MEMORANDUM

DATE: October 26, 1995

SUBJECT: Oral and Inhalation Toxicity Information for 1,1-Dichloroethane (CASRN 75-34-3)(Midco I Site/Gary, Indiana)

FROM: Harlal Choudhury
Administrator
Superfund Health Risk Technical Support Center

TO: Sally Jansen
U.S. EPA
Region 5

This memorandum responds to your request for oral and inhalation systemic and carcinogenic information for 1,1-dichloroethane.

Carcinogenicity (Attachment 1)

An update literature search was conducted on 1,1-dichloroethane to determine whether any new data are available that might affect the cancer weight-of-evidence classification for this chemical. No new data were located that would impact upon the verified weight-of-evidence classification available on IRIS. We are providing a brief description of our findings.

Oral Reference Dose (Attachment 2)

The Risk Assessment Issue Paper for Derivation of a Provisional RfD for 1,1-Dichloroethane (94-012/03-25-94) was updated, including a literature search to determine whether any new data are available that might affect the RfD for this chemical. No new data were located, and the RfD derivation was not changed. References were updated and minor revisions were made.
Inhalation Reference Concentration (Attachment 3)

The literature regarding 1,1-dichloroethane was examined to determine whether a provisional RfC could be derived for this chemical. A provisional RfC was derived using current methodology in a manner consistent with the RfD derivation (based on route-to-route extrapolation) and an RfC derivation previously submitted to the RfD/RfC Work Group (but never verified). We are providing a new issue paper on the derivation of a provisional RfC for 1,1-dichloroethane. This issue paper is very similar to the RfD issue paper which, being the basis for a route-to-route extrapolation, included discussion of all the inhalation studies.

Please feel free to contact the Superfund Technical Support Center at (513) 569-7300 if you need additional assistance.

cc: D. Bennett (5203G)
R. Boice (Region 5)
Risk Assessment Issue Paper for:
Update of Carcinogenicity Assessment
for 1,1-Dichloroethane (CASRN 75-34-3)

1,1-Dichloroethane has been assigned to cancer weight of evidence group C (possible human carcinogen), based on no evidence of carcinogenicity in humans and limited evidence in two animal species (rats and mice); this classification was verified by the CRAVE Work Group on 12/7/89 and is available on IRIS (U.S. EPA, 1995a,b). The available data were considered by the CRAVE Work Group to be inadequate to support quantitative assessment of carcinogenic risk (U.S. EPA, 1989, 1995b).

Computer searches of TOXLINE (1989-1995), CANCERLINE (1989-1995), CCRIS and TSCATS were conducted in October, 1995. No new data were located regarding the potential carcinogenicity of 1,1-dichloroethane. Therefore, the verified carcinogenicity assessment available on IRIS continues to reflect the best data available.

REFERENCES


Attachment 2

Risk Assessment Issue Paper for:
Derivation of a Provisional RfD for 1,1-Dichloroethane (CASRN 75-34-3)

INTRODUCTION


Oral and inhalation toxicity values for 1,1-dichloroethane are under discussion by the RfD/RfC Work Group (U.S. EPA, 1995b). U.S. EPA (1989a) proposed an RfD of 1E-1 mg/kg-day for 1,1-dichloroethane based on a LOAEL of 109.8 mg/kg-day for renal tubular degeneration in a subchronic inhalation study in cats exposed to the chemical at a TWA concentration of 3038 mg/m$^3$ 6 hours/day, 5 days/week for 26 weeks (Hofmann et al., 1971); an inhalation absorption factor of 0.5 was applied and an uncertainty factor of 1000 was used. Using the same exposure dose, U.S. EPA (1990) proposed an RfC of 5E-2 mg/m$^3$ for 1,1-dichloroethane based on a LOAEL$_{HEC}$ of 518 mg/m$^3$ for elevated BUN and creatinine and kidney lesions in cats exposed to the chemical at a TWA concentration of 2902 mg/m$^3$ 6 hours/day, 5 days/week for 23 weeks, the time at which renal toxicity became evident (Hofmann et al., 1971). An uncertainty factor of 10,000 was used.

The HEAST (U.S. EPA, 1995c) lists an RfD for 1,1-dichloroethane of 1E-1 mg/kg-day. This RfD is derived from U.S. EPA (1983, 1984) and is based on an inhalation study in rats by Hofmann et al. (1971). The derivation concluded that the NOAEL was 500 ppm (2025 mg/m$^3$, 6 hours/day, 5 days/week) 1,1-dichloroethane; no LOAEL was identified. The NOAEL was duration adjusted, multiplied by an absorption coefficient of 0.5 and by the ratio of the rat reference inhalation rate (0.22 m$^3$/day) to a reference body weight (0.35 kg). An uncertainty factor of 1000 was applied (for inter- and intraspecies variation and extrapolation from a subchronic study). The HEAST (U.S. EPA, 1995c) also lists an RfC for 1,1-
dichloroethane of $5 \times 10^{-1}$ mg/m$^3$. This RfC is derived from U.S. EPA (1984) and is based on the inhalation study in cats by Hofmann et al. (1971). The derivation concluded that the NOAEL was 500 ppm (2025 mg/m$^3)$, 1,1-dichloroethane and the LOAEL was 1000 ppm (4050 mg/m$^3$, 6 hours/day, 5 days/week) for kidney damage. The NOAEL was duration adjusted, multiplied by the ratio of the cat inhalation rate (1.26 mVday) to the cat body weight (3.3 kg) and multiplied by the ratio of the human reference body weight (70 kg) to the human reference inhalation rate (20 m$^3$/day). An uncertainty factor of 1000 was applied (for inter- and intraspecies variation and extrapolation from a subchronic study). This derivation is not consistent with current methodology for the development of inhalation RfCs (U.S. EPA, 1989b).

ACGIH (1991, 1995) has adopted a TLV-TWA of 100 ppm (405 mg/m$^3$) with no STEL to protect workers against liver injury and anesthetic effects. The OSHA PEL and NIOSH REL are 100 ppm (OSHA, 1989, 1993; NIOSH, 1992).

1,1-Dichloroethane was used in the past as a general anesthetic at a pressure of 0.026 atm. which is approximately equivalent to a concentration of 105,000 mg/m$^3$ (26,000 ppm) (Miller et al., 1965). Its use was discontinued when it was discovered that it induced cardiac arrhythmias at anesthetic doses (Browning, 1965).

1,1-Dichloroethane has a verified carcinogenicity classification of Group C, based on no evidence of carcinogenicity in humans and limited evidence in 2 animal species: rats and mice (U.S. EPA, 1995b).

**PHARMACOKINETICS**

Little is known regarding the pharmacokinetics of 1,1-dichloroethane. A breath-holding study in humans determined that approximately 88% of the inhaled 1,1-dichloroethane was absorbed into the lung (Morgan et al., 1970). A subsequent study by the same investigators estimated a 1-minute retention coefficient in humans of 68% (Morgan et al., 1972). Quantitative inhalation data in animals were not available, but toxicity data indicate that pulmonary absorption occurs (ATSDR, 1990; U.S. EPA, 1983, 1985, 1990). Limited data suggest that 1,1-dichloroethane is well absorbed from the gastrointestinal tract of rats and mice (Mitoma et al., 1985). Results based primarily on in vitro studies suggest that biotransformation of 1,1-dichloroethane is mediated by the hepatic microsomal cytochrome P-450 system. In rat liver microsomes, 1,1-dichloroethane was dechlorinated more rapidly than 1,2-dichloroethane and the metabolites included acetic acid, chloroacetic acid, 2,2-dichloroethanol and trace amounts of dichloroacetic acid and chloroacetaldehyde (McCall et al., 1983; Loew et al., 1973; Salmon et al., 1981). By using a pharmacokinetics model, Sato and Nakajima (1987) calculated a respiratory clearance rate of 72 L/hour (41%) and a metabolic clearance rate of 105 L/hour (59%) for 1,1-dichloroethane in humans. In rats, oral
administration of a dose of 700 mg/kg 1,1-dichloroethane resulted in excretion of 5% of the dose as CO₂ and 86% as unchanged compound in the expired air (Mitoma et al., 1985). In mice, 70% of a dose of 1800 mg/kg was excreted unchanged in expired air, whereas 25% was accounted for as CO₂ (Mitoma et al., 1985). Further information regarding pharmacokinetics of 1,1-dichloroethane was not located.

**NONCARCINOGENIC EFFECTS**

**Acute Data**

Smyth (1956) observed no deaths in rats exposed to 4000 ppm (16,190 mg/m³) 1,1-dichloroethane for 8 hours, but exposure to a concentration of 16,000 ppm (64,759 mg/m³) for 8 hours was lethal. Browning (1965) reported that the lethal exposure level of 1,1-dichloroethane in mice was 17.500 ppm. Dow Chemical (1960) reported the results of single exposure studies of rats to 1,1-dichloroethane vapors. Dose- and time-related lethality was observed in male rats exposed to concentrations of 8,000 to 64,000 ppm 1,1-dichloroethane (32.380-259.036 mg/m³ assuming 25°C and 760 mm Hg) for 0.1-7 hours. Autopsy of the animals that died revealed lung injury with slight liver and kidney pathology. Sax (1984) reported an oral LD₅₀ of 725 mg/kg of 1,1-dichloroethane in rats. Dow Chemical (1960) reported that single oral doses of 2 g/kg induced no adverse reactions in rats, but autopsy showed some kidney injury.

Plaa and Larson (1965) measured impaired kidney function (increased levels of protein and glucose in urine) in surviving mice given single intraperitoneal doses of 4 mL/kg 1,1-dichloroethane that produced deaths in 6/10 of the mice. Single doses of 2 mL/kg produced increased levels of urinary protein, but not glucose, in 4/10 mice. The kidneys of 5 mice treated with 2 mL/kg were examined histologically. No renal necrosis was found, but 3/5 kidneys showed proximal convoluted tubules with more than 50% of their area swollen. Treatment with doses of 1 mL/kg did not increase urinary protein or glucose in 10 mice. The authors did not specify if kidneys from mice treated at the 1 or 4 mL/kg dose levels were examined histologically.

**Subchronic and Chronic Data**

Groups of 10 Sprague-Dawley rats, 10 Pirbright-White guinea pigs, 4 "colored" rabbits and 4 cats were exposed to 0 or 500 ppm 1,1-dichloroethane (2024 mg/m³, assuming 25°C and 760 mm Hg) for 6 hours/day, 5 days/week for 13 weeks followed by a 10- to 13-week exposure period to 1000 ppm (4047 mg/m³) (Hermann et al., 1971). The TWA exposure concentration was 717 ppm (2902 mg/m³) for cats and 750 ppm (3036 mg/m³) for guinea pigs and rabbits (because effects were noticeable in cats after a total of 23 weeks, 23 weeks was used as the total duration in estimating the TWA for cats). Each group was composed of an equal number of males and females (2 each for cats and rabbits, 5 each for guinea pigs and
rats). Behavior and body weight were monitored in all species. Hematologic and urinalysis values, SGPT, SGOT, serum urea and serum creatinine were monitored in rats, rabbits and cats. Sulfobromphthalein excretion was tested in rabbits and cats. It was not clearly specified what endpoints were tested in guinea pigs. After 13 weeks of treatment, none of the species tested showed any clinical or biochemical changes attributable to treatment with 1,1-dichloroethane and were therefore, exposed to 1000 ppm for an additional 10-13 weeks. Upon study termination, all animals were necropsied; relative liver and kidney weights were determined and the liver, kidneys, and occasionally other selected organs (not specified) were processed for histopathological examination. No effects were reported in treated rats, rabbits or guinea pigs. Following the increase in concentration to 1000 ppm, cats had reduced body weight gain and elevated serum urea and serum creatinine levels relative to controls. One cat was removed from exposure due to poor general condition after 10 weeks at 1000 ppm; for the remaining animals exposure terminated at week 13. At the end of the experiment, histopathological examination of the kidneys revealed renal tubular dilation and degeneration in 3 of the 4 treated cats. No information was provided regarding effects at the portal of entry (i.e., pulmonary effects). 1,2-Dichloroethane, which was also tested in this study, appeared to be considerably more toxic than 1,1-dichloroethane. Based on this study, a LOAEL of 2902 mg/m$^3$ (TWA) for kidney effects in cats was derived. The TWA exposure of 3036 mg/m$^3$ was a NOAEL for rats, guinea pigs and rabbits.

Dow Chemical (1990) conducted a multispecies subchronic inhalation study, but the results were reported only as an unpublished summary. Groups of 24 male and 36 female Wistar-derived rats, 2 female dogs and 3 male and 3 female rabbits were exposed to 0, 500 or 1000 ppm 1,1-dichloroethane (0, 2024 or 4047 mg/m$^3$, assuming 25°C and 760 mm Hg) 7 hours/day, 5 days/week for 6 months. Guinea pigs (7 males and 8 females) were exposed to 2024 mg/m$^3$ for 3 months. Hematologic parameters (PCV, hemoglobin, total and differential leucocyte counts), determined at 4 months of treatment and prior to termination at 6 months, were not altered by exposure to 1,1-dichloroethane. Urinalyses performed at 5 months were unremarkable. Clinical chemistry values (alkaline phosphatase, urea nitrogen, SGPT) were within normal ranges. At necropsy, gross and microscopic examination of all major organs and tissues revealed no treatment-related adverse effects. The NOAEL for rats, dogs, and rabbits is 4047 mg/m$^3$; the guinea pig NOAEL is 2024 mg/m$^3$.

Union Carbide (1947) provided information on Sprague-Dawley rats (12/sex/group) and mongrel dogs (1/sex/group) exposed to 0 or 1000 ppm 1,1-dichloroethane 7 hours/day for a total of 75 exposures over a 6-month period. The results, however, are of questionable significance since high mortality occurred in rats due to endemic lung infection (50% in controls, 51% in 1,1-dichloroethane groups). At the end of the 6-month period, the only effects reported in the single dog exposed to 1,1-dichloroethane were significantly reduced body weight gain throughout the study and marked lung congestion, but no other pathology. According to the investigators, the only effect in rats attributed to exposure to 1,1-dichloroethane was a significant decrease (p < 0.004) in body weight gain in female rats.
NCI (1978) conducted a range-finding oral study in which groups of 5 Osborne-Mendel rats/sex and 5 B6C3F1 mice/sex were gavaged for 6 weeks with 1,1-dichloroethane in corn oil followed by a 2-week observation period. The test material was administered 5 days/week at dose levels of 0, 562, 1000, 1780, 3160 or 5620 mg/kg-day in rats and 0, 1000, 1780, 3160, 5620 or 10,000 mg/kg-day in mice. In male rats, body weight decreased by 16% and 29% at 562 and 1000 mg/kg-day, respectively. In female rats, body weight decreased by 20% at 1780 and 3160 mg/kg-day and two animals died at the latter level. Body weight was not altered in mice, but two males and three females died at the 5620 mg/kg-day dose level. No other endpoints were examined.

In a chronic oral study conducted by NCI (1978), Osborne-Mendel rats (50/sex/dose group) and B6C3F1 mice (50/sex/dose group) were administered 1,1-dichloroethane in corn oil 5 days/week for 78 weeks. An observation period of 33 weeks followed, after which all surviving animals were sacrificed and examinations for gross and microscopic organ pathology were made. The time-weighted average dosages over the 78-week treatment period were: 382 and 764 mg/kg-day for male rats, 475 and 950 mg/kg-day for female rats, 1442 and 2885 mg/kg-day for male mice, and 1665 and 3331 mg/kg-day for female mice. Twenty animals of each sex and species served as vehicle and untreated controls. Treatment-related effects were difficult to assess due to high mortality in rats due to pneumonia. Survival at the end of the study in the untreated control, vehicle control, low dose, and high dose groups was, respectively, 30, 5, 4, and 8% in male rats; 40, 20, 16, 18% in female rats; 35, 55, 62, and 32% in male mice; and 80, 80, 80 and 50% in female mice. In male rats, but not female rats, survival in both treated groups during the study was significantly lower (p<0.006) than in either the untreated control or vehicle treated group, although terminal survival rates between vehicle control and treated males were similar. In male mice, there was a significant association (significance not provided) between dosage and mortality and the trend for female mice was highly significant (p< 0.001); these findings were due mainly to mortality in the high-dose groups. The possible cause of death in mice was not discussed, but according to the investigators (NCI 1978) it was not tumor-related. No treatment-related effects were observed in rats or mice regarding body weight, food consumption, appearance and behavior, or incidence of nonneoplastic lesions. Hematology and clinical chemistry parameters were not monitored. No NOAELs or LOAELs can be defined in this study due to the high mortality observed at the lowest dose tested.

Limited information on the oral toxicity of 1,1-dichloroethane is available in a two-stage carcinogenesis study in mice (Klaunig et al., 1986). Groups of 35 male B6C3F1 mice were administered 1,1-dichloroethane in the drinking water at 0, 835 or 2500 mg/L for up to 52 weeks following treatment with either 10 mg/L diethylnitrosamine (DENA) in the drinking water or deionized water for 4 weeks. The investigators estimated that the weekly dose of 1,1-dichloroethane was approximately 3.8 mg/g body weight (543 mg/kg-day) for the groups given the chemical at 2500 mg/L, but provided no information regarding the low-dose level. At sacrifice at the end of 24 weeks (10 mice/group) or 52 weeks (25 mice/group) of
promotion, all tissues were examined for gross pathological lesions, and sections of the liver, kidney's and lungs were processed for light microscopy. Body weights in all 1,1-dichloroethane-treated groups were slightly lower than untreated controls, but the difference was not statistically significant. Treatment with 1,1-dichloroethane did not affect water intake or survival. No nonneoplastic lesions were reported in 1,1-dichloroethane-treated groups. In this study, the dose of 543 mg/kg-day represents a NOAEL for mice.

**Developmental and Reproductive Toxicity**

Groups of 46, 16 and 19 pregnant Sprague-Dawley rats were exposed to 0, 3800 or 6000 ppm 1,1-dichloroethane (15,380 or 24,284 mg/m³, assuming 25°C and 760 mm Hg) respectively, for 7 hours/day on gestation days 6-15 (Schwetz et al., 1974). Food consumption was significantly decreased (p<0.05) during treatment at both concentration levels. Body weights were significantly reduced (p<0.05) in treated rats at both concentration levels on day 13 and in the 3800 ppm group on day 21 (other time points not examined). Treatment with 1,1-dichloroethane had no effect on maternal SGPT activity or gross appearance of the liver, but relative liver weight was significantly increased in nonpregnant rats 6 days after the last exposure. Exposure to 1,1-dichloroethane did not affect conception rate, number of implantations, litter size, incidence of fetal resorptions, fetal body measurements or incidence of gross or soft tissue anomalies. Exposure to 6000 ppm 1,1-dichloroethane caused a significant increase (p<0.05) in the incidence of delayed ossification of sternebrae; the incidence at the 3800 ppm level was significantly lower than in controls. In this study, the exposure level of 15,380 mg/m³ represents a maternal LOAEL and a developmental NOAEL for 1,1-dichloroethane. The developmental LOAEL is 24,284 mg m³.

Studies of reproductive toxicity were not located.

**SCENARIO FOR THE DERIVATION OF AN ORAL RfD**

Relevant information is available from five studies for derivation of a provisional RfD for 1,1-dichloroethane. Three of these studies (Dow Chemical 1990; Hofmann et al., 1971; Schwetz et al., 1974) used the inhalation route of exposure; in studies conducted by NCI (1978) and Klaunig et al. (1986), the chemical was administered by the oral route. In the 78-week chronic oral study in rats and mice (NCI 1978), high mortality occurred at the lowest dose level tested (382 mg/kg-day for rats), and therefore, neither NOAELs nor LOAELs could be defined. In the 52-week drinking water study conducted by Klaunig et al. (1986), no adverse effects were observed in mice at 543 mg/kg-day and this dose level represented a NOAEL for 1,1-dichloroethane. However, the scope of this study was rather limited since only liver, kidney and lungs were examined histologically, and clinical chemistry and hematology values were not monitored. In the multispecies inhalation study conducted by Dow Chemical (1990) (reported only as an unpublished summary), a NOAEL of 2024 mg m³ was identified for guinea pigs and a NOAEL of 4047 mg/m³ was defined for rats, dogs and
rabbits; all species were exposed 7 hours/day, 5 days/week for 3 to 6 months; these concentration exposure levels were the highest tested. The results of Dow Chemical (1990) are supported by data reported by Hofmann et al. (1971), who found no adverse effects in rats and rabbits exposed to TWA concentrations of 3036 mg/m³ 1,1-dichloroethane (6 hours/day, 5 days/week) for 26 weeks. Hofmann et al. (1971), however, reported kidney lesions and altered serum urea and creatinine in cats exposed to TWA of 2902 mg/m³ 1,1-dichloroethane for 23 weeks. In the inhalation study conducted by Schwetz et al. (1974) in rats exposed during pregnancy, a developmental NOAEL of 15,380 mg/m³ was identified for 1,1-dichloroethane; the LOAEL was 24,284 mg/m³. Thus, it appears that cats, which were not tested in the Dow Chemical (1990) study, are the most sensitive species.

Based on the information summarized above, a provisional RfD might be calculated from the inhalation data in cats reported by Hofmann et al. (1971). In that study, one out of four cats showed kidney lesions after a total of 23 weeks of exposure (earliest monitoring time) to 1,1-dichloroethane. Two additional cats showed kidney lesions after 26 weeks of exposure. Lesions consisted of crystal precipitation and obstruction of the tubules, consistent with hydronephrosis, and tubule degeneration.

It does not seem appropriate to base this provisional RfD on a NOAEL for the first 13 weeks of exposure, a possibility raised by the RfD/RfC Work Group (U.S. EPA, 1990), because the kidneys were not examined during this first exposure period. Although serum creatinine and urea were monitored throughout the study, and appearance of increased levels appeared to coincide with raising the exposure concentration from 500 to 1000 ppm, it is not clear that these parameters are sufficiently sensitive to have revealed subtle renal damage that may have occurred during the 500 ppm exposure.

Supporting evidence that the kidney is a target for the toxicity of 1,1-dichloroethane is restricted to observations of altered renal histology or impaired renal function after acute intraperitoneal exposure to 2 or 4 mL/kg doses of 1,1-dichloroethane (Plaa and Larson, 1965) and kidney injury in rats following administration of single oral doses of 2 g/kg or single lethal inhalation exposures (Dow Chemical, 1960).

The provisional RfD might be calculated as follows:

\[
\text{LOAEL}_{\text{ADf}} = 2902 \, \text{mg/m}^3 \times \frac{6}{24} \times \frac{5}{7} = 518 \, \text{mg/m}^3
\]

Inhaled Dose = 518 mg/m³ x 0.6739 m³/day / 3.5 kg = 99.8 mg/kg-day

where:

0.6739 = Inhalation rate for a 3.5 kg cat; determined from an allometric relationship described in U.S. EPA (1987).
3.5 = Cat body weight throughout the study estimated from graphic
data in Hofmann et al. (1971).

The inhaled dose (LOAEL) of 99.8 mg/kg-day is lower than the lowest oral dose
associated with early mortality in rats (382 mg/kg-day) in the NCI (1978) study. A default
ratio of 1 was selected for oral:inhalation absorption factors, given the lack of data.

Thus,

\[ \text{RfD} = \frac{\text{Inhaled Dose}}{\text{UF}} = \frac{99.8 \text{ mg/kg-day}}{10,000} = 0.01 \text{ mg/kg-day} \]

where:

\[ \text{UF} = \text{Uncertainty factor} \]

\[ = \text{all five areas of uncertainty are involved, including use of a LOAEL, interspecies extrapolation, protection of sensitive individuals, use of a subchronic study, and for database limitations, including route-to-route extrapolation. Given that some areas of uncertainty may overlap, a maximum UF of 10,000 is applied}. \]

The provisional RfD of 0.01 mg/kg-day for 1,1-dichloroethane would be one order of
magnitude lower than that derived from the same data and currently under review by the
RfD/RfC Work Group (U.S. EPA, 1989a). The difference is due to the following: U.S. EPA
(1989a) considered a total exposure period of 26 weeks in estimating the TWA exposure: the
inhalation rate for cats was estimated at 1.215 mV/day (Guyton, 1947); the cat body weight
was estimated as 3 kg; and, an absorption factor of 50% was used.

If such a scenario would be used to define the RfD, confidence in the key study would
be graded low because of the small number of animals used and because, other than for the
kidneys, limited information was provided regarding organs and tissues examined. Confidence
in the database is low because adequate chronic oral studies were not available and because
developmental data in only one species were located. Confidence in the provisional RfD
would be low, reflecting low confidence in the database and key study.

Caution is advised in using the provisional RfD for 1,1-dichloroethane. Insufficient
pharmacokinetic data are available for accurately determining the absorption ratio for a route-
to-route extrapolation. Additionally, the Hofmann et al. (1971) cat study is, at best, marginal
for use in a risk assessment due to the small number of animals in the study and the lack of
corroborative data from other repeated exposure studies. Therefore, if this provisional RfD is
chosen, this office will not be able to attest to its scientific accuracy and use.

Deriving an RfD for 1,1-dichloroethane based on structural analogy to 1,2-
dichloroethane is not recommended because of the evidence that this isomer has different
pharmacokinetic and toxicologic properties from those of 1,1-dichloroethane. **In vitro** metabolism studies with rat liver microsomes showed that 1,1-dichloroethane is more rapidly dechlorinated than 1,2-dichloroethane (McCall et al., 1983; Loew et al., 1973; Salmon et al., 1981). Hofmann et al. (1971) reported that repeated inhalation exposure to 1,2-dichloroethane at 500 ppm was lethal to rats, guinea pigs and rabbits, but not to cats, within a few weeks commencement of exposure. In contrast, exposure to 500 or 1000 ppm 1,1-dichloroethane by the same protocol for up to 23 weeks produced no adverse effects in rats, guinea pigs or rabbits and only produced nonlethal renal effects in cats (Hofmann et al., 1971).

**REFERENCES**


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Union Carbide Corporation. 1947. Repeated exposure of rats and dogs to vapors of eight chlorinated hydrocarbons. TSCA Submission OTS#0515559.


INTRODUCTION

October, 1995. Documents listed on the CARA data bases (U.S. EPA, 1991, 1994) that were consulted include a Health Effects Assessment for 1,1-Dichloroethane (U.S. EPA 1984) and a Health and Environmental Effects Profile on Dichloroethanes (U.S. EPA. 1985). Other sources of information that were consulted were IRIS (U.S. EPA, 1995a), the RfD/RfC and CRAVE Status Reports (U.S. EPA, 1995b), the HEAST (U.S. EPA, 1995c), the Drinking Water Regulations and Health Advisories list (U.S. EPA, 1995d), updated NTP Status Reports (NTP, 1995a,b), and a Toxicological Profile on 1,1-Dichloroethane (ATSDR, 1990).

Inhalation and oral toxicity values for 1,1-dichloroethane are under discussion by the RfD/RfC Work Group (U.S. EPA, 1995b). U.S. EPA (1990) proposed an RfC of 5E-2 mg m$^{-3}$ for 1,1-dichloroethane based on a LOAEL_{HSC} of 518 mg/m$^3$ for elevated BUN and creatinine and kidney lesions in cats exposed to the chemical at a TWA concentration of 2902 mg/m$^3$ 6 hours/day, 5 days/week for 23 weeks, the time at which renal toxicity became evident (Hofmann et al., 1971). An uncertainty factor of 10,000 was used. U.S. EPA (1989a) proposed an RfD of 1E-1 mg/kg-day for 1,1-dichloroethane based on a route-to-route extrapolation from the Hofmann et al. (1971) subchronic inhalation study in cats. In this derivation, the full experimental period of 26 weeks (6 hours/day, 5 days/week) was used to calculate a TWA concentration of 3038 mg/m$^3$, which translated to a LOAEL of 109.8 mg/kg-day for renal tubular degeneration: an inhalation absorption factor of 0.5 was applied and an uncertainty factor of 1000 was used.

The HEAST (U.S. EPA, 1995c) lists an RfC for 1,1-dichloroethane of 5E-1 mg/m$^3$. This RfC, presented in U.S. EPA (1984), is also based on the inhalation study in cats by Hofmann et al. (1971). The derivation concluded that the NOAEL was 500 ppm (2025 mg/m$^3$) 1,1-dichloroethane and the LOAEL was 1000 ppm (4050 mg/m$^3$) for kidney damage. The NOAEL was duration adjusted (6 hours/day. 5 days/week), multiplied by the ratio of the cat inhalation rate (1.26 m$^3$/day) to the cat body weight (3.3 kg) and multiplied by the ratio of the human reference body weight (70 kg) to the human reference inhalation rate (20 m$^3$/day). An uncertainty factor of 1000 was applied (for inter- and intraspecies variation and extrapolation from a subchronic study). This derivation is not consistent with current methodology for the development of inhalation RfCs (U.S. EPA, 1995b). The HEAST (U.S. EPA, 1995c) also lists an RfD for 1,1-dichloroethane of 1E-1 mg/kg-day. This RfD, presented in U.S. EPA (1983, 1984), is based on an inhalation study in rats by Hofmann et al. (1971). The derivation concluded that the NOAEL was 500 ppm (2025 mg/m$^3$, 6 hours/day, 5 days/week) 1,1-dichloroethane; no LOAEL was identified. The NOAEL was duration adjusted, multiplied by an absorption coefficient of 0.5 and by the ratio of the rat reference inhalation rate (0.22 m$^3$/day)
to a reference body weight (0.35 kg). An uncertainty factor of 1000 was applied (for inter- and intraspecies variation and extrapolation from a subchronic study).

ACGIH (1991, 1995) has adopted a TLV-TWA of 100 ppm (405 mg/m³) with no STEL to protect workers against liver injury and anesthetic effects. The OSHA PEL and NIOSH REL are 100 ppm (OSHA, 1989, 1993; NIOSH, 1992).

1,1-Dichloroethane was used in the past as a general anesthetic at a pressure of 0.026 atm, which is approximately equivalent to a concentration of 105,000 mg/m³ (26,000 ppm) (Miller et al., 1965). Its use was discontinued when it was discovered that it induced cardiac arrhythmias at anesthetic doses (Browning, 1965).

1,1-Dichloroethane has a verified carcinogenicity classification of Group C, based on no evidence of carcinogenicity in humans and limited evidence in 2 animal species: rats and mice (U.S. EPA, 1995b).

PHARMACOKINETICS

Little is known regarding the pharmacokinetics of 1,1-dichloroethane. A breath-holding study in humans determined that approximately 88% of the inhaled 1,1-dichloroethane was absorbed into the lung (Morgan et al., 1970). A subsequent study by the same investigators estimated a 1-minute retention coefficient in humans of 68% (Morgan et al., 1972). Quantitative inhalation data in animals were not available, but toxicity data indicate that pulmonary absorption occurs (ATSDR, 1990; U.S. EPA, 1983, 1985, 1990). Limited data suggest that 1,1-dichloroethane is well absorbed from the gastrointestinal tract of rats and mice (Mitoma et al., 1985). Results based primarily on in vitro studies suggest that biotransformation of 1,1-dichloroethane is mediated by the hepatic microsomal cytochrome P-450 system. In rat liver microsomes, 1,1-dichloroethane was dechlorinated more rapidly than 1,2-dichloroethane, and the metabolites included acetic acid, chloroacetic acid, 2,2-dichloroethanol and trace amounts of dichloroacetic acid and chloroacetaldehyde (McCall et al., 1983; Loew et al., 1973; Salmon et al., 1981). By using a pharmacokinetics model, Sato and Nakajima (1987) calculated a respiratory clearance rate of 72 L/hour (41%) and a metabolic clearance rate of 105 L/hour (59%) for 1,1-dichloroethane in humans. In rats, oral administration of a dose of 700 mg/kg 1,1-dichloroethane resulted in excretion of 5% of the dose as CO₂ and 86% as unchanged compound in the expired air (Mitoma et al., 1985). In mice, 70% of a dose of 1800 mg/kg was excreted unchanged in expired air, whereas 25% was accounted for as CO₂ (Mitoma et al., 1985). Further information regarding pharmacokinetics of 1,1-dichloroethane was not located.

NONCARCINOGENIC EFFECTS

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Acute Data

Smyth (1956) observed no deaths in rats exposed to 4000 ppm (16,190 mg/m³) 1,1-dichloroethane for 8 hours, but exposure to a concentration of 16,000 ppm (64,759 mg/m³) for 8 hours was lethal. Browning (1965) reported that the lethal exposure level of 1,1-dichloroethane in mice was 17,500 ppm. Dow Chemical (1960) reported the results of single exposure studies of rats to 1,1-dichloroethane vapors. Dose- and time-related lethality was observed in male rats exposed to concentrations of 8,000 to 64,000 ppm 1,1-dichloroethane (32,380-259,036 mg/m³ assuming 25°C and 760 mm Hg) for 0.1-7 hours. Autopsy of the animals that died revealed lung injury with slight liver and kidney pathology. Sax (1984) reported an oral LD₅₀ of 725 mg/kg of 1,1-dichloroethane in rats. Dow Chemical (1960) reported that single oral doses of 2 g/kg induced no adverse reactions in rats, although autopsy showed some kidney injury.

Plaa and Larson (1965) measured impaired kidney function (increased levels of protein and glucose in urine) in surviving mice given single intraperitoneal doses of 4 mL/kg 1,1-dichloroethane that produced deaths in 6/10 of the mice. Single doses of 2 mL/kg produced increased levels of urinary protein, but not glucose, in 4/10 mice. The kidneys of 5 mice treated with 2 mL/kg were examined histologically. No renal necrosis was found, but 3/5 kidneys showed proximal convoluted tubules with more than 50% of their area swollen. Treatment with doses of 1 mL/kg did not increase urinary protein or glucose in 10 mice. The authors did not specify if kidneys from mice treated at the 1 or 4 mL/kg dose levels were examined histologically.

Subchronic and Chronic Data

Groups of 10 Sprague-Dawley rats, 10 Pirbright-White guinea pigs, 4 "colored" rabbits and 4 cats were exposed to 0 or 500 ppm 1,1-dichloroethane (2024 mg/m³, assuming 25°C and 760 mm Hg) for 6 hours/day, 5 days/week for 13 weeks followed by a 10- to 13-week exposure period to 1000 ppm (4047 mg/m³) (Hofmann et al., 1971). The TWA exposure concentration was 717 ppm (2902 mg/m³) for cats and 750 ppm (3036 mg/m³) for guinea pigs and rabbits (because effects were noticeable in cats after a total of 23 weeks, 23 weeks was used as the total duration in estimating the TWA for cats). Each group was composed of an equal number of males and females (2 each for cats and rabbits, 5 each for guinea pigs and rats). Behavior and body weight were monitored in all species. Hematologic and urinalysis values, SGPT, SGOT, serum urea and serum creatinine were monitored in rats, rabbits and cats. Sulfobromphthalein excretion was tested in rabbits and cats. It was not clearly specified what endpoints were tested in guinea pigs. After 13 weeks of treatment, none of the species tested showed any clinical or biochemical changes attributable to treatment with 1,1-dichloroethane and were therefore, exposed to 1000 ppm for an additional 10-13 weeks. Upon study termination, all animals were necropsied; relative liver and kidney weights were determined and the liver, kidneys, and occasionally other selected organs (not specified) were processed for histopathological examination. No effects were reported in treated rats, rabbits or guinea pigs. Following the increase in concentration to 1000 ppm, cats had reduced body weight gain and elevated serum urea and serum creatinine levels relative to
controls. One cat was removed from exposure due to poor general condition after 10 weeks at 1000 ppm; for the remaining animals exposure terminated at week 13. At the end of the experiment, histopathological examination of the kidneys revealed renal tubular dilation and degeneration in 3 of the 4 treated cats. No information was provided regarding effects at the portal of entry (i.e., pulmonary effects). 1,2-Dichloroethane, which was also tested in this study, appeared to be considerably more toxic than 1,1-dichloroethane. Based on this study, a LOAEL of 2902 mg/m$^3$ (TWA) for kidney effects in cats was derived. The TWA exposure of 3036 mg/m$^3$ was a NOAEL for rats, guinea pigs and rabbits.

Dow Chemical (1990) conducted a multispecies subchronic inhalation study, but the results were reported only as an unpublished summary. Groups of 24 male and 36 female Wistar-derived rats, 2 female dogs and 3 male and 3 female rabbits were exposed to 0, 500 or 1000 ppm 1,1-dichloroethane (0, 2024 or 4047 mg/m$^3$, assuming 25°C and 760 mm Hg) 7 hours/day, 5 days/week for 6 months. Guinea pigs (7 males and 8 females) were exposed to 2024 mg/m$^3$ for 3 months. Hematologic parameters (PCV, hemoglobin, total and differential leucocyte counts), determined at 4 months of treatment and prior to termination at 6 months, were not altered by exposure to 1,1-dichloroethane. Urinalyses performed at 5 months were unremarkable. Clinical chemistry values (alkaline phosphatase, urea nitrogen, SGPT) were within normal ranges. At necropsy, gross and microscopic examination of all major organs and tissues revealed no treatment-related adverse effects. The NOAEL for rats, dogs, and rabbits is 4047 mg/m$^3$; the guinea pig NOAEL is 2024 mg/m$^3$.

Union Carbide (1947) provided information on Sprague-Dawley rats (12/sex/group) and mongrel dogs (1/sex/group) exposed to 0 or 1000 ppm 1,1-dichloroethane 7 hours/day for a total of 75 exposures over a 6-month period. The results, however, are of questionable significance since high mortality occurred in rats due to endemic lung infection (50% in controls, 51% in 1,1-dichloroethane groups). At the end of the 6-month period, the only effects reported in the single dog exposed to 1,1-dichloroethane were significantly reduced body weight gain throughout the study and marked lung congestion, but no other pathology. According to the investigators, the only effect in rats attributed to exposure to 1,1-dichloroethane was a significant decrease (p < 0.004) in body weight gain in female rats.

Chronic oral cancer bioassays were conducted in rats and mice by NCI (1978) and Klaunig et al. (1986). In the NCI (1978) study, no treatment-related effects were observed in rats or mice regarding body weight, food consumption, appearance and behavior, or incidence of nonneoplastic lesions at doses up to 950 mg/kg-day in rats and 3331 mg/kg-day in mice (78-week gavage exposure). However, the study was compromised by high mortality in control and treatment groups, attributed in part to pneumonia. Klaunig et al. (1986) found no effect on survival, body weight, water intake, or incidence of nonneoplastic lesions in the kidney, liver and lung in male mice treated with up to 543 mg/kg-day in the drinking water for up to 52 weeks. The Risk Assessment Issue Paper for Derivation of a Provisional RfD for 1,1-Dichloroethane contains more details regarding these studies.

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Developmental and Reproductive Toxicity

Groups of 46, 16 and 19 pregnant Sprague-Dawley rats were exposed to 0, 3800 or 6000 ppm 1,1-dichloroethane (15,380 or 24,284 mg/m\(^3\), assuming 25°C and 760 mm Hg), respectively, for 7 hours/day on gestation days 6-15 (Schwetz et al., 1974). Food consumption was significantly decreased (p<0.05) during treatment at both concentration levels. Body weights were significantly reduced (p<0.05) in treated rats at both concentration levels on day 13 and in the 3800 ppm group on day 21 (other time points not examined). Treatment with 1,1-dichloroethane had no effect on maternal SGPT activity or gross appearance of the liver, but relative liver weight was significantly increased in nonpregnant rats 6 days after the last exposure. Exposure to 1,1-dichloroethane did not affect conception rate, number of implantations, litter size, incidence of fetal resorptions, fetal body measurements or incidence of gross or soft tissue anomalies. Exposure to 6000 ppm 1,1-dichloroethane caused a significant increase (p<0.05) in the incidence of delayed ossification of sternebrae; the incidence at the 3800 ppm level was significantly lower than in controls. In this study, the exposure level of 15,380 mg/m\(^3\) represents a maternal LOAEL and a developmental NOAEL for 1,1-dichloroethane. The developmental LOAEL is 24,284 mg/m\(^3\).

Studies of reproductive toxicity were not located.

SCENARIO FOR THE DERIVATION OF AN INHALATION RfC

Relevant information is available from three studies for derivation of a provisional RfC for 1,1-dichloroethane (Dow Chemical, 1990; Hofmann et al., 1971; Schwetz et al., 1974). In the multispecies inhalation study conducted by Dow Chemical (1990) (reported only as an unpublished summary), a NOAEL of 2024 mg/m\(^3\) was identified for guinea pigs and a NOAEL of 4047 mg/m\(^3\) was defined for rats, dogs and rabbits; all species were exposed 7 hours/day, 5 days/week for 3 to 6 months; these concentration exposure levels were the highest tested. The results of Dow Chemical (1990) are supported by data reported by Hofmann et al. (1971), who found no adverse effects in rats and rabbits exposed to TWA concentrations of 3036 mg/m\(^3\) 1,1-dichloroethane (6 hours/day, 5 days/week) for 26 weeks. Hofmann et al. (1971), however, reported kidney lesions and altered serum urea and creatinine in cats exposed to TWA of 2902 mg/m\(^3\) for 23 weeks. In the inhalation study conducted by Schwetz et al. (1974) in rats exposed during pregnancy, a developmental NOAEL of 15,380 mg/m\(^3\) was identified for 1,1-dichloroethane; the LOAEL was 24,284 mg/m\(^3\). Thus, it appears that cats, which were not tested in the Dow Chemical (1990) study, are the most sensitive species.

Based on the information summarized above, a provisional RfC might be calculated from the inhalation data in cats reported by Hofmann et al. (1971). In that study, one out of four cats showed kidney lesions after a total of 23 weeks of exposure (earliest monitoring time) to 1,1-dichloroethane. Two additional cats showed kidney lesions after 26 weeks of exposure. Lesions
consisted of crystal precipitation and obstruction of the tubules, consistent with hydronephrosis, and tubule degeneration.

It does not seem appropriate to base this provisional RfC on a NOAEL for the first 13 weeks of exposure, a possibility raised by the RfD/RfC Work Group (U.S. EPA, 1990), because the kidneys were not examined during this first exposure period. Although serum creatinine and urea were monitored throughout the study, and appearance of increased levels appeared to coincide with raising the exposure concentration from 500 to 1000 ppm, it is not clear that these parameters are sufficiently sensitive to have revealed subtle renal damage that may have occurred during the 500 ppm exposure.

Supporting evidence that the kidney is a target for the toxicity of 1,1-dichloroethane is restricted to observations of altered renal histology or impaired renal function after acute intraperitoneal exposure to 2 or 4 mL/kg doses of 1,1-dichloroethane (Plaa and Larson, 1965) and kidney injury in rats following administration of single oral doses of 2 g/kg or single lethal inhalation exposures (Dow Chemical, 1960).
The case of renal effects produced by 1,1-dichloroethane in cats corresponds to an extrarespiratory effect produced by a gas/vapor. Therefore, the LOAEL_{HEC} would be calculated as the product of the duration-adjusted exposure level and the blood:gas partition coefficient ratio in cats and humans (L_{A}/L_{H}). Because a value for L_{A} is not available for 1,1-dichloroethane in cats, the ratio is assumed to be 1 by default. The provisional RfC is calculated as the LOAEL_{HEC} divided by an uncertainty factor of 10,000 (10 for use of a LOAEL, 10 for use of a subchronic study, 3 for extrapolation from cats to humans using the dosimetric adjustments, 3 for database limitations including lack of adequate study of respiratory and reproductive effects and study of developmental effects in only one species, and 10 for protection of sensitive individuals). The derivation is shown below:

\[
\text{LOAEL}_{\text{ADJ}} = 2902 \text{ mg/m}^3 \times 6/24 \times 5/7 = 518 \text{ mg/m}^3
\]

\[
\text{LOAEL}_{\text{HEC}} = 518 \text{ mg/m}^3 \times L_{A}/L_{H} = 518 \text{ mg/m}^3 \times 1 = 518 \text{ mg/m}^3
\]

\[
\text{Provisional RfC} = \frac{\text{LOAEL}_{\text{HEC}}}{\text{UF}} = \frac{518 \text{ mg/m}^3}{10,000} = 5\times10^{-2} \text{ mg/m}^3
\]

The provisional RfC of $5\times10^{-2} \text{ mg/m}^3$ for 1,1-dichloroethane is the same as that currently under review by the RfD/RfC Work Group (U.S. EPA, 1990). Although there is a difference in calculation of the uncertainty factor (factor of 3 instead of 10 for species-to-species extrapolation using the dosimetric equations and factor of 3 added for database limitations), the total uncertainty factor remains unchanged.

For this provisional RfC, confidence in the key study is low because of the small number of animals used, the inclusion of only one treatment group, the limited information provided regarding organs and tissues examined and the lack of data regarding potential effects on the respiratory tract. Confidence in the database is low because details regarding the supporting subchronic study (Dow Chemical, 1990) are lacking and the study did not include cats (which appear to be the most sensitive species), chronic inhalation studies were not available, reproductive effects were not studied and developmental data were located for only one species. Confidence in the provisional RfC is low, reflecting low confidence in the database and key study.

**Caution** is advised in using the provisional RfC for 1,1-dichloroethane. The Hofmann et al. (1971) cat study is, at best, marginal for use in a risk assessment due to the small number of animals in the study, the limited nature of the histopathological examination (which did not include the respiratory tract) and the lack of corroborative data from other repeated exposure studies. Therefore, if this provisional RfC is chosen, this office will not be able to attest to its scientific accuracy and use.

Deriving an RfC for 1,1-dichloroethane based on structural analogy to 1,2-dichloroethane is not recommended because of the evidence that this isomer has different pharmacokinetic and
toxicologic properties from those of 1,1-dichloroethane. In vitro metabolism studies with rat liver microsomes showed that 1,1-dichloroethane is more rapidly dechlorinated than 1,2-dichloroethane (McCall et al., 1983; Loew et al., 1973; Salmon et al., 1981). Hofmann et al. (1971) reported that repeated inhalation exposure to 1,2-dichloroethane at 500 ppm was lethal to rats, guinea pigs and rabbits, but not to cats, within a few weeks commencement of exposure. In contrast, exposure to 500 or 1000 ppm 1,1-dichloroethane by the same protocol for up to 23 weeks produced no adverse effects in rats, guinea pigs or rabbits and only produced nonlethal renal effects in cats (Hofmann et al., 1971).

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