United States
Environmental Protection
Agency

Office of Emergency and
Remedial Response
Washington DC 20460

Office of Research and Development
Office of Health and Environmental
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Cincinnati OH 45268

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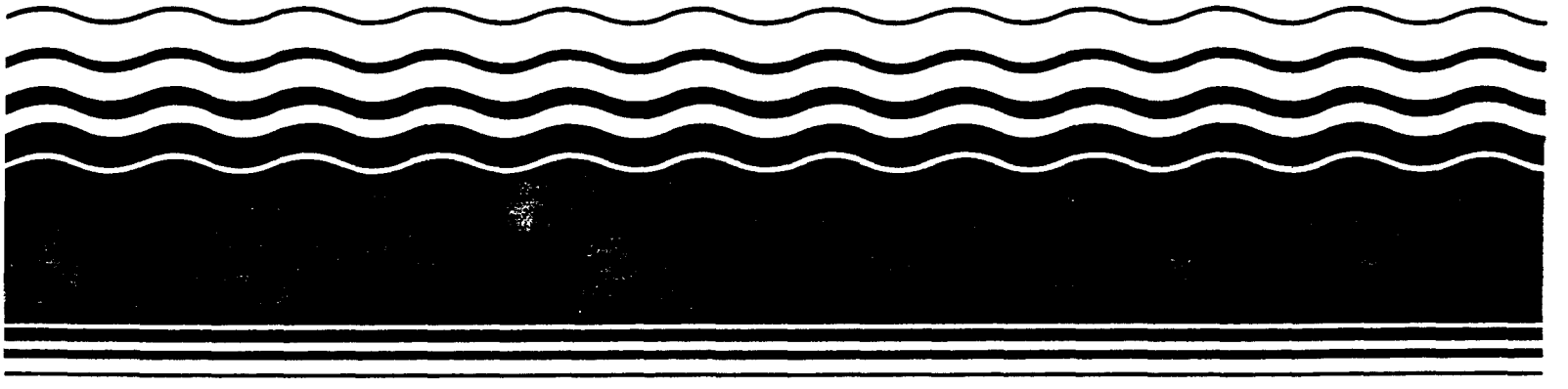
HEALTH EFFECTS ASSESSMENT FOR 1,1-DICHLOROETHYLENE



EPA/540/1-86-051
September 1984

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U.S. Environmental Protection Agency
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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with 1,1-dichloroethylene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Dichloroethylenes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-041. NTIS PB 81-117525.

U.S. EPA. 1983b. Health Assessment Document for Vinylidene Chloride. Environmental Criteria and Assessment Office, Research Triangle Park, NC. EPA 600/8-83-031A. NTIS PB 84-126762.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983a).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment in proper context, the reader is referred to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate use and interpretation of the quantitative estimates.

Evidence for the carcinogenicity of 1,1-dichloroethylene in animals is limited. There are essentially no useful human data. A number of oral exposure experiments have yielded negative results, as have inhalation studies. One inhalation study showed a significant increase in the incidence of kidney adenocarcinomas in mice exposed to 1,1-dichloroethylene vapors. Mutagenicity evaluations in numerous *in vitro* systems have yielded positive results.

The U.S. EPA (1983b) has used the kidney adenocarcinoma data in male mice for the computation of a human q_1^* for inhalation exposure to 1,1-dichloroethylene and derived a q_1^* of 1.47×10^{-1} $(mg/kg\ bw/day)^{-1}$.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3112 for EPA's Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa and Karen Blackburn were the Technical Project Monitors and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Emergency and Remedial Response, Washington, DC.

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Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Office of Air Quality Planning and Standards
Office of Solid Waste
Office of Toxic Substances
Office of Drinking Water

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
LOEL	Lowest-observed-effect level
ppm	Parts per million
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of 1,1-dichloroethylene (CAS No. 75-35-4), commonly known as vinylidene chloride, are as follows:

Chemical class: hydrocarbon	halogenated aliphatic
Molecular weight:	96.94 (Mabey et al., 1981)
Vapor pressure:	600 mm Hg at 25°C (U.S. EPA, 1983b)
Water solubility:	2250 mg/ℓ at 25°C (U.S. EPA, 1983b)
Octanol/water partition coefficient:	69 (estimated) (Mabey et al., 1981)
BCF:	7 (estimated from the equation of Veith et al., 1979)
Half-lives in	
Air:	2 days (Cupitt, 1980)
Water:	1-6 days (estimated)

The half-life of 1,1-dichloroethylene in aquatic media has been estimated from the reaeration rate ratio of 0.601 and the oxygen reaeration rate constant of 0.19-0.96 day^{-1} as given by Mabey et al. (1981).

The half-life of 1,1-dichloroethylene in soil could not be located in the literature available; however, evaporation is expected to be the predominant loss mechanism from the soil surface. Based on the octanol/water partition coefficient and aqueous solubility it can be speculated that leaching may play a significant role in determining the fate of this chemical in soils. In fact, the detection of this compound in several groundwaters (U.S. EPA, 1983b) is indicative of the leachability of this compound from soils.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

A number of investigators have reported the rapid appearance of labeled 1,1,-dichloroethylene in the urine and expired air of rats given an intragastric dose of [^{14}C] 1,1-dichloroethylene (position of label unspecified) (McKenna et al., 1978; Reichert et al., 1979; Jones and Hathway, 1978). These investigators concluded that the systemic absorption of 1,1-dichloroethylene following intragastric administration is rapid and fairly complete.

2.2. INHALATION

Andersen et al. (1979) exposed fasted male rats to atmospheres containing various concentrations of 1,1-dichloroethylene in a closed chamber. They observed an initial rapid phase followed by a slow phase of uptake. The rapid phase was believed to represent whole body equilibrium and was first-order with a rate constant of 2.2 hour^{-1} ($t_{1/2}$=0.315 hour). The slow phase was believed to represent metabolism.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Rampy et al. (1977) administered 50, 100 or 200 mg 1,1-dichloroethylene/ℓ drinking water to groups of 10 male and 10 female Sprague-Dawley rats for 90 days. There was an increased incidence of cytoplasmic vacuolization of hepatocytes in the high dose groups.

Quast et al. (1983) administered capsules containing 1,1-dichloroethylene in peanut oil (0, 6.25, 12.5 or 25 mg/kg bw/day) to groups of four male and four female beagle dogs for 97 days. No effects were observed on general appearance or demeanor, body weight, food consumption, hematology, clinical chemistry, urinalysis, organ weights, gross pathology or histopathology.

3.1.2. Inhalation. Subchronic exposure to 1,1-dichloroethylene results predominantly in damage to the liver and kidneys (Irish, 1962; Prendergast et al., 1967; Gage, 1970; Rampy et al., 1977). The most thorough of these studies was the study by Prendergast et al. (1967) in which rats, guinea pigs, rabbits, dogs and monkeys were exposed to atmospheric concentrations ranging from 20-395 mg/m^3 1,1-dichloroethylene for up to 90 days (Table 3-1). Intermittent exposure (8 hours/day, 5 days/week, for 6 weeks) to 395 mg/m^3 produced no deaths, visible signs of toxicity or histopathological changes in any species. At each dose level, the inhalation chamber typically contained 50 rats (Long-Evans or Sprague-Dawley), 15 Hartley guinea pigs, 3 squirrel monkeys, 3 New Zealand rabbits and 2 beagle dogs. The controls consisted of 304 rats, 314 guinea pigs, 57 monkeys, 48 rabbits and 34 dogs. Continuous exposure to concentrations up to 189 mg/m^3 produced dose-related mortality in guinea pigs and monkeys. For guinea pigs, mortality was significantly increased over controls in the three highest dose

TABLE 3-1

Effect on Experimental Animals of Long Term Inhalation of 1,1-Dichloroethylene*

Concentration	Schedule	Species	Mortality	Significant Findings
100 ppm (395 ± 32 mg/m^3)	30 exposures, 8 hours/day, 5 days/week	rat	0/15	None
		guinea pig	0/15	None
		rabbit	0/3	Weight loss in treated animals
		dog	0/2	None
		monkey	0/3	Weight loss in treated animals
48 ppm (189 ± 6.2 mg/m^3)	90 days, 24 hours/day	rat	0/15	Animals gained less weight than controls. Hepatic lesions. Renal lesions.
		guinea pig	7/15	Mortality occurred between day 4 and day 9 of exposure. Slight elevation of liver alkaline phosphatase activity and serum glutamic-pyruvic transaminase activity.
		dog	0/2	Animals lost weight. Hepatic lesions. One dog developed an adrenal cortical adenoma.
		monkey	3/9	Mortality occurred on days 26, 60 and 64. Animals lost weight. Hepatic lesions.
26 ppm (101 ± 4.4 mg/m^3)	90 days, 24 hours/day	rat	0/15	None
		guinea pig	3/15	Mortality occurred between day 3 and day 5 of exposure.
		rabbit	0/3	Animals lost weight.
		dog	0/2	Animals lost weight.
		monkey	2/3	Mortality occurred between day 3 and day 6 of exposure.

TABLE 3-1 (cont.)

Concentration	Schedule	Species	Mortality	Significant Findings
16 ppm	90 days,	rat	0/15	Animals gained less weight than controls.
(61±5.7 mg/m³)	24 hours/day	guinea pig	3/15	Mortality occurred on day 3 and day 4.
		dog	0/2	None
		monkey	0/9	Animals lost weight.
5 ppm	90 days,	rat	2/45	Animals gained less weight than controls.
(20±2.1 mg/m³)	24 hours/day	guinea pig	2/45	None
		dog	0/6	Animals lost weight.
		monkey	1/21	None
Control	NR	rat	7/304	None
		guinea pig	2/314	
		rabbit	2/48	
		dog	0/34	
		monkey	1/57	

*Source: Prendergast et al., 1967

NR = Not reported

groups (61, 101 and 189 mg/m³) and was of borderline significance at the 20 mg/m³ exposure level (p=0.078, 1-tailed Fisher exact test). Growth depression was noted in all species at the high dose level. Renal lesions were observed in rats and hepatic lesions and/or enzyme changes were observed in all species at the high dose level; however, no histological lesions were found at concentrations of <101 mg/m³. Depressed weight gain and increased mortality were observed in some species at all exposure levels.

3.2. CHRONIC

3.2.1. Oral. 1,1-Dichloroethylene was administered in the drinking water (50, 100 or 200 mg/ℓ) to groups of 48 male and 48 female Sprague-Dawley rats for 2 years (Quast et al., 1983; Humiston et al., 1978; Rampy et al., 1977). These water concentrations provided doses of 5-12, 8-20 and 16-40 mg/kg bw/day, respectively. The control groups consisted of 80 males and 80 females. 1,1-Dichloroethylene had no significant effect on general appearance, body weight, food consumption, water consumption, hematology, urinalysis, clinical chemistry or organ weights. Gross and histopathological examination revealed a number of statistically significant lesions (Table 3-2), the most important of which were hepatocellular fatty changes and periportal hepatocellular hypertrophy.

The chronic toxicity of 1,1-dichloroethylene has also been determined in F344/N rats and B6C3F1/N mice. Fifty animals/sex/dose were given 0, 1 or 5 mg/kg bw/day (rats) or 0, 2 or 10 mg/kg bw/day (mice) by gavage, 5 days/week for 2 years (NTP, 1982). Mortality and growth rates were not affected at either dose level in either species. Increased incidences of chronic renal inflammation were observed in the high dose rats (males, 43/48 vs. 26/50 controls; females, 9/44 vs. 3/49 controls) and liver necrosis in high dose male mice (7/49 vs. 1/46 controls).

TABLE 3-2

Pathologic Effects of Long-Term Ingestion of 1,1-Dichloroethylene Incorporated in the Drinking Water of Sprague-Dawley Rats*

Effect	Dose Level					
	50 ppm		100 ppm		200 ppm	
	M	F	M	F	M	F
Increased incidence of intra-abdominal fluid or blood in abdominal cavity			✓			
Increased incidence in the total number of rats with hepatocellular fatty change or fatty degeneration				✓	✓	✓
Increased incidence of hepatocellular fatty change with location in lobule not specified		✓		✓		✓
Increased incidence in periportal hepatocellular fatty change						✓
Increased incidence of periportal hepatocellular hypertrophy		✓		✓	✓	✓
Increased incidence of hepatic centrilobular atrophy						✓
Increased incidence of mammary gland fibroadenomas/adenofibromas		✓				

*Source: U.S. EPA, 1983b; Humiston et al., 1978

M = male; F = female

3.2.2. Inhalation. Rampy et al. (1977) and McKenna et al. (1982) reported the results of a Dow Chemical Company 2-year inhalation study in which groups of 104 male and 104 female Sprague-Dawley rats were exposed to 0, 10 or 40 ppm (0, 39.7 or 158.6 mg/m³) 1,1-dichloroethylene 6 hours/day, 5 days/week, for 5 weeks, after which the exposures were increased to 0, 25 or 75 ppm (0, 99.1 or 297.4 mg/m³) for the remainder of the 18-month exposure period (~73 weeks). No dose-related changes were observed in mortality, body weight, hematology or clinical chemistry. Hepatocellular fatty changes were observed in both sexes at both dose levels. This effect was reversible after treatment was discontinued. Similar hepatic changes have been reported in mice and rats exposed to 55 ppm (218.1 mg/m³) 6 hours/day, 5 days/week for 6-12 months (TWA=38.9 mg/m³) (Lee et al., 1977; Hong et al., 1981).

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Nitschke et al. (1980, 1983) administered 1,1-dichloroethylene in the drinking water (50, 100 or 200 mg/ℓ) to Sprague-Dawley rats for 3 generations. Each parental generation consisted of 10 males and 20 females. There were a number of statistically significant effects on reproduction; however, these effects were not dose-related and occurred sporadically throughout the 3 generations. These effects were, therefore, probably not related to exposure to 1,1-dichloroethylene. At doses of 100 and 200 mg/ℓ, statistically significant increases in hepatocellular fatty changes were observed in the F_1 males and females and the F_2 females.

3.3.2. Inhalation. The teratogenicity of inhaled 1,1-dichloroethylene has been tested in rats, rabbits and mice (Short et al., 1977a; Murray et al., 1979). Signs of fetal toxicity, minor skeletal alterations and soft-tissue alterations were observed at doses that produced maternal toxicity

and were considered to be feto- and embryotoxic manifestations of maternal toxicity. Maternal toxicity in rats was observed by Short et al. (1977a) at exposure levels as low as 15 ppm.

3.4. TOXICANT INTERACTIONS

The metabolism of dichloroethylenes involves the production of reactive epoxide intermediates that bind covalently to cellular macromolecules (Bonse et al., 1975; Hathway, 1977; McKenna et al., 1978). Compounds such as disulfiram decrease the covalent binding of 1,1-dichloroethylene and protect against lethality and hepatotoxicity (Short et al., 1977b). Pretreatment with inducers of microsomal enzyme systems also decreased the hepatotoxicity of 1,1-dichloroethylene (Reynolds et al., 1975; Jenkins et al., 1972), but increased mortality (Carlson and Fuller, 1972). Compounds that deplete cellular glutathione increase the hepatotoxicity of 1,1-dichloroethylene (Jaeger et al., 1973a,b, 1974, 1977).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Pertinent data regarding the oral carcinogenicity of 1,1-dichloroethylene in humans could not be located in the available literature.

4.1.2. Inhalation. Ott et al. (1976) investigated the effects of occupational exposure to 1,1-dichloroethylene (<0.2% vinyl chloride) among 138 Dow Chemical Company workers. TWA concentrations were estimated based on job descriptions and industrial hygiene surveys; the subjects were divided into groups exposed to <10 ppm (assumed 5 ppm average), 10-24 ppm (assumed 17 ppm average) and ≥25 ppm (assumed 43 ppm average). There were no statistically significant differences between the exposed groups and controls matched for age and smoking habits; however, the population examined in the study may not be adequate for the detection of cancer.

4.2. BIOASSAYS

4.2.1. Oral. The available data regarding the oral carcinogenicity of 1,1-dichloroethylene in experimental animals are summarized in Table 4-1. These studies have failed to demonstrate a carcinogenic potential for 1,1-dichloroethylene in either rats or mice following oral exposure.

4.2.2. Inhalation. The available data on the inhalation carcinogenicity of 1,1-dichloroethylene in experimental animals are summarized in Table 4-2. The only studies in which 1,1-dichloroethylene has produced positive results are those of Maltoni et al. (1977, 1980) in which Sprague-Dawley rats and Swiss mice were used. There were at least 30 animals/sex/dose at the beginning of the exposure period, with 90-100 animals/sex in the controls. Rats were exposed to atmospheres containing 0, 10, 25, 50, 100 or 150 ppm (0, 39.7, 99.1, 198.3, 396.5 or 594.8 mg/m^3) 1,1-dichloroethylene, 4 hours/day, 4-5 days/week, for 12 months.

TABLE 4-1

Results of Oral Carcinogenicity Bioassays of 1,1-Dichloroethylene*

Species	Dose	Route of Administration	Total Duration of Observation (weeks)	Findings	Reference
Sprague-Dawley rats	20, 10, 5, 0.5 mg/kg for 12 months	gavage, daily	147	No statistically significant increase	Maltoni et al., 1977
Sprague-Dawley rats	50, 100, 200 ppm in drinking water	ingestion	104	No statistically significant increase	Quast et al., 1983
Fischer 344 rats	5 mℓ/kg of a 1000 or 200 ppm solution	gavage, 5 days/week	103	No statistically significant increase	NTP, 1982
B6C3F1 mice	10 mℓ/kg of a 1000 or 200 ppm solution	gavage, 5 days/week	103	No statistically significant increase	NTP, 1982
Sprague-Dawley rats	0.5, 5, 10, 20 mg/kg/day	gavage, 5 days/week	52-59	No brain tumors	Maltoni et al., 1982

*Source: U.S. EPA, 1983b

TABLE 4-2

Results of Inhalation Carcinogenicity Bioassays of 1,1-Dichloroethylene*

Species	Dose	Route of Administration	Total Duration of Observation	Findings	Reference
Sprague-Dawley rats	10, 25, 50, 100, 150 ppm, 4-5 days/week for 12 months	inhalation, 4 hours/day	137 weeks	Statistically significant increase in total mammary tumors, but not carcinomas alone, only at 10 and 100 ppm; no dose response	Maltoni et al., 1977, 1980
Swiss mice	10, 25 ppm, 4-5 days/ week for 12 months	inhalation, 4 hours/day	121 weeks	Kidney carcinomas at 25 ppm in males (none in controls) Statistically significant increase in mammary carcinomas in females; no dose response	Maltoni et al., 1977, 1980
Chinese hamsters	25 ppm, 4-5 days/week for 12 months	inhalation, 4 hours/day	157 weeks	No statistically significant increase	Maltoni et al., 1977, 1980
Wistar rats	200 ppm for 6 months, followed by 100 ppm for 6 months, 5 days/ week	inhalation, 4 hours/day	lifetime	No statistically significant increase	Viola and Caputo, 1977
Sprague-Dawley rats	100, 75 ppm, 5 days/ week for 12 months	inhalation, 4 hours/day	lifetime	No statistically significant increase	Viola and Caputo, 1977
CD-1 mice	55 ppm, 5 days/week	inhalation, 6 hours/day	12 months	No statistically significant increase	Lee et al., 1978
CD rats	55 ppm, 5 days/week for 12 months	inhalation, 6 hours/day	12 months	No statistically significant increase	Lee et al., 1978
Sprague-Dawley rats	25, 75 ppm for 24 months	inhalation	104 weeks	No statistically significant increase	McKenna et al., 1982
CD mice	55 ppm, 5 days/week 1, 3 or 6 months	inhalation, 6 hours/day	13, 15 or 18 months	No statistically significant increase	Hong et al., 1981
CD rats	55 ppm, 5 days/week 1, 3, 6 or 10 months	inhalation, 6 hours/day	13, 15, 18 or 22 months	No statistically significant increase	Hong et al., 1981
Sprague-Dawley rats	10, 25, 50, 100, 150 ppm	inhalation, 4-5 days/week	52 weeks	No brain tumors	Maltoni et al., 1982

*Source: U.S. EPA, 1983b

The results of these studies are summarized in Tables 4-3 and 4-4. There were indications that 1,1-dichloroethylene induced mammary tumors in both rats and mice; however, there was no clear dose-response relationship and these tumors could not positively be attributed to exposure to 1,1-dichloroethylene. The only tumors that the authors considered related to the treatment were kidney adenocarcinomas in male mice.

4.3. OTHER RELEVANT DATA

1,1-Dichloroethylene has been tested for yeast and bacterial mutagenicity in the Ames assay, the liquid suspension assay, the host-mediated assay and exposure of bacteria to atmospheres containing 1,1-dichloroethylene, both with and without mammalian metabolic activating systems (Bartsch et al., 1975, 1979; Malaveille et al., 1977; Simmon et al., 1977, 1979; Simmon, 1978; Baden et al., 1976, 1977, 1978; Waskell, 1978; Greim et al., 1975; Cerna and Kypenova, 1977; Laumbach et al., 1977; Bartsch, 1976; Barbin et al., 1978; Bonse et al., 1975). 1,1-Dichloroethylene is mutagenic to Escherichia coli, Salmonella typhimurium, Bacillis subtilis and Saccharomyces cerevisiae, in the presence, but not the absence, of a mammalian metabolic activating system.

1,1-Dichloroethylene vapors have been demonstrated to be mutagenic to the plant, Tradescantia, following a 24-hour exposure to concentrations as low as 22 ppm (87.2 mg/m^3); however, a 6-hour exposure to 1288 ppm (5107 mg/m^3) did not produce a mutagenic effect (Van't Hof and Schairer, 1982). In contrast, negative results have been obtained in assays using cultured mammalian cells (Drevon and Kuroki, 1979) and in dominant lethal assays in mice (Andersen and Jenkins, 1977) and rats (Short et al., 1977c).

TABLE 4-3

Distribution of the Different Types of Mammary Tumors After Exposure by Inhalation to 1,1-Dichloroethylene in Air After 137 Weeks[a,b]

Group No.	Concentrations	Animals (Sprague-Dawley rats, 16 Weeks Old at Start) Sex	No. at Start	Corrected[d] Number	% [e]	Average Latency Time[f] (weeks)	No. of Tumors/ Tumor-Bearing Animals	% [g]	Histologically Examined Histotype[c] No.	Fibromas and Fibroadenomas % [h]	Fibromas and Fibroadenomas Average Latency Time[f] (weeks)	Carcinomas No.	Carcinomas % [h]	Carcinomas Average Latency Time[f] (weeks)
I	150 ppm	M	60	60	13.3	97±14	1.0	100.0	6	75.0	109±8	1	12.5	26
		F	60	60	73.3	82±3	1.5	97.7	38[i]	88.4	83±3	9	20.9	78±8
		M/F	120	120	43.3	82±3	1.4	98.1	44	86.3	86±3	10	19.6	73±8
II	100 ppm	M	30	30	16.7	104±9	1.0	100.0	5	100.0	104±9	0	0	0
		F	30	30	83.3	82±4	1.7	92.0	21[i]	91.3	83±5	3	13.0	102±10
		M/F	60	60	50.0	85±4	1.6	93.3	26	92.8	87±4	3	10.7	102±10
III	50 ppm	M	30	30	23.3	106±5	1.0	100.0	7	100.0	106±5	0	0	0
		F	30	30	76.7	79±4	1.9	95.6	21[i]	95.4	82±4	1	4.5	68
		M/F	60	60	50.0	86±4	1.7	96.7	28	96.5	88±4	1	3.4	68
IV	25 ppm	M	30	28	14.3	103±10	1.0	100.0	4	100.0	103±10	0	0	0
		F	30	30	70.0	86±4	1.6	95.2	20[i]	100.0	87±4	4	20.0	82±10
		M/F	60	58	43.1	88±4	1.5	96.0	24	100.0	90±4	4	16.7	82±10
V	10 ppm	M	30	29	10.3	81±23	1.0	100.0	3	100.0	81±23	0	0	0
		F	30	30	93.3	83±4	1.6	85.7	24[i]	100.0	85±4	5	20.8	90±14
		M/F	60	59	52.5	81±4	1.5	87.1	27	100.0	85±4	5	18.5	90±14
VI	no treatment (controls)	M	100	87	12.6	115±6	1.0	100.0	11	100.0	115±6	0	0	0
		F	100	99	61.6	87±2	1.5	91.8	44	78.6	88±3	16	28.6	95±5
		M/F	200	186	38.7	91±3	1.4	93.0	55	82.1	93±3	16	23.9	95±5

[a]Source: Maltoni et al., 1980

[b]Exposure was for 4 hours/day, 4-5 days/week for 52 weeks

[c]Two or more tumors of the same and/or different types (fibroadenomas, carcinomas, sarcomas, carcinosarcomas) may be present in the same animals. A carcinoma was found in one male in the 150 ppm group, and no animals were observed to have sarcomas.

[d]Live animals after 10 weeks, when the first tumor (a leukemia) was observed.

[e]The percentages refer to the corrected numbers.

[f]Average age at the onset of the first mammary tumor per animal, detected at the periodic control or at autopsy.

[g]The percentages refer to total numbers of animals bearing mammary tumors.

[h]The percentages refer to total numbers of animals bearing mammary tumors, histologically examined.

[i]Statistically significant increase compared to control by chi-square test ($p<0.05$). Comparisons are made between numbers with tumors/corrected numbers.

TABLE 4-4

Distribution of the Different Types of Tumors After Exposure by Inhalation to 1,1-Dichloroethylene in Air After 121 Weeks[a,b]

Groups No.	Treatment: Concentrations	Treatment: Length	Animals (Swiss mice 16 weeks old [(Groups I,II,III,IV, V,VI) and 9 weeks old (Groups IV bis, VII at start]: Sex	Animals: No. at Start	Animals with Tumors: Kidney Adenocarcinomas: Corrected Number[e]	Kidney Adenocarcinomas: No.	Kidney Adenocarcinomas: %	Kidney Adenocarcinomas: Average Latency Time[f] (weeks)	Mammary Tumors[c]: Corrected Number[e]	Mammary Tumors[c]: No.	Mammary Tumors[c]: %	Mammary Tumors[c]: Average Latency Time[e] (weeks)	Pulmonary Adenomas[d]: Corrected Number[e]	Pulmonary Adenomas[d]: No.	Pulmonary Adenomas[d]: %	Pulmonary Adenomas[d]: Average Latency Time[f] (weeks)
I	200 ppm	2 days	M	60	1	0	0	0	6	0	0	0	5	0	0	0
			F	60	28	0	0	0	53	1	1.9	87	46	1	2.2	57
			M/F	120	29	0	0	0	59	1	1.7	87	53	1	1.9	57
II	100 ppm	2 days	M	30	12	0	0	0	21	0	0	0	18	2	11.1	62±7
			F	30	13	0	0	0	28	3	10.7	46±3	26	2	7.7	53±2
			M/F	60	25	0	0	0	49	3	6.1	46±5	44	4	9.1	58±4
III	50 ppm	1 week	M	30	17	1	5.9	64	27	0	0	0	26	1	3.8	62
			F	30	14	0	0	0	28	2	7.1	39±13	27	3	11.1	80±8
			M/F	60	31	1	3.2	64	55	2	3.6	39±13	53	4	7.5	75±7
IV	25 ppm	52 weeks	M	30	21	3[g]	14.3	71±5	29	0	0	0	28	7[i]	25.0	73±6
			F	30	26	0	0	0	30	4[h]	13.3	68±11	29	7[i]	24.1	85±6
			M/F	60	47	3	6.4	71±5	59	4	6.8	68±11	57	14	24.6	30±4
IV bis	25 ppm	52 weeks	M	120	98	25[g]	25.5	75±2	117	1	0.8	46	113	16[i]	14.2	77±3
			F	120	112	1	0.9	77	118	12[h]	10.2	69±4	118	11[i]	9.3	78±6
			M/F	240	210	26	12.4	75±2	235	13	5.5	67±4	231	27	11.7	77±3
V	10 ppm	52 weeks	M	30	25	0	0	0	30	0	0	0	28	11[i]	39.3	71±5
			F	30	26	0	0	-	30	6[h]	20.0	63±5	30	3[i]	16.0	68±4
			M/F	60	51	0	0	0	60	6	10.0	63±5	58	14	24.1	70±4
VI	no treatment (controls)	NA	M	100	56	0	0	0	92	1	1.1	25	80	3	3.7	66±7
			F	100	73	0	0	0	97	2	2.1	49±7	92	4	4.3	56±7
			M/F	200	129	0	0	0	189	3	1.6	41±9	172	7	4.1	60±4

TABLE 4-4 (cont.)

Groups No.	Treatment: Concentrations	Treatment: Length	Animals (Swiss mice 16 weeks old [(Groups I,II,III,IV, V,VI) and 9 weeks old (Groups IV bis, VII at start]: Sex	Animals (Swiss mice 16 weeks old [(Groups I,II,III,IV, V,VI) and 9 weeks old (Groups IV bis, VII at start]: No. at Start	Animals with Tumors: Kidney Adenocarcinomas: Corrected Number[e]	Kidney Adenocarcinomas: No.	Kidney Adenocarcinomas: %	Kidney Adenocarcinomas: Average Latency Time[f] (weeks)	Mammary Tumors[c]: Corrected Number[e]	Mammary Tumors[c]: No.	Mammary Tumors[c]: %	Mammary Tumors[c]: Average Latency Time[e] (weeks)	Pulmonary Adenomas[d]: Corrected Number[e]	Pulmonary Adenomas[d]: No.	Pulmonary Adenomas[d]: %	Pulmonary Adenomas[d]: Average Latency Time[f] (weeks)
VII	no treatment (controls)	NA	M	90	70	0	0	0	80	0	0	0	73	3	4.1	56±11
			F	90	85	0	0	0	88	0	0	0	86	2	2.3	75±12
			M/F	180	155	0	0	0	168	1	0.6	83	159	5	3.1	64±8

[a]Source: Maltoni et al., 1980

[b]Exposure was for 4 hours/day, 4-5 days/week for 52 weeks

[c]All mammary tumors in females were histologically diagnosed as carcinomas.

[d]Some pulmonary adenomas were cellular atypias.

[e]Alive animals when the first tumor was observed: kidney adenocarcinoma, 55 weeks; mammary tumor, 27 weeks; pulmonary adenoma, 36 weeks. The percentages refer to the corrected numbers.

[f]Average time from the start of the experiment to the detection (at the periodic control or at autopsy).

[g]$p<0.01$, combined 25 ppm (28/119) males vs. control males (0/196) by chi-square test. Based on corrected numbers.

[h]$p<0.01$ combined control males (6/153) vs. 10 ppm males (11/28) and vs. combined 25 ppm males (29/294). Also, combined control females (6/178) vs. 10 ppm females (3/30) and vs. combined 25 ppm females (18/147)

[i]$p<0.01$ combined control females (3/185) vs. 10 ppm females (6/30) and vs. combined 25 ppm females (16/148). Based on corrected numbers.

NA = Not applicable

4.4. WEIGHT OF EVIDENCE

IARC (1982) has evaluated the evidence for carcinogenicity of 1,1-dichloroethylene and concluded that the evidence for carcinogenicity in humans is "inadequate," the evidence for carcinogenicity in animals is "limited," and the evidence for activity in short-term tests is "sufficient." Applying the criteria for weight of evidence proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984) 1,1-dichloroethylene is most appropriately classified in Group C - Possible Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1980) has established a TLV of 5 ppm (~20 mg/m^3) and a STEL of 20 ppm (~80 mg/m^3), which are believed low enough to prevent overt toxicity in exposed workers.

The U.S. EPA (1980b) has estimated that an ambient water concentration of 0.33 µg/ℓ would result in excess carcinogenic potency over a lifetime exposure. Both NIOSH and OSHA consider 1,1-dichloroethylene to be a potential carcinogen and have established an exposure limit of 1.0 ppm (~4 mg/m^3) as a TWA or 5 ppm (~20 mg/m^3) as a 15-minute ceiling (ACGIH, 1980).

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

1,1-Dichloroethylene is a chemical associated with cancer in animals and for which data are sufficient for computing a q_1^*. It is, therefore, inappropriate to calculate an oral or inhalation AIS for 1,1-dichloroethylene.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

1,1-Dichloroethylene is a chemical associated with cancer in animals and for which data are sufficient for computing a q_1^*. It is, therefore, inappropriate to calculate an oral or inhalation AIC for 1,1-dichloroethylene.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. No data were located in the available literature that indicated a carcinogenic potential for orally administered 1,1-dichloroethylene. Therefore, no q_1^* could be derived.

6.3.2. Inhalation. Only one study was located in the available literature that indicated a carcinogenic response to inhaled 1,1-dichloroethylene (Maltoni, et al., 1977, 1980). In this study, groups of at least 30 Swiss mice/sex/dose were exposed to 0, 39.7 or 99.1 mg 1,1-dichloroethylene/m^3, 4 hours/day, 4-5 days/week, for 12 months. Kidney adenocarcinomas were observed in 28/119 male mice in the high dose groups as compared with 0/126 control male mice. The U.S. EPA (1983b) has analyzed these data and derived a q_1^* of 1.47×10^{-1} $(mg/kg\ bw/day)^{-1}$. The data base from which this q_1^* is calculated is presented in Appendix B. This assessment uses the same study as U.S. EPA (1980b); however, when the water quality document was developed, only interim results of this study were available, hence the difference in estimates.

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APPENDIX A

Summary Table for 1,1-Dichloroethylene

	Species	Experimental Dose/Exposure	Effect	q_1*	Reference
Inhalation					
AIS				ND	
AIC				ND	
Carcinogenic potency	mouse	39.7 or 99.1 mg/m³	kidney adenocarcinomas	1.47×10^{-1} $(mg/kg\ bw/day)^{-1}$	Maltoni et al., 1977, 1980; U.S. EPA, 1983b
Oral					
AIS				ND	
AIC				ND	
Carcinogenic potency				ND	

ND = Not derived

APPENDIX B1

Cancer Data Sheet for Derivation of q_1^*

Compound: 1,1-dichloroethylene

Reference: Maltoni et al., 1980

Species, Strain, Sex: mice, Swiss, male

Body weight: 0.03 kg (assumed)

Length of exposure (le) = 52 weeks

Length of experiment (Le) = 104 weeks

Lifespan of animal (L) = 104 weeks

Tumor site and type: kidney, adenocarcinoma

Route, vehicle: inhalation

Experimental Doses or Exposures (ppm)	Transformed Dose† (ppm)	Incidence No. Responding/No. Tested or Examined
0	0	0/126
10	0.54	0/25
25	1.35	28/119

†Total dose period = 1/2 total lifetime

Unadjusted q_1^* from study = 1.7×10^{-1} $(ppm)^{-1}$

Human $q_1^* = 1.47 \times 10^{-1}$ $(mg/kg/day)^{-1}$ (see Appendix B2)

APPENDIX B2

Calculation for q_1^*

Lifetime risk of cancer associated with 1 ppm, p:

$$p=1-e^{-0.17}$$

For 1,1-dichloroethylene: 1 $\mu g/m^3$ = 0.25 ppm by the formula

C (mg/m^3) = C (ppm) x MW (molecular weight of chemical) ÷ 24.45 (moles/ℓ of air)

Lifetime risk of cancer associated with 1 mg/m^3, p:

$$p = 1-e^{-(0.17)(0.25)} = 4.2\times10^{-2}$$

$$q_1^* \ (mg/kg/day)^{-1} = 70 \text{ kg} \times 4.2 \times 10^{-2} \div 20 \ m^3/day \cdot 1 \ mg/m^3 = 0.147$$

where:

70 = assumed body weight of humans in kg

20 = human inhalation rate in m^3/day.