TOXICITY SUMMARY FOR 1,1-DICHLOROETHYLENE

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EXECUTIVE SUMMARY

1,1-Dichloroethylene (CAS No. 75-35-4), also known as 1,1-dichloroethene and vinylidine chloride, is a colorless liquid that is used primarily in the production of polyvinylidine chloride (PVC) copolymers and as an intermediate for synthesis of organic chemicals. The major application for PVC copolymers is the production of flexible films for food packaging such as Saran® wrap (ATSDR, 1993).

1,1-Dichloroethylene does not occur naturally (IARC, 1986), but is found in the environment due to releases associated with its production and transport and with the production of its polymers. Because of its high volatility, releases to the atmosphere are the greatest source of ambient 1,1-dichloroethylene. Smaller amounts are released to surface waters and soils (ATSDR, 1993). Loss of 1,1-dichloroethylene from water and soils is primarily due to volatilization. In the atmosphere, reaction with photochemically generated hydroxyl radicals is expected to be the predominant removal mechanism (U.S. EPA, 1987). Human exposure to 1,1-dichloroethylene is potentially highest in workplace settings and in the vicinity of hazardous waste sites where the compound may contaminate environmental media (ATSDR, 1993).

The primary effect of acute exposure to high concentrations (approximately 4000 ppm) of 1,1-dichloroethylene vapor in humans is central nervous system (CNS) depression which may progress to unconsciousness (Gosselin et al., 1984). Occupational exposure has been reported to cause liver dysfunction in workers (Tierney et al., 1979). 1,1-Dichloroethylene is irritating when applied to the skin and prolonged contact can cause first degree burns (Tierney et al., 1979). Direct contact with the eyes may cause conjunctivitis and transient corneal injury (IARC, 1986).

In experimental animals, the liver and kidneys are target organs for the toxic effects of 1,1-dichloroethylene. Subchronic oral exposure to 1,1-dichloroethylene for 90 days in drinking water produced slight hepatotoxic effects at 200 ppm (Rampy et al., 1977) and chronic oral exposure in drinking water for 2 years produced hepatocellular changes in males at $\geq$100 ppm and in females at $\geq$50 ppm (Quast et al., 1983). Gavage administration of 10 mg/kg/day, 5 days/week for 2 years produced chronic inflammation of the kidney in male and female rats, and liver necrosis in male and female mice (NTP, 1982). Exposure by inhalation to 55 ppm 1,1-dichloroethylene, 6 hours/day, 5 days/week for up to 1 year produced fatty liver changes in rats and focal degeneration and necrosis in mice (Lee et al., 1977).

In a three-generation study, no treatment-related effects on reproduction or neonatal development were seen in male and female Sprague-Dawley rats administered up to 200 ppm of 1,1-dichloroethylene in the drinking water (Nitschke et al., 1983). However, inhalation exposure during gestation produced increased resorptions and minor skeletal alterations in rodents at concentrations that caused maternal toxicity. These effects were reported in rats and mice at $\geq$15 ppm (Short et al., 1977a) and in rats and rabbits at $\geq$80 ppm and $\geq$160 ppm, respectively (Murray et al., 1979).

An oral Reference Dose (RfD) of 9E-3 mg/kg/day was derived for chronic exposure (U.S. EPA, 1994a) and subchronic exposure to 1,1-dichloroethylene (U.S. EPA, 1994b), based on liver lesions seen in rats in a 2-year drinking water study (Quast et al., 1983). The oral RfD is currently under review and may be subject to change. An inhalation Reference Concentration (RfC) for 1,1-dichloroethylene is under review (U.S. EPA, 1994a).

An epidemiology study using a small cohort found no association between the occurrence of cancer or cancer mortality and exposure to 1,1-dichloroethylene (Ott et al., 1976). Oral carcinogenicity bioassays (drinking water or gavage exposures) with experimental animals gave generally negative results (NTP, 1982; Quast et al., 1983; Maltoni et al., 1984, 1985). In one inhalation study (Maltoni et al., 1985), statistically significant increases in renal adenocarcinomas were noted in male Swiss mice exposed to 25 ppm for 12 months. Also observed were statistically significant increases in mammary gland carcinomas in females and lung tumors in both sexes. Results of other inhalation studies with rats, mice, and hamsters have been negative (Hong et al., 1981; Maltoni et al., 1984; Quast et al., 1986).

Based on U.S. EPA guidelines, 1,1-dichloroethylene was assigned to weight-of-evidence group C, possible human carcinogen. For oral exposure, the slope factor is 6E-1 $(mg/kg/day)^{-1}$ and the unit risk is

1.7E-5 $(\mu g/L)^{-1}$ (U.S. EPA, 1994a). The inhalation slope factor and unit risk are 1.2E+0 $(mg/kg/day)^{-1}$ and 5.0E-5 $(\mu g/m^3)^{-1}$ (U.S. EPA, 1994a), respectively.

1. INTRODUCTION

1,1-Dichloroethylene (CAS No. 75-35-4), also known as 1,1-dichloroethene and vinylidine chloride, is a colorless liquid with a molecular weight of 96.95 and a chemical formula of $C_2H_2Cl_2$. It has a boiling point of 31.7°C, a melting point of -122.5°C, a density of 1.2129 g/mL (Budavari et al., 1989), and a vapor pressure of 600 mm Hg at 25°C (U.S. EPA, 1987). 1,1-Dichloro-ethylene is produced commercially by the dehydrochlorination of 1,1,2-trichloroethane by lime or sodium hydroxide (IARC, 1986).

1,1-Dichloroethylene is used primarily in the production of polyvinylidine chloride (PVC) copolymers and as an intermediate for synthesis of organic chemicals. The major application for PVC copolymers is the production of flexible films for food packaging such as Saran® wrap (ATSDR, 1993). 1,1-Dichloroethylene is also used as an intermediate in the production of 1,1,1-trichloroethane and in the manufacture of modacrylic fibers where it is combined with acrylonitrile. Because 1,1-dichloroethylene polymerizes readily and can form explosive peroxides, hydroquinone monomethyl ether (MEHQ) or phenol are generally added as a stabilizer to prevent these reactions (Haley, 1975).

1,1-Dichloroethylene does not occur naturally (IARC, 1986), but is found in the environment due to releases associated with its production and transport and with the production of its polymers. Because of its high volatility, releases to the atmosphere are the greatest source of ambient 1,1-dichloroethylene. Smaller amounts of 1,1-dichloroethylene are released to surface waters and soils (ATSDR, 1993). Estimated half-lives in air and water are 2 days and 1-6 days, respectively. Loss of 1,1-dichloroethylene from water and soils is primarily due to volatilization. In the atmosphere, reaction with photochemically generated hydroxyl radicals is expected to be the predominant removal mechanism (U.S. EPA, 1987).

Human exposure to 1,1-dichloroethylene is potentially highest in workplace settings and in the vicinity of hazardous waste sites where the compound may contaminate environmental media (ATSDR, 1993). It is found as a contaminant in nuclear submarines and spacecraft (Gosselin et al., 1984). The general population may be exposed to low levels of 1,1-dichloroethylene in ambient air, indoor air, contaminated drinking water, and food which has come in contact with plastic wrap containing residual monomer (HSDB, 1994).

2. METABOLISM AND DISPOSITION

2.1. ABSORPTION

No human data were available regarding the absorption of 1,1-dichloroethylene by any route of exposure. The rapid appearance of labeled 1,1-dichloroethylene in the urine and expired air of rats given intragastric doses of [^{14}C] 1,1-dichloroethylene indicates that systemic absorption following oral dosing is rapid (U.S. EPA, 1987). 1,1-Dichloroethylene is also readily absorbed following inhalation exposure. In rats exposed to 25, 75, or 150 ppm 1,1-dichloroethylene, equilibrium levels were reached in the blood by 45 minutes, while at 300 ppm the blood level of 1,1-dichloroethylene tended to increase gradually for 3 hours (Dallas et al., 1983).

2.2. DISTRIBUTION

No data were available regarding the tissue distribution of 1,1-dichloroethylene in humans. In rats, 1,1-dichloroethylene is rapidly distributed to tissues following oral or inhalation exposure. Following administration of a single oral dose of 350 or 500 µg/kg, the highest concentrations were found in the liver and kidneys within 30 minutes of dosing; general tissue distribution followed (Jones and Hathway, 1978b). After 72 hours, 3% or less of the administered dose was present, indicating that 1,1-dichloroethylene is not extensively stored in body tissues. Following inhalation exposure to 2000 ppm for 2 hours, rats preferentially accumulated 1,1-dichloroethylene in the kidney and liver, with fasted rats having higher levels in these tissues than nonfasted rats (Jaeger et al., 1977).

2.3. METABOLISM

Pharmacokinetic data in animals show that metabolism is dose-dependent and saturable at inhalation concentrations of 150-200 ppm or approximately 50 mg/kg orally (U.S. EPA, 1987). Metabolic conversion of 1,1-dichloroethylene to an epoxide as an intermediate reactive metabolite has been proposed (IARC, 1986). The main biotransformation pathway in the rat most likely involves conjugation with glutathione (GHS), either with the epoxide or following rearrangement of the epoxide to chloroacetylchloride, with subsequent hydrolysis to monochloroacetic acid (ATSDR, 1993). Major urinary metabolites of 1,1-dichloroethylene identified in rats are thiodihydroxyacetic acid and *N*-acetyl-*S*-cysteinylacetyl derivatives. Additional metabolites identified are chloroacetic acid, dithiohydroxyacetic acid (dithioglycolic acid), thiohydroxyacetic acid (thioglycolic acid), and methylthioacetylamino-ethanol. Comparative studies with rodents have shown that mice metabolize 1,1-dichloroethylene to a greater extent than rats (IARC, 1986).

2.4. EXCRETION

No human data were available regarding the excretion of 1,1-dichloroethylene. After oral administration of 5 mg radiolabeled 1,1-dichloroethylene to rats, most of the radioactivity was recovered within 72 hours (Reichert et al., 1979). Twenty one percent of the dose was recovered in the expired air, 53.9% in urine, 14.5% in feces, 2.8 % in the carcass, and 7.5% was found in the cage rinse.

3. NONCARCINOGENIC HEALTH EFFECTS

3.1. ORAL EXPOSURES

3.1.1. Acute Toxicity

3.1.1.1. Human

Information on the acute oral toxicity of 1,1-dichloroethylene in humans was not available.

3.1.1.2. Animal

Jones and Hathway (1978a) reported oral LD_{50} values of 1550 mg/kg for rats and 194 and 217 mg/kg, respectively, for male and female mice. A lethal dose of 5750 mg/kg was reported for dogs (Tierney et al., 1979).

Increased kidney weights, increased plasma urea nitrogen and creatinine concentrations, and histopathological changes of the kidneys (vacuolization, tubular dilatation, and necrosis) were seen in rats administered a single oral dose of 400 mg/kg of 1,1-dichloroethylene (Jenkins and Andersen, 1978). Fasting rats were more susceptible to the nephrotoxic effects of 1,1-dichloroethylene than nonfasting rats.

Forkert et al. (1985) reported histopathological changes in Clara cells, pulmonary edema, hemorrhage, and focal lung collapse in mice administered a single oral dose of 200 mg/kg of 1,1-dichloroethylene. In contrast, Chieco et al. (1981) found no histopathological lung changes in fasted or nonfasted rats administered a single oral dose of 200 mg/kg of 1,1-dichloroethylene.

After oral treatment of rats with 1000 mg/kg of 1,1-dichloroethylene, liver glutathione levels were decreased to 33% of the control values within 4 hours, but returned to the control levels after 24 hours (Reichert et al., 1978).

3.1.2. Subchronic Toxicity

3.1.2.1. Human

Information on the subchronic oral toxicity of 1,1-dichloroethylene in humans was not available.

3.1.2.2. Animal

Rampy et al. (1977) administered 50, 100, or 200 ppm 1,1-dichloroethylene in drinking water to male and female Sprague-Dawley rats for 90 days. The only adverse effect noted was an increased incidence of cytoplasmic vacuolization of hepatocytes in the high dose group.

No adverse effects were observed in beagle dogs administered daily doses of 6.25, 12.5, or 25 mg/kg of 1,1-dichloroethylene in gelatin capsules for 97 days (Quast et al., 1983).

3.1.3. Chronic Toxicity

3.1.3.1. Human

Information on the chronic oral toxicity of 1,1-dichloroethylene in humans was not available.

3.1.3.2. Animal

Male and female Sprague-Dawley rats were administered 50, 100, or 200 ppm 1,1-dichloroethylene in drinking water for 2 years (Quast et al., 1983). The authors calculated a daily intake of 7, 10, or 20 mg/kg/day for males and 9, 14, or 30 mg/kg/day for females. There were no treatment-related effects on mortality, body weight, clinical chemistry, urinalysis, hematology, or tumor incidence. Female rats at all dose levels developed hepatic lesions, characterized as minimal hepatocellular fatty change and hepatocellular hypertrophy. In male rats, hepatocellular hypertrophy was seen at 100 and 200 ppm.

In a 2-year gavage study conducted by NTP (1982), F344 rats and $B6C3F_1$ mice were administered 1,1-dichloroethylene at doses of 1 or 5 mg/kg/day (rats) and 2 or 10 mg/kg/day (mice), 5 days/week for 2 years. Mortality and growth rates were not affected in either species at either dose level. Compared with controls, an increased incidence of chronic inflammation of the kidneys occurred in high-dose male and female rats, and an increased incidence of liver necrosis was observed in high-dose male and low-dose female mice.

3.1.4. Developmental and Reproductive Toxicity

3.1.4.1. Human

Information on the developmental and reproductive oral toxicity of 1,1-dichloroethylene in humans was not available.

3.1.4.2. Animal

No adverse effects were reported in Sprague-Dawley rats given 200 mg/L of 1,1-dichloroethylene in drinking water on gestation days 6-15 (Murray et al., 1979). In a three-generation study, Nitschke et al. (1983) found no treatment-related effects on reproduction or neonatal development in male and female Sprague-Dawley rats administered 50, 100, or 200 mg/L of 1,1-dichloroethylene in the drinking water.

When rats were exposed to feed fumigated with 250 or 500 pmm 1,1-dichloroethylene, no changes in fetal mortality or fetal weight were found over several generations during a 2-year period (Alumot et al., 1976). Based on the amount eaten and the measured residue level, the investigators calculated that due to volatility only 60 to 70% of the fumigant was actually consumed.

3.1.5. Reference Dose

3.1.5.1. Subchronic

ORAL RfD: 9E-3 mg/kg/day (U.S. EPA, 1994b)
LOAEL: 9 mg/kg/day
UNCERTAINTY FACTOR: 1000

PRINCIPAL STUDY: Quast et al., 1983

COMMENTS: The chronic RfD was adopted as the subchronic RfD. The chronic RfD is under review and may be subject to change (U.S. EPA, 1994a).

3.1.5.2. Chronic

ORAL RfD: 9E-3 mg/kg/day (U.S. EPA, 1994a)
LOAEL: 9 mg/kg/day

UNCERTAINTY FACTOR: 1000

PRINCIPAL STUDY: Quast et al., 1983

CONFIDENCE: Medium
DATA BASE: Medium
RfD: Medium

VERIFICATION DATE: 1/22/85

COMMENTS: The RfD is based on liver lesions seen in a 2-year drinking water study with rats. An uncertainty factor of 10 each was applied for use of a LOAEL, for interspecies variation, and for protection of sensitive populations. The chronic RfD is under review and may be subject to change (U.S. EPA, 1994a).

3.2. INHALATION EXPOSURES
3.2.1. Acute Toxicity
3.2.1.1. Human

The primary effect of acute exposure to high concentrations (approximately 4000 ppm) of 1,1-dichloroethylene vapor is central nervous system (CNS) depression which may progress to unconsciousness (Gosselin et al., 1984). Lesions of the trigeminal nerve, causing motor weakness of the jaw, eye, and tongue muscles have been reported following acute inhalation exposure to 1,1-dichloroethylene (Henschler et al., 1970). However, subsequent evaluation suggested that the toxic agent was either mono- or dichloroacetylene (Haley, 1975).

3.2.1.2. Animal

The lethality of 1,1-dichloroethylene appears to be dependent on dietary parameters. Inhalation LC_{50}s for 4-hour exposures were 10,000-15,000 ppm in fed rats and 500-2500 ppm in fasted rats; death was due to vascular collapse and shock (Jaeger et al., 1973).

Twenty 6-hour exposures to 500 ppm caused nasal irritation, reduced weight gain, and histopathological changes in the liver of rats (Gage, 1970). Exposure of fasted rats to 200 ppm 1,1-dichloroethylene for 4 hours produced injury to liver parenchymal cells (Reynolds et al., 1980).

3.2.2. Subchronic Toxicity
3.2.2.1. Human

Information on the subchronic inhalation toxicity of 1,1-dichloroethylene in humans was not available.

3.2.2.2. Animal

Prendergast et al. (1967) exposed rats, guinea pigs, squirrel monkeys, rabbits, and beagle dogs continuously to 20, 61, or 189 mg/m^3 (5, 15, or 48 ppm) 1,1-dichloroethylene for 90 days. Early mortality occurred in guinea pigs and monkeys at all exposure concentrations without visible signs of toxicity compared with controls. All species had reduced body weight gains at 189 mg/m^3. Also seen at the highest exposure level were increased liver alkaline phosphatase and serum glutamic-pyruvic transaminase activities in rats and guinea pigs; kidney lesions in rats; and liver lesions in rats, dogs, and monkeys. The liver lesions were described as fatty changes, focal necrosis, hemosiderin deposition, lymphocytic infiltration, bile duct proliferation, fibrosis, and pseudo-lobule formation.

3.2.3. Chronic Toxicity
3.2.3.1. Human

Ott et al. (1976) studied mortality and health examination data of 138 Dow Chemical Company workers who had been exposed to 1,1-dichloroethylene at concentrations ranging from <5 ppm to

>70 ppm (time-weighted averages) in various job categories. The length of exposure ranged from <1 year to >10 years. Except for hepatic effects noted in two individuals with a history of alcohol consumption, mortality, spirometry, blood chemistry (including liver and renal tests), hematological parameters, and blood pressure measurements did not differ from controls matched for age and smoking.

In a preliminary study, Tierney et al. (1979) reported that 27 of 46 workers exposed to 1,1-dichloroethylene for 6 years or less in a 1,1-dichloroethylene polymerization plant showed a 50% or greater loss of liver function. The study provided few details and a follow-up study has not been reported.

3.2.3.2. Animal

Lee et al. (1977) exposed both sexes of CD rats and CD-1 mice to 55 ppm 1,1-dichloroethylene vapor, 6 hours/day, 5 days/week for up to 1 year. Most treated rats developed hepatocellular fatty changes and treated mice developed various hepatocellular changes, as well as focal degeneration, and necrosis of the liver.

Male and female Sprague-Dawley rats were exposed by inhalation to 10 or 40 ppm 1,1-dichloroethylene, 6 hours/day, 5 days/week for 1 month (Quast et al., 1986). Because of lack of treatment-related effects, exposure was then increased to 25 or 75 ppm for 17 months and surviving animals were held for an additional 6 months. The only effects attributed to 1,1-dichloroethylene inhalation were hepatocellular changes in both male and female rats at both exposure levels.

3.2.4. Developmental and Reproductive Toxicity

3.2.4.1. Human

Information on the developmental and reproductive toxicity of 1,1-dichloroethylene following inhalation exposure in humans was not available.

3.2.4.2. Animal

Short et al. (1977a) exposed CD rats and CD-1 mice to 1,1-dichloroethylene for 23 hours/day on days 6-16 of gestation. Rats were exposed to 15, 57, 300, or 449 ppm and mice to 15, 30, 57, 144, or 300 ppm. Maternal toxicity was seen in both species. In rats, 25% mortality occurred in dams exposed to the two highest concentrations; food consumption and weight gain was adversely affected at $ 15 ppm. No pregnant mice survived exposure to 144 or 300 ppm. Early resorptions were common in all exposed groups, with 49 and 64% resorptions in rats exposed to 57 and 449 ppm, respectively, and 100% resorptions in mice exposed to 30 and 57 ppm, respectively. Some soft tissue anomalies were observed in offspring of rats at 15 and 57 ppm and a significantly (p value not given) increased incidence of incomplete ossification of sternebrae occurred in offspring of mice at 15 ppm and in offspring of rats at 15, 57, and 300 ppm.

Murray et al. (1979) exposed Sprague-Dawley rats and New Zealand rabbits to 20 ppm (rats only), 80, or 160 ppm 1,1-dichloroethylene vapor for 7 hours/day during organogenesis. Maternal toxicity (decreased weight gain, decreased food consumption, and increased liver weights) was observed in rats at 80 and 160 ppm and in rabbits at 160 ppm. A statistically significant ($p<0.05$) increase of skeletal variations such as delayed ossification and wavy ribs was seen in offspring of rats exposed to both 80 and 160 ppm and in offspring of rabbits exposed to 160 ppm. In rabbits, resorptions were significantly ($p<0.05$) greater at 160 ppm than in control dams.

In a dominant lethal assay by Short et al. (1977b), exposure of male rats to 55 ppm 1,1-dichloroethylene, 6 hours/day, 5 days/week for 11 weeks before gestation had no effects on their fertility. No pre- or postimplantation losses occurred in untreated females mated to treated males.

3.2.5. Reference Concentration

An inhalation reference concentration (RfC) for 1,1-dichloroethylene has not been derived. A risk assessment for this chemical is under review by an EPA work group (U.S. EPA, 1994a).

3.3. OTHER ROUTES OF EXPOSURE
3.3.1. Acute Toxicity
3.3.1.1. Humans

1,1-Dichloroethylene is irritating when applied to the skin of humans; prolonged contact can cause first degree burns (Tierney et al., 1979). It has been suggested that the irritant effect is due to the presence of the inhibitor MEHQ, a compound that produces skin depigmentation at concentrations of 0.25% or higher (ATSDR, 1993). Direct contact with the eyes may cause conjunctivitis and transient corneal injury (IARC, 1986).

3.3.2.2. Animals

Intravenous injection of 225 mg/kg of 1,1-dichloroethylene and subcutaneous injection of 3700 mg/kg was lethal to dogs and rabbits, respectively (Tierney et al., 1979).

1,1-Dichloroethylene is moderately irritating to the eyes of rabbits, causing pain, conjunctival irritation, and some transient corneal injury (Torkelson and Rowe, 1982). Permanent injury is unlikely. Skin irritation, noted in rabbits a few minutes after application of liquid 1,1-dichloroethylene, was attributed in part to the presence of the stabilizer MEHQ.

Mice exhibited a decrease of cytochrome P-450 levels and related monooxygenases in lung microsomes 24 hours after an intraperitoneal injection of 125 mg/kg of 1,1-dichloroethylene (Krijgsheld et al., 1983). Examination of the lung tissues revealed necrosis that was restricted to the Clara cells.

3.3.2. Subchronic Toxicity

Information on the subchronic toxicity of 1,1-dichloroethylene in humans or animals by other routes of exposure was not available.

3.3.3. Chronic Toxicity

Information on the chronic toxicity of 1,1-dichloroethylene in humans or animals by other routes of exposure was not available.

3.3.4. Developmental and Reproductive Toxicity

Information on the developmental and reproductive toxicity of 1,1-dichloroethylene in humans or animals by other routes of exposure was not available.

3.4. TARGET ORGANS/CRITICAL EFFECTS
3.4.1. Oral Exposures
3.4.1.1. Primary Target Organs

1. Liver. Chronic oral exposure to 1,1-dichloroethylene produced hepatocellular changes in rats and liver necrosis in mice.

2. Kidneys. Chronic oral exposure to 1,1-dichloroethylene produced inflammation of the kidneys in rats.

3.4.1.2. Other Target Organs

Other target organs following oral exposure to 1,1-dichloroethylene were not identified.

3.4.2. Inhalation Exposures
3.4.2.1. Primary Target Organs

1. Liver. A preliminary study reported loss of liver function in workers exposed to 1,1-dichloroethylene. Subchronic and chronic inhalation exposure to produced mild to marked histological changes in the liver of several animal species.

2. Kidneys. Subchronic exposure to 1,1-dichloroethylene produced kidney lesions in rats.

3. Development: Exposure to 1,1-dichloroethylene during gestation produced increased resorptions and minor skeletal alterations in rats, rabbits, and mice at concentrations that caused maternal toxicity.

3.4.2.2. Other Target Organs

Other target organs following inhalation exposure 1,1-dichloroethylene were not identified.

3.4.3. Other Routes of Exposure
3.4.3.1. Primary Target Organs

1. Skin. 1,1-Dichloroethylene is irritating to the skin of humans.

2. Eyes. Direct contact of 1,1-dichloroethylene with the eyes may cause conjunctivitis and transient corneal injury in humans.

3.4.3.2. Other Target Organs

Other target organs by other routes of exposure to 1,1-dichloroethylene were not identified.

4. CARCINOGENICITY
4.1. ORAL EXPOSURES
4.1.1. Human

Information on the carcinogenicity of 1,1-dichloroethylene in humans following oral exposure was not available.

4.1.2. Animal

Oral carcinogenicity studies with rats and mice gave negative results. In a 2-year gavage study conducted by NTP (1982), F344 rats and B6C3F_1 mice were administered 1,1-dichloroethylene at doses of 1 or 5 mg/kg/day (rats) and 2 or 10 mg/kg/day (mice), 5 days/week for 2 years. An increased incidence (not statistically significant) of adrenal pheocytochromas was seen in high-dose male rats but not in female rats. Female mice administered the low dose exhibited an increased incidence of lymphomas and leukemia that was not considered treatment-related. In another gavage study, male and female Sprague-Dawley rats received 0.5, 5, 10, or 20 mg/kg/day, 4 to 5 days/week for 78 weeks, followed by a 147-week observation period (Maltoni et al., 1984, 1985). The pattern of neoplasms and their incidences was similar to that seen in controls.

No carcinogenic effects were observed in Sprague-Dawley rats administered 50 to 200 ppm (7 to 30 mg/kg/day) 1,1-dichloroethylene in drinking water for 2 years (Quast et al., 1983).

4.2. INHALATION EXPOSURES
4.2.1. Human

Ott et al. (1976) found no relationship between the occurrence of cancer or cancer mortality in 138 workers primarily exposed to 1,1-dichloroethylene during 1950 to 1959 and 55 workers exposed from

1960 to 1969. The subjects were divided into groups exposed to <5 ppm, 10-24 ppm, and $25 ppm. Five deaths were observed (compared with 7.5 expected in the U.S. white male population) and 27 workers were lost to follow-up. The study was inadequate to assess cancer risk because the cohorts were limited and no allowance was made for latency period.

4.2.2. Animal

Male and female Sprague-Dawley rats were exposed by inhalation to 10 or 40 ppm 1,1-dichloroethylene, 6 hours/day, 5 days/week for 1 month (Quast et al., 1986). Because of the lack of treatment-related effects, exposure was then increased to 25 or 75 ppm for 17 months and surviving animals were held for an additional 6 months. No treatment-related neoplasms were observed.

Maltoni et al. (1985) exposed male and female Swiss mice to 10 or 25 ppm 1,1-dichloroethylene, 4 to 5 days/week for 12 months. [Interim results of this study were reported in Maltoni et al., 1977.] A statistically significant (p value not given) increase in kidney adenocarcinomas was reported in male mice exposed to 25 ppm. There were also statistically significant increases in mammary adenocarcinomas in female mice and pulmonary adenomas in both sexes; however, a dose-response relationship was not apparent. In a second study, Sprague-Dawley rats were exposed to 10, 25, 50, 100, or 150 ppm, 4 to 5 days/week for 12 months and observed until death. A statistically significant (p value not given) increase in total mammary tumors (but not carcinomas) was seen only at 10 ppm and 100 ppm, but not at the other concentrations tested.

In a study by Hong et al. (1981), small groups of CD rats and CD-1 mice of both sexes were exposed to 55 ppm 1,1-dichloroethylene, 6 hours/day, 5 days/week for 1, 3, 6 (rats and mice), or 10 months (rats only). Following treatment, all groups were observed for 12 months. There was a dose-related decrease in survival in male and female mice; survival in rats was similar to controls. No treatment-related tumors were reported in rats or mice.

Female Chinese hamsters were exposed to 25 ppm 1,1,-dichloroethylene for 4 hours/day, 4-5 days/week for 52 weeks and observed for life (164 weeks) (Maltoni et al., 1984). The tumor incidence was comparable to that in controls.

4.3. OTHER ROUTES OF EXPOSURE

4.3.1. Human

Information on the carcinogenicity of 1,1-dichloroethylene in humans by other routes of exposure was not available.

4.3.2. Animal

Van Duuren et al. (1979) applied 40 or 121 mg 1,1-dichloroethylene to the skin of Swiss mice three times weekly for 595 days. No skin tumors were observed. However, when 121 mg 1,1-dichloroethylene was applied once, followed 2 weeks later by dermal applications of the tumor promoter, phorbol myristate acetate (three times weekly for about 576 days), there was a statistically significant ($p<0.05$) increase in the incidence of skin papillomas in treated animals compared with controls treated with the promoter only.

In another experiment, Van Duuren et al. (1979) injected female Ha:ICR mice subcutaneously with 2 mg 1,1-dichloroethylene in trioctanoin once weekly for 78 weeks. No local sarcomas were observed.

4.4. EPA WEIGHT-OF-EVIDENCE

Classification -- Group C - Possible human carcinogen (U.S. EPA, 1994a)

Basis -- Tumors observed in one mouse strain after inhalation exposure. Other studies were of inadequate design. 1,1,-Dichloroethylene is mutagenic, and a metabolite has been shown to

alkylate and bind covalently to DNA. It is structurally related to the human carcinogen, vinyl chloride.

4.5. CARCINOGENICITY SLOPE FACTORS

4.5.1. Oral

SLOPE FACTOR: 6E-1 $(mg/kg/day)^{-1}$ (U.S. EPA, 1994a)
UNIT RISK: 1.7E-5 $(\mu g/L)^{-1}$ (U.S. EPA, 1994a)
PRINCIPAL STUDIES: Quast et al., 1983; NTP, 1982

COMMENT: The unit risk was derived from the highest of four oral slope factors calculated from two studies that did not show a statistically significant increase in tumor incidence attributable to oral exposure to 1,1-dichloroethylene. The drinking water study in rats (Quast et al., 1983) produced the lowest slope factor of 0.2 $(mg/kg/day)^{-1}$. The highest slope factor [0.6 $(mg/kg/day)^{-1}$] was based on renal tumors in male rats (NTP, 1982). EPA indicated that use of data showing no statistically significant increased in tumor incidence appeared justified, since the slope factor derived was within a factor of 2 of the slope factor based on data from the inhalation study by Maltoni et al. (1977, 1985).

4.5.2. Inhalation

SLOPE FACTOR: 1.2E+0 $(mg/kg/day)^{-1}$ (U.S. EPA, 1994b)
UNIT RISK: 5.0E-5 $(\mu g/m^3)^{-1}$ (U.S. EPA, 1994a)
PRINCIPAL STUDIES: Maltoni et al., 1977, 1985

COMMENT: The inhalation slope factor is based on kidney adenocarcinomas in male mice exposed for 12 months by inhalation.

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