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

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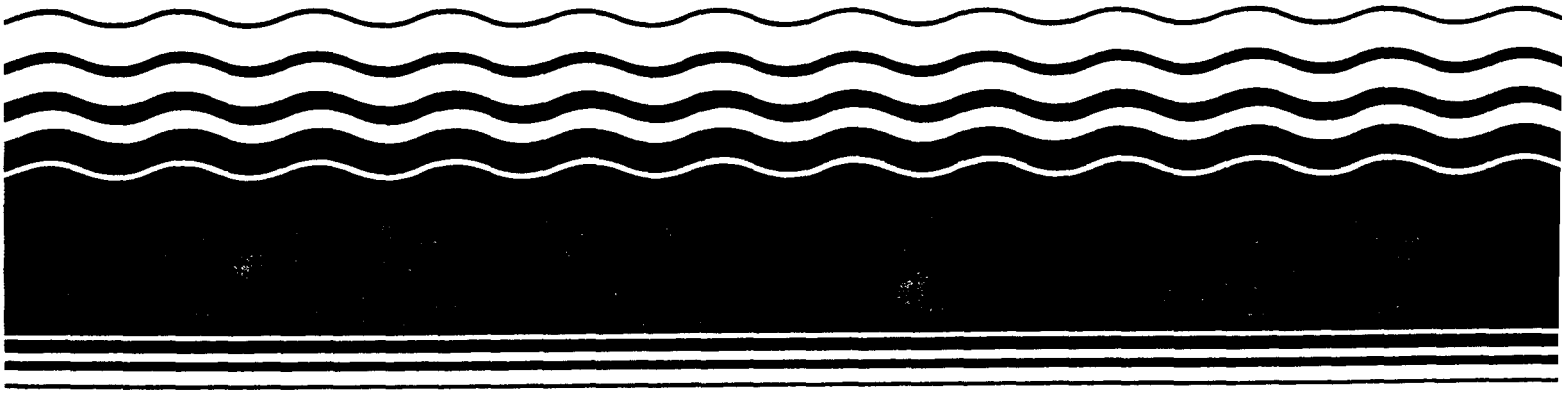
HEALTH EFFECTS ASSESSMENT FOR 1,1-DICHLOROETHANE



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HEALTH EFFECTS ASSESSMENT FOR 1,1-DICHLOROETHANE

U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
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Cincinnati, OH 45268

U.S. Environmental Protection Agency
Office of Emergency and Remedial Response
Office of Solid Waste and Emergency Response
Washington, DC 20460

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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-dichloroethane. 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 Chlorinated Ethanes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-029. NTIS PB 81-117624. (Cited in U.S. EPA, 1983b)

U.S. EPA. 1983b. Drinking Water Criteria Document for 1,1-Dichloroethane. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Drinking Water, Washington, DC. Final draft.

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, <u>any</u> 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 evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates.

Toxicological data are limited to subchronic inhalation studies. The U.S. EPA (1983b) has employed these data to estimate an acceptable oral exposure level of 8.1 mg/day which is adopted here as the oral AIC. An inhalation AIC of 9.7 mg/day has been estimated based on subchronic inhalation data. A CS of 9.8 was calculated based on kidney damage in cats exposed for 26 weeks to a TWA level of 750 ppm.

Limited data indicate that 1,1-dichloroethane may have the potential for carcinogenic activity in experimental animals. Data were inadequate for quantitative risk assessment. Additional experimental data are needed in order to adequately address the issue of potential carcinogenicity.

ACKNOWLEDGEMENTS

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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
CNS	Central nervous system
CS	Composite score
K_{ow}	Octanol/water partition coefficient
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOEL	No-observed-effect level
ppm	Parts per million
RV_d	Dose-rating value
RV_e	Effect-rating value
SGOT	Serum glutamate oxaloacetate transaminase
SGPT	Serum glutamate pyruvate transaminase
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-dichloroethane (CAS Registry No. 75-34-3), also known as ethylidene chloride or ethylidene dichloride, are given below.

Chemical class:	halogenated aliphatic hydrocarbon
Molecular weight:	98.96
Vapor pressure:	182 mm Hg at 20°C (Archer, 1979)
Water solubility:	5500 mg/ℓ at 20°C (Archer, 1979)
K_{ow}:	61.6 (Valvani et al., 1981)
Soil mobility: (predicted as retardation factor for a soil depth of 140 cm and organic carbon content of 0.087%)	1.2 (estimated)
BCF:	6.6 (estimated)
Half-life in air:	1.5 months (Callahan et al., 1979)
Half-life in water:	1-5 days (estimated)

A soil retardation factor of 1.2 has been estimated for 1,1 dichloroethane using the soil adsorption coefficient and K_{ow} (Schwarzenbach and Westall, 1981). The K_{ow} value for 1,1-dichloroethane (61.6) is intermediate between the K_{ow} values for chloroform (93) and 1,2-dichloroethane (30). The soil retardation factor for a soil depth of 140 cm and organic carbon content of 0.087% is 1.2 for both 1,2-dichloroethane and chloroform (Wilson et al., 1981). Therefore, the retardation factor for 1,1-dichloroethane has been estimated to be 1.2.

The BCF value of 6.6 given above has been estimated from the following equation: $\log BCF = 0.85 \log K_{ow} - 0.70$ (Veith et al., 1979).

The ratio of the reaeration rate constants for 1,1-dichloroethane has been experimentally determined to be 0.71 (Smith et al., 1980). The half-life value has been estimated from this reaeration rate ratio and the oxygen reaeration rates in representative water bodies (0.19-0.96 day^{-1}), with the assumption that the volatilization is a first order process (Mabey et al., 1981).

The half-life value for 1,1-dichloroethane in soil could not be located in the available literature; however, evaporation is expected to be the predominant loss mechanism from the soil surface. The half-life for soil evaporation should be longer than its evaporation half-life from water. In subsurface soil, the loss of 1,1-dichloroethane through biodegradation is expected to be insignificant (Wilson et al., 1983). Therefore, 1,1-dichloroethane may persist in soil and is expected to be removed primarily through leaching into groundwater.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

No studies have been conducted regarding gastrointestinal absorption of 1,1-dichloroethane. Based on similarities of molecular size and lipophilicity as evidenced by olive oil/water partition coefficients (69.2 for 1,1-dichloroethane and 39.8 for 1,2-dichloroethane) (Sato and Nakajima, 1979), it was suggested that gastrointestinal absorption of 1,1-dichloroethane may proceed somewhat faster than absorption of 1,2-dichloroethane. Spreafico et al. (1980) reported rapid absorption of 1,2-dichloroethane in rats after single oral doses of 25 mg/kg bw or 150 mg/kg bw in corn oil.

2.2. INHALATION

No studies regarding the extent or rate of absorption from inhalation of 1,1-dichloroethane have been located. Goldstein et al. (1974) suggested that with gases having a blood/air partition coefficient of $\geq$1.2, respiration is the limiting factor in reaching equilibrium. Sato and Nakajima (1979) reported blood/air coefficients of 4.7 and 19.5 for 1,1- and 1,2-dichloroethane, respectively. Therefore, it might be expected that 1,1-dichloroethane would be absorbed moderately from inhalation exposure, but absorbed less and eliminated more rapidly than 1,2-dichloroethane, which helps explain the observation that the inhalation toxicity of 1,1-dichloroethane is less than the toxicity of 1,2-dichloroethane (Lazarew, 1929).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Few studies of the effects of subchronic oral administration of 1,1-dichloroethane on animals have been located. In a very limited study, Larson et al. (1955) intubated three mongrel dogs with 200 mg/kg bw 1,1-dichloroethane 6 days/week for 8 weeks to study the effects on the adrenal gland. All three test animals survived the treatment and none had significant histological changes in the adrenals. Other parameters of toxicity were not reported.

Preliminary to conducting a long-term carcinogenesis bioassay in rats and mice, NCI (1978) conducted a subchronic range-finding study by administering 1,1-dichloroethane in corn oil by gavage. Groups of five male and five female Osborne-Mendel rats were given 562, 1000, 1780, 3160 or 5620 mg/kg bw/day 5 days/week for 6 weeks. Male rats in the 1000 and 1780 dose groups and females in the 1780 and 3160 mg/kg/day groups exhibited body weight depression. Mortality occurred in two female rats in the 3160 mg/kg/day group. Groups of five male and five female $B6C3F_1$ mice were treated with 1000, 1780, 3160, 5620 or 10,000 mg/kg/day 5 days/week for 6 weeks. No body weight depression occurred in mice, but mortality occurred in two male and three female mice in the 5620 mg/kg/day dose group. These studies were too limited in their assessment of criteria of toxicity to be useful in risk assessment.

3.1.2. Inhalation. In a subchronic inhalation study, Hofmann et al. (1971) exposed groups of 10 rats, 4 cats, 4 rabbits and 10 guinea pigs to 500 ppm (~2025 mg/m^3) 1,1-dichloroethane 6 hours/day, 5 days/week for 13 weeks. No effects were reported in any of the animals tested. Exposure to 1000 ppm (~4050 mg/m^3) 6 hours/day, 5 days/week using the same test

animals continued for another 13 weeks. The most sensitive animal tested appeared to be the cat, the only animal in which adverse effects were noted. Blood urea nitrogen levels were immediately elevated and rose steadily to week 24, at which time they peaked at ~3 times the control levels. Blood creatinine levels showed a parallel but less dramatic increase. No increase of SGOT or SGPT was noted. Histopathological examination of the cats revealed renal tubular dilatation and degeneration, indicating renal damage.

Torkelson and Rowe (1981) summarized an unpublished subchronic inhalation study by Dow Chemical Company in which unspecified numbers of rats, guinea pigs, rabbits and dogs were exposed to 500 or 1000 ppm (2025 or 4050 mg/m^3, respectively) 1,1-dichloroethane for 7 hours/day, 5 days/week for 6 months. Blood chemistries, necropsy and histological examinations revealed no changes attributed to the exposure. Based on the studies by Torkelson and Rowe (1981) and Hoffman et al. (1971), a NOEL of 500 ppm (2025 mg/m^3) can be suggested for subchronic inhalation exposure to 1,1-dichloroethane in rats, cats, rabbits, guinea pigs and dogs.

3.2. CHRONIC

3.2.1. Oral. The only study of chronic oral toxicity to 1,1-dichloroethane was reported in the NCI carcinogenicity assay (NCI, 1978). Groups of 50 male and 50 female Osborne-Mendel rats and B6C3F$_1$ mice were intubated with 1,1-dichloroethane in corn oil. Control and vehicle control groups consisted of 20 male and 20 female animals of each species. Treatments were administered 5 days/week for 3 weeks, followed by 1 dose-free week and 3 additional treatment weeks over the 78-week treatment period. The following time weighted dosages for treatment days were obtained: male rats, high-dose group 764 mg/kg bw/day, low-dose group 382 mg/kg bw/day; female rats, high-dose group 950 mg/kg bw/day, low-dose group 475 mg/kg bw/day. Mice

were treated 5 days/week for 78 weeks with the dosage increased after 6 weeks and again after 9 weeks. The TWA doses for treatment days for male mice were 2885 and 1442 mg/kg bw/day for low- and high-dose groups, respectively; for female mice, these doses were 3331 and 1665 mg/kg bw/day, respectively. Rats were observed for an additional 33 weeks and mice for an additional 13 weeks, after which survivors were killed. All animals that died or were killed when moribund or at the conclusion of the observation period were subjected to necropsy.

For both male and female rats, body weight curves for treatment and vehicle control groups were similar and somewhat below untreated controls. All groups of rats exhibited a hunched appearance, abdominal urine stains, labored breathing, wheezing and nasal discharge. By the conclusion of the trial, all surviving rats exhibited these signs, though the incidence early in the study appeared to be slightly higher in the treatment groups. Mortality was high in both male and female groups of rats and appeared to be slightly higher in 1,1-dichloroethane-exposed groups, though no significantly greater mortality was observed in the high-dose groups. Chronic murine pneumonia and kidney inflammation accounted for the vast majority of mortality among both control and treatment groups.

Body weight curves for male and female mice seemed unaffected by treatment or vehicle; there appeared to be no definitive signs of 1,1-dichloroethane toxicity in physical appearance or behavior throughout the study. Examination of statistically predicted survival curves indicated that survival of both male and female mice had been adversely affected by the high dose of 1,1-dichloroethane, although no specific pathological lesions were observed at significantly higher incidences in treated groups. Because of the increased mortality associated with treatment, no NOEL or LOAEL was defined by this study for mice.

3.2.2. Inhalation. No pertinent data concerning chronic inhalation exposure to 1,1-dichloroethane could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding teratogenicity or reproductive dysfunction in humans or animals associated with ingestion of 1,1-dichloroethane could not be located in the available literature.

3.3.2. Inhalation. Pertinent data regarding teratogenicity or reproductive dysfunction in humans related to inhalation exposure to 1,1-dichloroethane could not be located in the available literature. Schwetz et al. (1974) exposed rats to 0, 3800 or 6000 ppm 1,1-dichloroethane for 7 hours/day on days 5-15 of gestation. A significantly increased incidence of delayed ossification of sternebrae resulted from exposure to 6000 ppm 1,1-dichloroethane. Assuming a body weight of 0.35 kg and an inhalation rate of 0.26 m^3/day for rats, exposure to 3800 ppm for 7 hours/day, corresponding to an intake of ~3333 mg/kg/day, was found to be a NOEL in this study. Because this intake (~3333 mg/kg/day) is greater than the intake (269 mg/kg/day) calculated for rats in the study by Hofmann et al. (1971), the Schwetz et al. (1974) study will not impact risk assessment.

3.4. TOXICANT INTERACTIONS

Pertinent data on the toxic interactions of 1,1-dichloroethane with other xenobiotics could not be located in the available literature; however, it can be anticipated that exposure to other agents which deplete glutathion would enhance its toxicity.

3.5. HEALTH EFFECTS IN HUMANS

Limited information is available concerning the effects of 1,1-dichloroethane on humans. At one time the compound was used as an anesthetic, with an anesthetic pressure of 0.026 atmospheres, ~105,000 mg/m^3 (Miller et

al., 1965). The ability of the compound to induce cardiac arrhythmias caused discontinuation of its use as an anesthetic (Browning, 1965). It is probable that human exposure to sufficiently high levels would cause CNS depression and respiratory tract and skin irritation, since many other chlorinated aliphatics do (Parker et al., 1979). No dose-response data concerning these phenomena are available.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data concerning the carcinogenicity of 1,1-dichloroethane in humans could not be located in the available literature.

4.2. BIOASSAYS

The only carcinogenicity bioassay concerning 1,1-dichloroethane located in the available literature was conducted by NCI (1978). The protocol and noncarcinogenic data generated by this study were discussed in Section 3.2. Under the conditions of this study, male rats showed no significant change in the incidence of neoplasia which were compound related. Female rats (Table 4-1) showed a significant dose-response relationship in the incidence of hemangiosarcoma when measured by the Cochran-Armitage test for linear trend in proportions comparing the two dose groups with either the matched vehicle control ($p=0.041$) or the pooled vehicle control groups ($p=0.021$). By the Cochran-Armitage test, a significant ($p=0.043$) dose-related incidence of mammary adenocarcinomas was also observed. Results of the Fisher Exact test showed no significant incidence of either of these tumors. Because of high mortality early in the study, statistical analysis of data only from survivors of $\geq$1 year of exposure was also performed. Using the Cochran-Armitage test, statistical significance ($p=0.034$) was demonstrated only for mammary adenocarcinoma in female rats. Results using the Fisher Exact test were statistically negative.

In male mice surviving $\geq$1 year, the Cochran-Armitage test demonstrated a significant ($p=0.016$) dose-related incidence of hepatocellular carcinoma compared with pooled vehicle controls. Using the Fisher Exact test, a probability level of $p=0.027$ was calculated by comparing high dose and pooled vehicle control groups. Applying the Bonferroni criterion, which

TABLE 4-1

Summary of Incidence of Statistically Significant Primary Tumors in Osborne-Mendel Rats and B6C3F$_1$ Mice[a,b]

Species	Tumor Type	Pooled Vehicle Control	Matched Vehicle Control	Low Dose	High Dose
Female rats	mammary adenocarcinoma	1/39 (0.03)	0/19 (0.00)	1/50 (0.02)	5/50 (0.10)
p values[c]		NS	p=0.043	NS	NS
Female rats	hemangiosarcoma	0/39 (0.00)	0/19 (0.00)	0/50 (0.00)	4/50 (0.08)
p values[c]		p=0.021	p=0.041	NS	NS
Female rats surviving >52 weeks	mammary adenocarcinomas	NR	0/16 (0.00)	1/28 (0.04)	5/31 (0.16)
p values[c]			p=0.034	NS	NS
Female mice	endometrial stromal polyp	0/79 (0.00)	0/20 (0.00)	0/47 (0.00)	4/46 (0.09)
p values[c]		p=0.005	p=0.036	NS	p=0.017*
Male mice surviving >52 weeks	hepatocellular carcinoma	6/72 (0.08)	1/19 (0.05)	8/48 (0.17)	8/32 (0.25)
p values[c]		p=0.016	NS	NS	p=0.027*,[d]

[a]Source: NCI, 1978

[b]Experimental design summarized in text

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the corresponding control group when $p<0.05$; otherwise, not significant (NS) is indicated. The probability level for the Fisher Exact test for the comparison of a treated group with a control group is given beneath the incidence of tumors in that treated group when $p<0.05$; the asterisk (*) indicates comparison of the treated group with the pooled vehicle control group.

[d]The Fisher Exact test probability level of p=0.027 was marginal and not considered significant under the Bonferroni criterion.

NR = Not reported; NS = Not significant

requires that the normally accepted level of statistical significance ($p<0.05$) be divided by the number of dose levels (2), resulted in an acceptable p value of <0.025 for statistical significance. By this criterion, the incidence of hepatocellular carcinoma in the high dose group was considered to be marginal and not statistically different from the incidence in the pooled vehicle control group.

In female mice, the Cochran-Armitage test showed a significantly positive dose-response relationship in the incidence of benign endometrial stromal polyps when compared with the matched vehicle control ($p=0.036$) or pooled vehicle control ($p=0.005$) groups. By the Fisher Exact test, the incidence of endometrial stromal polyps in the high groups was significantly ($p=0.017$) higher than in pooled vehicle controls.

Based on the results of statistical analysis and the low survival of all groups, the NCI (1978) concluded that "these findings are indicative of the possible carcinogenic potential of the test compound. However, ... there was no conclusive evidence for the carcinogenicity of 1,1-dichloroethane in Osborne-Mendel rats or $B6C3F_1$ mice."

4.3. OTHER RELEVANT INFORMATION

4.3.1. Mutagenicity Tests. Simmon et al. (1977) tested the mutagenic activity of several chemicals identified in drinking water in the Ames Salmonella typhimurium/microsomal activation assay. Doses of the chemicals ranged up to 5 mg/plate. Negative results were reported for 1,1-dichloroethane in S. typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100, although the specific dose of 1,1-dichloroethane used and corresponding plate counts were not specified.

Nesnow (1982) reported a positive response of 1,1-dichloroethane in an enhanced viral transformation assay in Syrian hamster embryo cells, using the methods of Hatch et al. (1982). Details of protocol were not reported.

4.4. WEIGHT OF EVIDENCE

The only bioassay of the carcinogenicity of 1,1-dichloroethane located was the NCI (1978) bioassay described previously. High mortality among all groups probably precluded significant occurrence of tumors related to long-term exposure. Weisburger (1977) reviewed NCI bioassays of several halogenated aliphatics and noted striking similarities in the types of tumors produced. An example was the formation of hepatocellular carcinoma induced in mice by 1,1-dichloroethane and tetrachloroethylene. Although the incidence of hepatocellular carcinoma in mice exposed to 1,1-dichloroethane was not significant (see Section 4.2.), the similarity in lesions produced by other halogenated aliphatics raises a concern that the marginal results obtained with 1,1-dichloroethane are biologically, if not statistically, significant. Nevertheless, neither IARC nor the Carcinogen Assessment Group of the U.S. EPA has officially classified 1,1-dichloroethane as to carcinogenicity, based presumably on a lack of evidence for human carcinogenicity and the marginal signficance of the NCI bioassay which is considered to be limited evidence for animal carcinogenicity. Applying the criteria for evaluating weight of evidence proposed by the Carcinogen Assessment Group (Federal Register, 1984), 1,1-dichloroethane is most appropriately classified a Group D-Not Classified chemical.

5. REGULATORY STANDARDS AND CRITERIA

Table 5-1 lists the various regulatory standards and criteria for 1,1-dichloroethane.

The ACGIH (1980) recommended a TWA-TLV of 200 ppm (~810 mg/m^3) for occupational exposure to 1,1-dichloroethane, with a STEL of 250 ppm (~101 mg/m^3). This recommendation is based in part on the data of Hofmann et al. (1971) and the unpublished data of the Dow Chemical Company cited in Torkelson and Rowe (1981) (see Chapter 3). The current OSHA standard for occupational exposure to 1,1-dichloroethane is 100 ppm (~405 mg/m^3), but no NIOSH criterion for occupational exposure exists (Parker et al., 1979).

In discussing the derivation of ambient water quality criteria for chlorinated ethanes, the U.S. EPA (1980b) concluded that "insufficiency in the available data" precluded establishment of a satisfactory criterion for 1,1-dichloroethane. The nature of the deficiencies in the data was not discussed. In a subsequent review (U.S. EPA, 1983b), an ADI of 8.1 mg/day for a 70 kg man was proposed. This estimate was based on the NOEL of 2025 mg/m^3 defined in Hofmann et al. (1971) and employed a rat 24-hour breathing volume of 0.22 m^3/day, an absorption coefficient of 0.5 and an uncertainty factor of 1000.

No currently available information described human populations that may be particularly sensitive to 1,1-dichloroethane. The U.S. EPA (1980b, 1983b) stated that no information was available on unusual sensitivity of any groups to any of the chlorinated ethanes. The U.S. EPA (1980b) suggested, however, that individuals with liver insufficiency or exposure to other hepatotoxins may be at increased risk. Presumably, individuals with impaired renal function may also be unusually sensitive to exposure to 1,1-dichloroethane.

TABLE 5-1

Regulatory Standards and Criteria

Criterion	Standard	Reference
TLV	200 ppm (~810 mg/m^3)	ACGIH, 1980
STEL	250 ppm (~1010 mg/m^3)	ACGIH, 1980
OSHA	100 ppm (~405 mg/m^3)	Parker et al., 1979

6. RISK ASSESSMENT

Risk assessment data for 1,1-dichloroethane are presented in the Appendix to this report.

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. Only two reports were located regarding subchronic oral exposure in animals. These reports and their limitations were discussed in Section 3.1. Because of the limited scope of these studies, it was not possible to derive a maximum tolerable daily dose for subchronic oral exposure. However, U.S. EPA (1983b) has used the subchronic inhalation data of Hofmann et al. (1971) to estimate acceptable oral exposure. Using their approach, this study defines a NOEL for rats in units of mg/kg/day as follows:

$$\text{NOEL} = \frac{(2025\ \text{mg/m}^3)\ (0.22\ \text{m}^3\text{/day})\ (0.5)\ (6\ \text{hr}/24\ \text{hr})\ (5\ \text{days}/7\ \text{days})}{0.35\ \text{kg}}$$

$$= 115\ \text{mg/kg/day}$$

The value of 0.22 m^3/day represents the default 24-hour rat breathing volume employed, 0.5 represents the assumed absorption coefficient and 0.35 kg the default rat body weight. Multiplying by 70 kg and dividing by an uncertainty factor of 100 (10 for interspecies variability and 10 for inter-individual variability) results in an estimated AIS of 81 mg/day.

6.1.2. Inhalation. Reports of two subchronic inhalation studies of 1,1-dichloroethane in animals were discussed in Section 3.1. The study by Hofmann et al. (1971) demonstrated a NOEL of 500 ppm (~2025 mg/m^3) in rats, cats, rabbits and guinea pigs when exposed for 6 hours/day, 5 days/week for 13 weeks. After this exposure schedule, the 1,1-dichloroethane concentration was increased to 1000 ppm (4050 mg/m^3) for an additional 13

weeks. The 1000 ppm level also represented a NOEL for all test animals except cats in which elevated blood urea nitrogen was detected and adverse histologic changes in the kidney observed. For the cat, 1000 ppm represents a LOAEL. An unpublished subchronic inhalation study conducted by Dow Chemical Company and summarized by Torkelson and Rowe (1981) supports the NOEL suggested by the earlier study.

Estimated inhaled doses may be calculated for each exposed species and will vary in accordance with the ratio of ventilation volume/time to body weight. Estimates of ventilation volume are rough estimates since these values are particularly sensitive to experimental conditions and manipulations. The estimated animal doses are presented in Table 6-1. Since the cat data provide the most protective dose estimate (138 mg/kg/day), this dose is chosen as a starting point for the AIS estimate. Assuming a human body weight of 70 kg and applying an uncertainty factor of 100 results in an AIS of 96.6 mg/day.

A CS for 1,1-dichloroethane was calculated based on the kidney damage observed by Hofmann et al. (1971) in cats exposed to 500 ppm for 13 weeks and 1000 ppm for an additional 13 weeks. An RV_e of 7 was chosen for the effects on the kidneys because there was histologic evidence of kidney damage with demonstrable decrement in organ functions (i.e., elevated blood urea nitrogen). A human MED was calculated by expanding the TWA exposure, 750 ppm, from 6-24 hours/day and from 5-7 days/week. It was also assumed that humans inhale 20 m^3 of air/24 hours and that 1,1-dichloroethane absorption is 50%. An uncertainty factor of 10 was applied to convert from subchronic to chronic data resulting in a human MED of 542 mg/day, which corresponds to an RV_d of 1.4. A CS of 9.8, the product of RV_d and RV_e, is calculated.

TABLE 6-1

Calculated Animal Dose in mg/kg/day[a]

Species	Inhalation Rate (m^3/day)[b]	Body Weight (kg)[b]	Dose in mg/kg bw/day	
			2025 mg/m^3	4050 mg/m^3
Rats	0.22	0.35	227	455
Cats	1.26	3.3	138	276
Rabbits	1.6	1.13	512	1024
Guinea pigs	0.23	0.43	193	387

[a]Source: Hofmann et al., 1971

[b]Estimated inhalation rates and body weights

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. The only report of chronic oral exposure to 1,1-dichloroethane was the NCI (1978) bioassay discussed in Section 3.2. As noted before, animals in both dosage levels and control groups experienced pronounced early mortality. Although not statistically significant, some potentiation of mortality in rats appeared to be related to treatment. U.S. EPA (1983b) has used the subchronic inhalation data for the rat from Hofmann et al. (1971) to develop an ADI. It is suggested that their estimate be used for the AIC. The basis for the proposed AIC of 8.1 mg/day is explained in Section 6.1.1. with the addition of an uncertainty factor of 10 (combined uncertainty factor of 1000) to extrapolate from subchronic to chronic exposure.

6.2.2. Inhalation. No reports of chronic inhalation exposure of humans or animals to 1,1-dichloroethane could not be located in the available literature. The ACGIH (1980) recommended a TLV of 200 ppm, based on the studies by Hofmann et al. (1971) and Dow Chemical Company (n.d.), while the OSHA standard for occupational exposure to 1,1-dichloroethane is a TLV of 100 ppm. The TLV of 100 ppm could be used to estimate acceptable exposure, using an uncertainty factor of 10. The uncertainty factor of 10 is used to protect especially sensitive members of populations.

Calculation of the dose is as follows: The TLV (405 mg/m^3) x 10 m^3 inhaled/workday x (5 workdays ÷ 7 days/week) ÷ 10 (UF) = 289 mg/day. The AIC derived from the TLV is ~3-fold higher than the interim AIS derived for subchronic exposure. The discrepancy may reflect differences and uncertainties in the methodologies for obtaining TLVs and calculating acceptable intakes from animal data, or species differences in sensitivity between cats and humans to the toxicity of 1,1-dichloroethane. It is proposed that the more protective approach to AIC development be employed.

Starting with the AIS of 96.6 mg/day and applying an additional uncertainty factor of 10 to extrapolate from subchronic to chronic exposure results in an AIC of 9.7 mg/day. This value should be reevaluated when additional data are available.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Results of the NCI (1978) bioassay of 1,1-dichloroethane suggested that this compound may have carcinogenic properties. The significant positive treatment-response associations elucidated by the Cochran-Armitage test for hemangiosarcoma and mammary adenoma in female rats are not necessarily invalidated by the negative results of the Fisher exact test. Heavy mortality among the control groups as well as the treatment groups and application of the Bonferroni criterion undoubtedly contributed to the lack of statistical significance of the Fisher exact test. The heavy mortality among treatment groups probably resulted in underestimating the true carcinogenic potential of 1,1-dichloroethane, especially in light of the positive treatment-response association manifest by the Cochran-Armitage test. Furthermore, as pointed out by Weisburger (1977) (see Section 4.4.), striking similarities in the types of tumors produced by other chlorinated aliphatics are suggestive of a carcinogenic role for 1,1-dichloroethane.

Nonetheless, as indicated by the review panel for the NCI (1978) bioassay on 1,1-dichloroethane, the compound should be retested to resolve the issue of carcinogenicity. Heavy mortality among both treatment and control groups precluded using the data from this study to generate unit carcinogenic risk estimates. Also, the physical condition of the animals was markedly stressed and did not appoximate a normal human population.

6.3.2. Inhalation. Pertinent data regarding the carcinogenicity of 1,1-dichloroethane could not be located in the available literature.

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APPENDIX

Summary Table for 1,1-Dichloroethane

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	cat	500 ppm (2025 mg/m^3)	none	96.6 mg/day	Hofmann et al., 1971
AIC	cat	500 ppm (2025 mg/m^3)	none	9.7 mg/day	Hofmann et al., 1971
Maximum composite score	cat	TWA 750 ppm 6 hours/day, 5 days/week for 26 weeks (RV_d = 1.4)	kidney damage, elevated blood urea nitrogen (RV_e = 7)	9.8	Hofmann et al., 1971
Oral					
AIS	rat	500 ppm (2025 mg/m^3)	none	81 mg/day	Hofmann et al., 1971
AIC	rat	500 ppm* (2025 mg/m^3)	none	8.1 mg/day	Hofmann et al., 1971; U.S. EPA, 1983b

*Based on inhalation data as proposed by U.S. EPA (1983b)