*, 2.06 (United States National Library of Medicine, 1997a)

(*j*) *Conversion factor*: mg/m$^3$ = 3.62 × ppm[1]

1.1.4 *Technical products and impurities*

Chloroprene is available commercially on a restricted basis in the United States as crude β-chloroprene with a minimum purity of 95% (Lewis, 1993; DuPont Dow Elastomers, 1997). The principal impurities are dichlorobutene and solvents, with smaller amounts of 1-chlorobutadiene (α-chloroprene), chlorobutenes and dimers of both chloroprene and butadiene. Due to its reactivity, chloroprene is stored at 0°C or below under nitrogen and contains significant quantities of inhibitors, such as phenothiazine, *tert*-butylcatechol, picric acid and the ammonium salt of *N*-nitroso-*N*-phenylhydroxylamine, to prevent degradation and polymerization (Stewart, 1993). Generally within six weeks of manufacture, crude chloroprene is distilled to produce polymerization grade, which is used within approximately 24 h of distillation.

1.1.5 *Analysis*

The United States National Institute for Occupational Safety and Health has approved a method for the analysis of chloroprene in workplace air. The method [Method 1002] involves passing the sample through a solid sorbent tube of coconut shell charcoal, desorbing with carbon disulfide, and analysis by gas chromatography with flame ionization detection. The estimated limit of detection for this method is 0.03 mg per sample or 3.8 mg/m$^3$ assuming a maximum air sample of 8 L (Eller, 1994).

Several methods have been described for the determination of chloroprene in water. Huang *et al*. (1996) described a method for wastewater and underground water using gas extraction, thermal desorption and gas chromatography/mass spectrometry; the detection limit for this method was 0.02 μg/L. Kessels *et al*. (1992) described a purge-and-trap method for drinking-water using capillary gas chromatography with electron capture or flame ionization detection; the detection limit for this method was 0.01–0.09 μg/L.

Gas chromatography has been used to determine chloroprene as a residual monomer in polychloroprene latexes, with a sensitivity of less than 0.002 wt % (Bunyatyants *et al.*, 1976).

## 1.2 Production and use

1.2.1 *Production*

Chloroprene was first obtained as a by-product from the synthesis of divinylacetylene. When a rubbery polymer was found to form spontaneously, investigations were begun that defined the two methods of synthesis of chloroprene that have since been the basis of commercial production, and the first successful synthetic elastomer, Neoprene, or DuPrene as it was first called, was introduced in 1932 (Kleinschmidt, 1986; Stewart, 1993).

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[1]Calculated from: mg/m$^3$ = (relative molecular mass/24.47) × ppm, assuming a temperature of 25°C and a pressure of 101 kPa

Production of chloroprene today is completely determined by demand for the polymer. The only other use accounting for a significant volume is the synthesis of 2,3-dichloro-1,3-butadiene, which is used as a monomer in selected copolymerizations with chloroprene. The original commercial production was from acetylene through monovinylacetylene. Since the 1960s, because of the increasing price of acetylene and decreasing price of butadiene, the latter has displaced acetylene as the feedstock in most countries (Kleinschmidt, 1986; Stewart, 1993).

In the production of chloroprene from butadiene, there are three essential steps: liquid- or vapour-phase chlorination of butadiene to a mixture of 3,4-dichloro-1-butene and 1,4-dichloro-2-butene; catalytic isomerization of 1,4-dichloro-2-butene to 3,4-dichloro-1-butene; and caustic dehydrochlorination of the 3,4-dichloro-1-butene to chloroprene. By-products in the first step include hydrochloric acid, 1-chloro-1,3-butadiene, trichlorobutenes and tetrachlorobutanes, butadiene dimer and higher-boiling products. In the second step, the mixture of 1,4-dichloro-2-butene and 3,4-dichloro-1-butene isolated by distillation is isomerized to pure 3,4-dichloro-1-butene by heating to temperatures of 60–120°C in the presence of a catalyst. Finally, dehydrochlorination of 3,4-dichloro-1-butene with dilute sodium hydroxide in the presence of inhibitors gives crude chloroprene (Kleinschmidt, 1986; Stewart, 1993; DuPont Dow Elastomers, 1997).

Chloroprene production can be equated approximately to the amount of polymer produced. World production of dry polychloroprene was 135 thousand tonnes in 1960, 254 thousand tonnes in 1970, 314 thousand tonnes in 1980 and 321 thousand tonnes in 1989 (Stewart, 1993). World polychloroprene capacity in 1983 was reported to be (thousand tonnes): United States, 213; Germany, 60; France, 40; United Kingdom, 30; Japan, 85; and centrally planned economy countries, 220 (Kleinschmidt, 1986). Current capacities are reported to be (thousand tonnes): United States, 163; Germany, 60; France, 40; United Kingdom, 33; Japan, 88; central Europe and the Commonwealth of Independent States, 40; and People’s Republic of China, 20 (International Institute of Synthetic Rubber Producers, 1997).

### 1.2.2 *Use*

Chloroprene is used almost exclusively in the production of the specialized elastomer known as polychloroprene. In the United States, more than 90% of the chloroprene produced annually is converted to the solid dry polychloroprene. Most of the remainder is used to produce polychloroprene latex, a colloidal suspension of polychloroprene in water. A small fraction is converted to the co-monomer, 2,3-dichloro-1,3-butadiene, for use in specialized copolymers (DuPont Dow Elastomers, 1997). The vulcanized products of polychloroprene have favourable physical properties and excellent resistance to weathering and ozone. Articles made with this rubber include electrical insulating and sheathing materials, hoses, conveyor belts, flexible bellows, transmission belts, sealing materials, diving suits and other protective suits. Adhesive grades of polychloroprene are used mainly in the footwear industry. Polychloroprene latexes have been used for dipped goods (balloons, gloves), latex foam, fibre binders, adhesives and rug backing (Kleinschmidt, 1986; Stewart, 1993).

## 1.3 Occurrence

### 1.3.1 *Natural occurrence*

Chloroprene is not known to occur as a natural product.

### 1.3.2 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (NOES, 1997), as many as 18 000 workers in the United States were potentially exposed to chloroprene (see General Remarks). National estimates of workers potentially exposed were not available from other countries. Occupational exposures to chloroprene have been measured mainly in polymer production.

During 1973, at a chloroprene polymerization plant in the United States, airborne concentrations of chloroprene were found to range from 14 to 1420 ppm [50–5140 mg/m$^3$] in the make-up area, from 130 to 6760 ppm [470–24 470 mg/m$^3$] in the reactor area, from 6 to 440 ppm [22–1660 mg/m$^3$] in the monomer recovery area and from 113 to 252 ppm [409–912 mg/m$^3$] in the latex area (Infante *et al*., 1977). Concentrations in the air inside a Russian polychloroprene rubber plant were 14.5–53.4 mg/m$^3$ (Mnatsakayan *et al*., 1972). In a Russian chloroprene latex manufacturing facility, chloroprene concentrations varied from 1 to 8 mg/m$^3$ (Volkova *et al*., 1976).

Recent data from two chloroprene polymerization plants in the United States with 650–800 exposed workers show relatively little decline in average exposure concentrations from the late 1970s through 1996 (Table 1). This is partly due to the fact that workers with jobs having low potential for exposure are no longer routinely monitored, resulting in upwardly biased time-weighted average exposures. At present, however, average exposures of process operators and mechanics are typically below 5 ppm, while other workers in these facilities are exposed to concentrations below 2 ppm (DuPont Dow Elastomers, 1997).

Exposure to residual chloroprene monomer in polychloroprene latex and polymer has also been described. In 1977, mean airborne concentrations of chloroprene of up to 0.2 ppm [0.72 mg/m$^3$] were reported in a roll building area at a metal fabricating plant in the United States where polychloroprene was applied extensively to metal cylinders before vulcanization (Infante, 1977). Workers in a Russian shoe factory were reportedly often exposed to chloroprene concentrations of 20–25 mg/m$^3$ (Buyanov & Svishchev, 1973).

### 1.3.3 *Environmental occurrence*

Industrial chloroprene emissions to the atmosphere reported to the United States Environmental Protection Agency for the Toxic Chemical Release Inventory totalled about 838 tonnes in 1987, 667 tonnes in 1991 and 446 tonnes in 1995 (United States National Library of Medicine, 1997b).

Chloroprene has been detected in industrial wastewater and nearby groundwater in the People's Republic of China (Huang *et al*., 1996), in wastewaters from polychloroprene and dichlorobutadiene production plants in Russia (Avetisyan *et al*., 1981; Geodakyan *et al*., 1981) and in waste gas from a chloroprene plant in Japan (Kawata *et al*., 1982).

**Table 1. Average chloroprene concentrations in two polymerization plants in the United States, 1976–96**

| Year | Plant 1 | | Plant 2 | |
|---|---|---|---|---|
| | No. of samples | Mean TWA[a] ($mg/m^3$) | No. of samples | Mean TWA[a] ($mg/m^3$) |
| 1976 | 2331 | 19.0 | | |
| 1977 | 2691 | 17.4 | | |
| 1978 | 3676 | 10.2 | | |
| 1979 | 1739 | 7.2 | | |
| 1980 | 1520 | 4.9 | | |
| 1981 | 1288 | 3.3 | | |
| 1982 | 678 | 3.9 | | |
| 1983 | 594 | 2.6 | | |
| 1984 | 574 | 4.1 | | |
| 1985 | 568 | 2.8 | | |
| 1986 | 245 | 5.8 | | |
| 1987 | 73 | 8.8 | | |
| 1988 | 78 | 9.0 | | |
| 1989 | 137 | 9.0 | | |
| 1990 | 9 | 1.2 | | |
| 1991 | 13 | 3.9 | | |
| 1992 | 26 | 7.5 | | |
| 1993 | 15 | 4.5 | 58 | 7.2 |
| 1994 | 8 | 22.3 | 72 | 7.3 |
| 1995 | 35 | 5.0 | 35 | 6.8 |
| 1996 | 14 | 0.6 | 35 | 2.3 |

From DuPont Dow Elastomers (1997)
[Means for 1993–96 were calculated by the Working Group from the raw data.]
[a] Time-weighted average

### 1.3.4 *Other*

It is reported that dry polychloroprene no longer contains detectable chloroprene (detection limit, 0.5 ppm). In polychloroprene latexes, residual chloroprene is less than 1%, varying with the manufacturing process and intended use (DuPont Dow Elastomers, 1998).

Chloroprene has been detected as an impurity at levels of several parts per million in commercial vinyl chloride in Italy (Sassu *et al.*, 1968) and in Japan (Kurosaki *et al.*, 1968), and in acrylonitrile in the USSR (Panina & Fain, 1968).

## 1.4 Regulations and guidelines

Occupational exposure limits and guidelines for chloroprene in several countries are given in Table 2.

**Table 2. Occupational exposure limits and guidelines for chloroprene[a]**

| Country | Year | Concentration ($mg/m^3$) | Interpretation[b] |
|---|---|---|---|
| Australia | 1993 | 36 (sk) | TWA |
| Belgium | 1993 | 36 (sk) | TWA |
| Czechoslovakia | 1991 | 50 | TWA |
| | | 100 | STEL |
| Denmark | 1993 | 3.6 (sk) | TWA |
| Finland | 1998 | 36 (sk) | TWA |
| | | 72 | STEL (15-min) |
| France | 1993 | 36 | TWA |
| Germany | 1998 | None* | MAK |
| Hungary | 1993 | 10 | TWA |
| | | 30 | STEL |
| Netherlands | 1992 | 36 | TWA |
| Poland | 1993 | 2 | TWA |
| Russia | 1993 | 0.05 | STEL |
| Sweden | 1993 | 36 (sk) | TWA |
| | | 60 | STEL |
| Switzerland | 1993 | 36 (sk) | TWA |
| | | 72 | STEL |
| United Kingdom | 1993 | 30 (sk) | TWA |
| United States | | | |
| ACGIH (TLV)[b,c] | 1997 | 36 (sk) | TWA |
| NIOSH (REL) | 1997 | 3.6 (Ca) | Ceiling (15-min) |
| OSHA (PEL) | 1996 | 90 (sk) | TWA |

[a] From International Labour Office (1991); United States Occupational Safety and Health Administration (OSHA) (1996); American Conference of Governmental Industrial Hygienists (ACGIH) (1997a,b); United States National Library of Medicine (1997b); Deutsche Forschungsgemeinschaft (1998); Ministry of Social Affairs and Health (1998)

[b] TWA, time-weighted average; STEL, short-term exposure limit; MAK, maximum workplace concentration; TLV, threshold limit value; REL, recommended exposure limit; PEL, permissible exposure limit; Ca, potential occupational carcinogen; sk, skin notation

[c] Countries that follow the ACGIH recommendations for threshold limit values include Bulgaria, Colombia, Jordan, Korea, New Zealand, Singapore and Viet Nam

* Considered to be carcinogenic to man

## 2. Studies of Cancer in Humans

### 2.1 Case report and case series

One case has been reported of liver angiosarcoma (pathologically confirmed) in a worker exposed to polychloroprene who had no known occupational exposure to vinyl chloride (IARC, 1987b) or medical exposure to thorotrast (Infante, 1977). [It is unclear whether and how much this worker was exposed to chloroprene monomer.]

Khachatryan (1972a,b) reported on patients with skin and lung cancer who attended an oncology department in an industrial area of Armenia with a high prevalence of workers employed in the chemical industry. These included 18 cases of lung cancer and 21 of skin cancer among workers with high exposure to chloroprene.

### 2.2 Cohort studies

A historical prospective study of workers employed in the production of neoprene in two plants in the United States was conducted by Pell (1978). The cohort at the first plant comprised 234 male workers first employed at any time between 1931 and 1948. These men were followed from 1957 or 15 years after first exposure, whichever was later, until 1974. During this period, 39 deaths occurred in operation workers, giving a standardized mortality ratio (SMR) of 0.8 in comparison with United States mortality rates and 1.0 in comparison with death rates in the company as a whole. Twelve deaths were from cancer (9.7 expected from national rates) and five from cancer of the urinary organs (0.5 expected from national rates). Three of these deaths were from bladder cancer in men who had worked with β-naphthylamine (IARC, 1987c) and two were from cancer of the kidney. The cohort from the second plant comprised 1576 men identified from a wage roll of employees dated 30 June 1957. During follow-up to 1974 (99% successful), 193 deaths were observed [SMR, 0.7 based on national rates; 0.99 based on company rates], including 51 from cancer [SMR, 0.97 based on national rates]. There were 19 deaths from cancer of the digestive organs [SMR, 1.3 based on national rates] and two from cancer of the urinary organs [SMR, 0.7 based on national rates]. [The numbers of deaths from specific digestive tract cancers were not specified.]

Shouqi *et al*. (1989) investigated mortality from cancer at a plant in the People's Republic of China producing chloroprene monomer and neoprene. The cohort comprised 1258 employees identified from personnel records who could be assigned to certain exposure categories. In follow-up to 30 June 1983, 96.4% of the cohort were traced. Overall 16 cancer deaths were recorded among workers with a history of exposure to chloroprene, giving an SMR of 2.4 in comparison with mortality rates in the local area during 1973–75. A significant excess of liver cancer was reported among workers in the monomer workshop (4 observed versus 0.83 expected; SMR, 4.8). [The selection criteria for the cohort were not entirely clear and the use of reference rates from only a three-year period may have led to bias.]

Bulbulyan *et al*. (1998) conducted a cohort study among 5185 shoe-manufacturing workers, of whom 4569 were women, employed for at least two years during 1940–76 in

a factory in Moscow, Russia. The follow-up for mortality was between 1979 and 1993. A total of 131 workers (2.5%) were lost to follow-up. Chloroprene was the main solvent used in the glue and gluers were considered to be subject to high exposure. Workers employed in the same departments as gluers but indirectly exposed to chloroprene were considered to have medium exposure and workers only employed in other departments were considered to be unexposed to chloroprene. In the 1970s, chloroprene exposure for gluers was of the order of 20 mg/m$^3$. Other solvents to which gluers were exposed were benzene (IARC, 1987d), until the 1950s, and ethyl acetate. Other workers were exposed to leather dust and formaldehyde (IARC, 1995). The authors used Moscow mortality as a reference and conducted additional analyses based on internal comparisons. The overall SMR was 1.03 (95% CI, 0.97–1.1; 900 deaths) and there was an excess of cancer mortality (SMR, 1.2; 95% CI, 1.0–1.3; 265 deaths). The whole cohort experienced excess mortality from liver cancer (SMR, 2.4; 95% CI, 1.1–4.3; 10 deaths) and leukaemia (SMR, 1.9; 95% CI, 1.0–3.3; 13 deaths). When workers exposed to chloroprene were compared with unexposed workers, the relative risks were 4.2 (95% CI, 0.5–33; 9 deaths) for liver cancer, 3.8 (95% CI, 0.5–31; 9 deaths) for kidney cancer and 1.1 (95% CI, 0.3–3.7; 9 deaths) for leukaemia. Liver cancer mortality increased with duration of employment as a gluer ($p = 0.02$) and with cumulative exposure index ($p = 0.07$). [This trend may have included the unexposed group, in which case it would not provide evidence independent of the overall elevated relative risk for liver cancer.] No such trend was present for any other neoplasm. No information was available on the histology of the cases of liver cancer.

## 3. Studies of Cancer in Experimental Animals

Studies of the carcinogenicity of chloroprene by the oral route or inhalation, intratracheal administration, subcutaneous or intramuscular injection or skin application were reviewed by IARC (1979) and found inadequate for evaluation. These studies are not considered further.

### 3.1 Oral administration

#### 3.1.1 *Rat*

Groups of 17 female BDIV rats were administered a single oral dose of 100 mg/kg bw chloroprene (99% pure, containing 0.8% 1-chlorobutadiene) in olive oil by gavage on day 17 of pregnancy; a control group of 14 females received olive oil alone. Progeny were treated once per week by gavage for up to 120 weeks with 50 mg/kg bw chloroprene in olive oil or olive oil alone. Litter sizes and preweanling body weights were not affected by exposure of the dams to chloroprene. The numbers of offspring receiving chloroprene were 81 males and 64 females. Fifty-three male and 53 female offspring served as controls. Survival of dams to 120 weeks was 13/17 exposed and 11/14 control rats. Survival of exposed offspring was 40/81 males and 43/64 females. Survival of control offspring was 27/53 males and 26/53 females. Body weights of exposed offspring did not

differ from those of controls. No increase was reported in site-specific or total tumours in the dams or offspring receiving chloroprene (Ponomarkov & Tomatis, 1980). [The Working Group noted that the animals may have tolerated higher doses.]

### 3.2 Inhalation exposure

#### 3.2.1 *Mouse*

Groups of Kunming albino mice [age, initial numbers and sex unspecified] were exposed to chloroprene (99.8% pure) by whole-body inhalation at concentrations of 0, 2.9, 19 or 189 mg/m$^3$ in static inhalation chambers for 4 h per day on six days per week for seven months. [Details of the method of generation, exposure conditions and chamber analyses were lacking.] Survivors were killed when moribund or at the end of eight months. The first lung tumour was observed at six months and the effective numbers of mice were 77 control, 111 low-dose, 106 mid-dose and 132 high-dose. The incidences of mice with lung adenomas (predominantly papillary) were 1/77 (1.3%) control, 9/111 (8.1%) low-dose, 10/106 (9.4%) mid-dose and 26/132 (19.7%) high-dose. No other organs were examined (Dong *et al.*, 1989).

Groups of 50 male and 50 female B6C3F$_1$ mice, six weeks of age, were exposed to chloroprene for two years by whole-body inhalation at concentrations of 0, 12.8, 32 and 80 ppm [0, 46, 116 and 290 mg/m$^3$]. The chloroprene was > 99% pure, with seven more volatile components comprising 0.13% and less volatile components including chlorobutene (0.52%) and 1-chlorobutadiene (0.15%). The chloroprene vapour was generated at approximately 65°C and the vapour concentration in the chamber was regularly monitored and revealed no decomposition or degradation products exceeding 0.5%. No chloroprene dimers were found. All mice were killed and evaluated. Survival of exposed mice was reduced in males exposed to 32 and 80 ppm (27/50 controls, 27/50 low-dose, 14/50 mid-dose, 13/50 high-dose) and in all exposed females (35/50 controls, 16/50 low-dose, 1/50 mid-dose and 3/50 high-dose), with poor survival attributed to high rates of neoplasia. Body weight gain was similar in the exposed and control groups. Neoplasms of the lung, circulatory system, Harderian gland and mammary gland (females only) occurred with significantly increased incidence compared with controls (Table 3), and tumours of the forestomach, liver (females), kidney (males), skin and mesentery (females) and Zymbal gland (females) were also increased by chloroprene exposure (United States National Toxicology Program, 1998). [The Working Group noted that the livers of most control and exposed males, but not females, contained a spectrum of lesions consistent with *Helicobacter hepaticus* infection which may have compromised the detection of neoplastic effects in this organ.]

#### 3.2.2 *Rat*

Groups of 50 male and 50 female Fischer 344/N rats, six weeks of age, were exposed to chloroprene for two years by whole-body inhalation at concentrations of 0, 12.8, 32 and 80 ppm [0, 46, 116 and 290 mg/m$^3$]. The chloroprene was > 99% pure, with seven more volatile components comprising 0.13%, and less volatile components including

**Table 3. Incidence of neoplasms in chloroprene-treated B6C3F$_1$ mice**

| Sex | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| Number | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Exposure concentration (ppm) | 0 | 12.8 | 32 | 80 | 0 | 12.8 | 32 | 80 |
| Lung, alveolar bronchiolar | | | | | | | | |
| Adenoma | 8 | 18* | 22* | 28* | 2 | 16[a]* | 29* | 26* |
| Carcinoma | 6 | 12 | 23* | 28* | 2 | 14[a]* | 16* | 28* |
| Combined | 13 | 28* | 36* | 43* | 4 | 28[a]* | 34* | 42* |
| Circulatory system | | | | | | | | |
| Haemangioma/haemangiosarcoma[b] | 1 | 12* | 18* | 17* | 4 | 6 | 18* | 8 |
| Harderian gland | | | | | | | | |
| Adenoma/carcinoma | 2 | 5 | 10* | 12* | 2 | 5 | 3 | 9* |
| Forestomach | | | | | | | | |
| Papilloma | 1 | 0 | 2 | 4 | 0 | 0 | 0 | 4 |
| Kidney | | | | | | | | |
| Tubular-cell adenoma | 0 | 2[a] | 3* | 9* | | | | |
| Liver, hepatocellular | | | | | | | | |
| Adenoma/carcinoma | | | | | 20 | 26[a] | 20 | 30* |
| Zymbal gland | | | | | | | | |
| Carcinoma | | | | | 0 | 0 | 0 | 3 |
| Mammary gland | | | | | | | | |
| Carcinoma | | | | | 3 | 4 | 7 | 12* |
| Skin | | | | | | | | |
| Sarcoma | | | | | 0 | 11* | 11* | 18* |
| Mesentery | | | | | | | | |
| Sarcoma | | | | | 0 | 4 | 8* | 3 |

[a] $n = 49$

[b] Excludes haemangiomas/haemangiosarcomas of the liver in males, because these tumours have been associated with *Helicobacter hepaticus* infection which was present in these mice.

* $p < 0.05$ pairwise logistic regression

chlorobutene (0.52%) and 1-chlorobutadiene (0.15%); chloroprene dimers were not detected. The generation of the chloroprene vapour was the same as that described for the mouse study by the same investigators. The rats were then killed and evaluated. Survival of exposed rats was reduced in males exposed to 32 and 80 ppm (13/50 controls, 9/50 low-dose, 5/50 mid-dose, 4/50 high-dose), but not females (29/50 controls, 28/50 low-dose, 26/50 mid-dose and 21/50 high-dose). Body weight gain was similar in the exposed and control groups. The incidences of neoplasms of the oral cavity, thyroid gland, kidney, lung (males) and mammary gland (females) were increased by chloroprene exposure (see Table 4) (United States National Toxicology Program, 1998).

**Table 4. Incidence of neoplasms in chloroprene-treated Fischer 344/N rats**

| Sex | Male | | | | Female | | | |
|---|---|---|---|---|---|---|---|---|
| Number | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Exposure concentration (ppm) | 0 | 12.8 | 32 | 80 | 0 | 12.8 | 32 | 80 |
| Oral cavity, squamous-cell Papilloma/carcinoma | 0 | 2 | 5* | 12* | 1[a] | 3 | 5 | 11* |
| Kidney, tubular-cell Adenoma/carcinoma | 1 | 9* | 6* | 8* | 0[a] | 1 | 0 | 4 |
| Thyroid gland, follicular-cell Adenoma/carcinoma | 0 | 2 | 4[a]* | 5* | 1[a] | 1 | 1 | 5** |
| Mammary gland Fibroadenoma | | | | | 24[a] | 32 | 36* | 36* |
| Lung, alveolar/bronchiolar Adenoma/carcinoma | 2 | 2 | 4[a] | 6** | | | | |

[a] $n = 49$
* $p < 0.05$ pairwise logistic regression
** $p < 0.05$ trend logistic regression

Three groups of 100 male and 100 female Wistar rats, five weeks of age, were exposed by whole-body inhalation to 0 (control), 10 or 50 ppm [0, 36 or 180 mg/m$^3$] chloroprene for 6 h per day on five days per week for up to 24 months. Chloroprene vapour was generated from freshly distilled chloroprene (99.6% chloroprene, 0.3% α-chloroprene and < 50 ppm chloroprene dimers) by passing nitrogen through liquid chloroprene at 0°C. After 72 weeks on test, a technical fault in chamber operation procedures resulted in the accidental death of 87 male and 73 female low-dose rats. A slight but consistent growth retardation was found in males (approximately 10%) and females (approximately 5%) of the high-dose groups. Survival of high-dose rats (70–80%) was similar to that of the controls. Histological examinations were performed on 97 control, 13 low-dose and 100 high-dose males and 99 control, 24 low-dose and 100 high-dose females. The number of exposed females with mammary tumours was significantly increased compared with controls ($p < 0.05$). The incidence of adenomas was 3/99 in controls and 7/100 in high-dose females; that of fibroadenomas was 24/99 and 36/100; and that of adenocarcinomas was 5/99 and 3/100, respectively. The increases in individual incidences were not significant. In the region of the nose, squamous-cell carcinomas of uncertain origin were found in 3/100 high-dose males and 1/99 control females. Neither macroscopic nor microscopic examination clarified the exact origin of these tumours. If the tumours in males originated from the epidermis, the total number of squamous-cell carcinomas of the skin would be 5/100 in high-dose males, which would be significantly different ($p < 0.05$) from the incidence in the control group (0/97).

All other tumours were similarly distributed in test and control animals (Trochimowicz *et al*., 1998).

3.2.3 *Hamster*

Groups of 100 male and 100 female Syrian golden hamsters, six weeks of age, were exposed to chloroprene (99.6% pure) by whole-body inhalation at concentrations of 0 (control), 10 or 50 ppm [0, 36 or 180 mg/m$^3$] for 6 h per day on five days per week for 18 months. The chloroprene was generated in the same manner as that described for the rat study by the same investigators. Surviving animals were killed and all animals evaluated. Survival was 88% in control, 92% in 10-ppm and 93% in 50-ppm males and 63%, 75% and 72% for females. No increase in tumour incidence was observed in exposed animals (Trochimowicz *et al*., 1998).

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

### 4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Mouse liver microsomal preparations metabolized chloroprene *in vitro* into a volatile alkylating metabolite (Barbin *et al*., 1977; Bartsch *et al*., 1978).

Haley (1978) reviewed data on chloroprene metabolism. The most probable route is epoxidation and subsequent glutathione conjugation and mercapturic acid formation. [The Working Group noted that there is no information on the contribution of epoxide hydrolase to chloroprene epoxide metabolism.] Summer and Greim (1980) demonstrated the formation of glutathione conjugate, depletion of hepatic glutathione and increased excretion of urinary thioethers in the rat *in vivo* after oral administration of chloroprene. In isolated rat hepatocytes, the rate of glutathione depletion was dependent on cytochrome P450 activity, as deduced from an increased rate of depletion in cells from phenobarbital- or clophen-pretreated animals.

### 4.2 Toxic effects

4.2.1 *Humans*

The primary symptoms of acute exposure to high concentrations of chloroprene by inhalation in the chloroprene-rubber industry include nervous system depression, injury to the lungs, liver and kidney, irritation of the skin and mucous membrane, and respiratory difficulties (Nyström, 1948). Arevshatyan (1972) also reported pathomorphological changes in the peridontium (periodontitis, gingivitis, erosion of teeth and caries)

after inhalation of chloroprene. Dermal exposure to chloroprene and its polymers may result in dermatitis and hair loss (Schwartz, 1945; Nyström, 1948; Ritter & Carter, 1948).

Chronic exposure to chloroprene may result in symptoms such as headache, irritability, dizziness, insomnia, fatigue, respiratory irritation, cardiac palpitations, chest pain, gastrointestinal disorders, dermatitis, temporary loss of hair, conjunctivitis and corneal necrosis (Schwartz, 1945; Nyström, 1948; Barskii *et al*., 1972; Lloyd *et al*., 1975). According to Khachatryan and Oganesyan (1974), 44% of patients with chronic chloroprene poisoning had pathological changes in the cardiovascular and nervous systems. Reports have also been published of hepatomegaly, with a decrease in liver function tests, toxic hepatitis, dystrophy of the myocardium and changes in the nervous system (Orlova & Solov'ena, 1962), circulatory changes (Khachatryan & Oganesyan, 1974), anaemia (Nyström, 1948), hypoglycaemia (Mkhitaryan, 1960), and dysfunction of the central and peripheral nervous systems, particularly the cholinergic branch, as well as decreased blood cholinesterase activity (Gasparyan, 1965).

Bascom *et al*. (1988) reported a spectrum of respiratory illnesses which occurred in a group of workers who were exposed to heated chloroprene-based rubber. These included an acute sensitizing illness with dyspnoea and wheezing in some workers and pulmonary infiltrates with eosinophilia in others. One worker developed chronic obstruction of the airways with recurrent bronchitic illnesses.

Gooch and Hawn (1981) found no clinically significant or biochemical alterations in 563 workers occupationally exposed to chloroprene, as compared with workers never exposed to the chemical.

### 4.2.2 *Experimental systems*

The oral $LD_{50}$ values for chloroprene in rats and mice are 251 and 260 mg/kg bw, respectively (Asmangulyan & Badalyan, 1971). The approximate $LC_{50}$ for a 4-h inhalation exposure in Charles River male rats is 2300 ppm [8330 mg/m$^3$] (Clary *et al*., 1978).

von Oettingen *et al*. (1936) reported that the dose that killed 100% of the animals administered chloroprene by inhalation for 8 h was 2000 ppm [7240 mg/m$^3$] in rabbits and 4000–5000 ppm [14 500–18 100 mg/m$^3$] in rats. Death resulted from respiratory failure following symptoms that included inflammation of the mucous membranes of the eyes and nose, and depression of the central nervous system. The same study reported toxic effects in mice after an 8-h exposure to chloroprene levels of 12–130 ppm [43–470 mg/m$^3$]; the minimum lethal dose was 170 ppm [615 mg/m$^3$].

Plugge and Jaeger (1979) exposed fasted adult male Sprague-Dawley rats to 100, 150, 225 or 300 ppm [360, 540, 810 or 1090 mg/m$^3$] chloroprene by inhalation for 4 h and killed the animals 24 h after exposure ended. Liver non-protein sulfhydryl (NPSH) concentrations were increased 24 h after all exposures. Liver injury, as evidenced by increased serum sorbitol dehydrogenase activity, was observed in animals exposed to 225 and 300 ppm chloroprene. Lung NPSH concentrations were decreased significantly 24 h after the 100 and 300 ppm exposures. No other evidence of lung injury was

observed. A polychlorinated biphenyl mixture given orally before dosing with chloroprene prevented the liver damage and the reduction in lung NPSH.

Jaeger *et al*. (1975) found that chloroprene is markedly more hepatotoxic to fasted adult male Holtzman rats (250–350 g bw) than to rats fed *ad libitum*, following inhalation exposure to 500, 1000 or 2000 ppm [1810, 3620 or 7240 mg/m$^3$] chloroprene. These concentrations produced increases in serum alanine α-ketoglutarate transaminase activity and caused death in the fasted rats, while producing no effect in the fed rats. At 10 000 ppm [36 200 mg/m$^3$], the fed–fasted difference following chloroprene exposure disappeared.

Clary *et al*. (1978) conducted four-week inhalation studies (6 h per day, five days per week) in adult male and female Wistar rats, as well as Syrian hamsters. The animals were exposed to 39 [141 mg/m$^3$], 161 [582 mg/m$^3$] or 625–630 ppm [approximately 2260 mg/m$^3$]. Exposure to 39 ppm caused skin and eye irritation in both species and significant growth retardation. In the rats, repeated exposure to 625 ppm resulted in growth retardation and mortality. Mid-zonal liver degeneration and necrosis as well as increased liver and kidney weights were noted at the 625 ppm exposure level. Eye irritation, restlessness, lethargy, nasal discharge and discoloured urine were also observed. Gross pathological examination showed dark, swollen livers and greyish lungs containing haemorrhagic areas in most of the animals that died during exposure. Renal tubular epithelial degeneration in rats was also noted. Hair loss was observed primarily in the female rats at the highest and middle exposure levels. In hamsters, a single exposure to 630 ppm was lethal. Mid-zonal liver degeneration and necrosis and increased liver and kidney weights were found in most of the survivors of the middle exposure group. Some irritation of the nasal mucous membrane of the hamsters, evident as a slight flattening and thinning of the olfactory epithelium, was observed at both the 39 and 161 ppm exposure levels. Haematology and urinalysis were not affected significantly by exposure to chloroprene at any dose in either species.

Melnick *et al*. (1996) conducted 13-week inhalation studies in 4–5-week-old male and female Fischer 344/N rats and B6C3F$_1$ mice. The chloroprene vapour was generated at 65°C. All animals were exposed to chloroprene concentrations of 0, 5, 12, 32 or 80 ppm [0, 18, 43, 116 or 240 mg/m$^3$] for 6 h per day on five days per week. Rats were also exposed to 200 ppm [720 mg/m$^3$]; a pilot study had shown that this concentration was lethal to mice. In mice exposed to 80 ppm, there was a marginal decrease in body weight gain in males and epithelial hyperplasia of the forestomach in both sexes. No exposure-related effects were observed in organ weights, haematology or blood chemistry. In rats, exposure to 80 or 200 ppm chloroprene resulted in degeneration and metaplasia of the olfactory epithelium. Moreover, at the 200 ppm level, anaemia, hepatocellular necrosis and reduced sperm motility were also observed. Neurobehavioural assessment showed no effect on motor activity, startle response or forelimb/hindlimb grip strength of the rats.

No lethal effects were observed by Asmangulyan and Badalyan (1971) after repeated oral exposure of rats to 15 mg/kg bw chloroprene daily for five months, but renal and splenic damage was reported.

## 4.3 Reproductive and developmental effects

### 4.3.1 *Humans*

Data from a single study of the effects of chloroprene on male reproductive function, reported in a review article (Sanotskii, 1976), were inadequate for evaluation by the Working Group.

### 4.3.2 *Experimental systems*

Salnikova and Fomenko (1973, 1975) exposed pregnant rats by inhalation to concentrations of chloroprene between 0.056 and 13 mg/m$^3$. Embryotoxic effects were observed at concentrations higher than 0.13 mg/m$^3$. The highest embryotoxic effect was seen when the dams inhaled 4.0 mg/m$^3$ chloroprene during the entire pregnancy, or intermittently on days 1–2, 3–4 or 11–12, or were given an oral dose of 0.5 mg/kg bw daily for 14 days or on days 3–4 or 11–12. Meningoencephaloceles, a teratogenic effect, was observed following chloroprene administration on days 5–6, 9–10, 11–12, 13–14 and 15–16 of gestation (Salnikova & Fomenko, 1975).

Davtyan *et al*. (1973) reported a significant increase in embryotoxicity when female white rats were fertilized by males that had been exposed to 3.8 mg/m$^3$ chloroprene for 4 h per day for 48 days. This report is not supported by a later study.

Culik *et al*. (1978) exposed male ChR-CD rats of reproductive age to 25 ppm [90 mg/m$^3$] chloroprene vapour for 4 h per day for 22 days and mated them weekly with untreated females for eight consecutive weeks. The reproductive capability of the males was not impaired.

Culik *et al*. (1978) also exposed pregnant ChR-CD rats to 0, 1, 10 and 25 ppm [0, 3.6, 36 and 90 mg/m$^3$] chloroprene vapour for 4 h per day during gestation days 3–20. They observed slight increases in resorptions and decreases in fetal body length in litters of dams exposed to 10 ppm and in fetal body weights and lengths in litters of dams exposed to 25 ppm. No other maternal, embryonal or fetal toxicity was observed.

As part of the investigation (Melnick *et al.*, 1996) with Fischer 344/N and B6C3F$_1$ mice described above (Section 4.2.2), reproductive tissue evaluations and oestrus cycle characterizations were made. Sperm mobility was reduced in rats from 87% in controls to 80% ($p < 0.01$) in the 200-ppm group, but there was no significant alteration in mice. Oestrus cycle length was unchanged in rats and mice.

## 4.4 Genetic and related effects

### 4.4.1 *Humans*

One study of chromosomal aberrations in chloroprene-exposed workers (Katosova & Pavlenko, 1985) was inadequately described for evaluation by the Working Group.

Cytogenetic examination was made of peripheral blood lymphocytes from women whose work involved exposure to chloroprene latex (Fomenko *et al.*, 1973). Twenty women, aged 19–23 years and employed for 1–4 years, were exposed to 3–7 mg/m$^3$; eight women, aged 19–50 years and employed for 1–20 years were exposed to 1–4 mg/m$^3$. These two groups were compared with a control group of 181 compiled

separately (Bochov *et al.*, 1972). The percentages of aberrant cells in the three groups were: controls, 1.19 ± 0.06; 1–4 mg/m$^3$ group, 2.5 ± 0.49 ($p < 0.05$); 3–7 mg/m$^3$ group, 3.49 ± 0.51 ($p < 0.001$).

4.4.2 *Experimental systems* (see Table 5 for references)

In one study involving vapour-phase exposure, chloroprene was mutagenic in *Salmonella typhimurium*, whereas a later investigation, also involving vapour-phase exposure, showed that freshly distilled chloroprene was not directly mutagenic, but direct mutagenic activity appeared upon storage for one or more day at –20°C (Westphal *et al.*, 1994). This study did not investigate the effect of metabolic activation; however, the most recent study (which did not involve vapour-phase exposure) did test chloroprene in the presence and absence of an exogenous metabolic system up to toxic doses and found no induction of mutation in *S. typhimurium*.

Chloroprene induced a small increase in sex-linked recessive lethal mutations in *Drosophila melanogaster* without a dose–response relationship in one study, but had no effect in another study. Chloroprene was not mutagenic to V79 Chinese hamster lung cells in the presence of S15 liver supernatants from phenobarbital-treated mice and rats.

Hamster lung cells exposed *in vitro* were transformed to phenotypes that could form tumours upon transplantation either subcutaneously into newborn hamsters or intraocularly into adults.

In one in-vivo study, induction of chromosomal aberrations in mouse bone-marrow cells and dominant lethal effects in male mice and rats were reported, following exposures to atmospheres containing any low concentration of chloroprene. Another in-vivo study, in which mice were exposed to atmospheres ranging up to 200 ppm [720 mg/m$^3$] chloroprene (a lethal concentration), found no induction of sister chromatid exchanges or chromosomal aberrations in bone-marrow cells or micronuclei in circulating blood cells.

## 5. Summary of Data Reported and Evaluation

### 5.1 Exposure data

Chloroprene is a monomer used almost exclusively for the production of polychloroprene elastomers and latexes. It readily forms dimers and oxidizes at room temperature. Occupational exposures occur in the polymerization of chloroprene and possibly in the manufacture of products from polychloroprene latexes.

Although few data are available on environmental occurrence, general population exposures are expected to be very low or negligible.

### 5.2 Human carcinogenicity data

The risk of cancer associated with occupational exposure to chloroprene has been examined in two well conducted studies, one in the United States and one in Russia. These investigations do not indicate a consistent excess of cancer at any site.

**Table 5. Genetic and related effects of chloroprene**

| Test system | Results[a] | | Dose[b] (LED or HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | + | + | 18 | Bartsch *et al*. (1979) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | –[c] | – | 177 | Westphal *et al*. (1994) |
| SA0, *Salmonella typhimurium* TA100, reverse mutation | – | – | 128 | Zeiger *et al*. (1987) |
| SA5, *Salmonella typhimurium* TA1535, reverse mutation | – | – | 128 | Zeiger *et al*. (1987) |
| SA7, *Salmonella typhimurium* TA1537, reverse mutation | – | – | 128 | Zeiger *et al*. (1987) |
| SA8, *Salmonella typhimurium* TA98, reverse mutation | – | – | 128 | Zeiger *et al*. (1987) |
| DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations | (+) | | 3000 feed × 72h | Vogel (1979) |
| DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations | – | | 1820 feed | Foureman *et al*. (1994) |
| DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations | – | | 1820 inj | Foureman *et al*. (1994)) |
| G9O, Gene mutation, Chinese hamster lung V79 cells, ouabain resistance *in vitro* | – | – | 0.2% in air | Drevon & Kuroki (1979) |
| G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro* | – | – | 0.2% in air | Drevon & Kuroki (1979) |
| TCL, Cell transformation, normal hamster lung cells, transplantability *in vitro* | + | NT | 1 | Menezes *et al.* (1979) |
| SVA, Sister chromatid exchange, male $B6C3F_1$ mouse bone-marrow cells *in vivo* | – | | 290 mg/m$^3$, 6 h/d × 12 | Tice *et al*. (1988) |
| MVM, Micronucleus test, male $B6C3F_1$ mouse peripheral blood *in vivo* | – | | 290 mg/m$^3$, 6 h/d × 12 | Tice *et al*. (1988) |

**Table 5 (contd)**

| Test system | Results[a] | | Dose[b] (LED or HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| CBA, Chromosomal aberrations, male B6C3F$_1$ mouse bone-marrow cells *in vivo* | + | | 1.85 mg/m$^3$, 2 mo | Sanotskii (1976) |
| CBA, Chromosomal aberrations, male B6C3F$_1$ mouse bone-marrow cells *in vivo* | – | | 290 mg/m$^3$, 6 h/d × 12 | Tice *et al*. (1988) |
| DLM, Dominant lethal test, male C57BL/6 mice | (+) | | 1.85 mg/m$^3$, 2 mo | Sanotskii (1976) |
| DLR, Dominant lethal test, male white rats | + | | 0.14 mg/m$^3$, 4.5 mo | Sanotskii (1976) |

[a] +, positive; (+), weakly positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, μg/mL; in-vivo tests, mg/kg bw/day; inj, injection

[c] Negative when freshly distilled, positive when aged

### 5.3 Animal carcinogenicity data

Chloroprene was tested for carcinogenicity in two studies in mice, in two studies in rats and in one study in hamsters, all by inhalation with samples of purity > 99%. Exposure of mice to chloroprene produced lung tumours in one study in which the lung was the only organ examined. In another study in mice, chloroprene produced neoplasia in the lung, circulatory system, Harderian gland, mammary gland, liver, kidney, skin, mesentery, forestomach and Zymbal gland. In one study in rats, chloroprene caused increased incidences of tumours of the oral cavity, thyroid gland, lung, mammary gland and kidney. In another study in a different strain of rats, the incidence of mammary tumours was increased in high-dose females only when mammary tumours of all types were combined. No increase in neoplasia was seen in hamsters.

### 5.4 Other relevant data

The observation of excretion of mercapturates of chloroprene indicates that glutathione conjugation occurs in rats.

Genetic toxicity assays with chloroprene may often have been complicated by impurities derived either from added stabilizers or from degradation and polymerization products. Consequently, positive and negative results have been reported for most assays, and it is notable that, often, the negative results were obtained using the higher dose levels of chloroprene.

### 5.5 Evaluation

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

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

**Overall evaluation**

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

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