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Provisional Peer Reviewed Toxicity Values for

1,1-Dichloroethane
(CASRN 75-34-3)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration

p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

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Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions or the EPA Headquarters Superfund Program sometimes request that a frequently used PPRTV be reassessed. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

IRIS (U.S. EPA, 2006) does not list RfD or RfC values for 1,1-dichloroethane. The HEAST (U.S. EPA, 1997) includes subchronic and chronic RfD and RfC values, based on a 1984 Health Effects Assessment (HEA) for 1,1-dichloroethane (U.S. EPA, 1984). The subchronic RfC of 5E+0 mg/m^3 and chronic RfC of 5E-1 mg/m^3 are based on a NOAEL of 500 ppm (2025 mg/m^3) for kidney damage in cats exposed to 1,1-dichloroethane intermittently for 13 weeks (Hofmann et al., 1971). The subchronic RfD of 1E+0 mg/kg-day and chronic RfD of 1E-1 mg/kg-day are based on a NOAEL of 115 mg/kg-day for systemic toxicity derived by route-to-route extrapolation from the NOAEL of 2025 mg/m^3 in the subchronic inhalation study in rats (Hofmann et al., 1971). The HEA (U.S. EPA, 1984) adopted the oral assessment for 1,1-dichloroethane from a Drinking Water Criteria Document (U.S. EPA, 1983). In addition to the HEA (U.S. EPA, 1984) and the Drinking Water Criteria Document (U.S. EPA, 1983), the CARA list (U.S. EPA, 1991, 1994) includes a Health and Environmental Effects Profile (HEEP) for 1,1-dichloroethane (U.S. EPA, 1985) that does not, however, present a noncancer assessment. 1,1-Dichloroethane is not included in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2004). The toxicity of 1,1-dichloroethane was reviewed by ATSDR (1990), but MRL values were not derived. The California Environmental Protection Agency has not established

an oral or inhalation reference exposure level for 1,1-dichloroethane (CalEPA, 2006a). ACGIH (2006) lists a TLV of 100 ppm (400 mg/m^3) for 1,1-dichloroethane based on liver, kidney, and irritant effects. The NIOSH (2006) REL and OSHA (2006) PEL are also 100 ppm. The World Health Organization (WHO) has not produced an Environmental Health Criteria document for 1,1-dichloroethane (WHO, 2006). The National Toxicology Program has prepared a health and safety information sheet and published a study results summary (NTP, 2006).

A cancer assessment for 1,1-dichloroethane is available on IRIS (U.S. EPA, 2006), in which the chemical is classified (according to U.S. EPA, 1986 guidelines for carcinogenic risk assessment), as Group C, a possible human carcinogen. This classification is based on no human data and limited evidence of carcinogenicity in two animal species (rats and mice), as shown by increased incidences of hemangiosarcomas and mammary gland adenocarcinomas in female rats and hepatocellular carcinomas and benign uterine polyps in mice (NCI, 1978). The data were considered inadequate to support quantitative assessment. The source document listed for the cancer assessment is the HEEP (U.S. EPA, 1985). The California Environmental Protection Agency (CalEPA, 2006b), however, has published cancer slope factor and unit risk values for 1,1-dichloroethane of 5.7E-3 $(mg/kg\text{-}day)^{-1}$ and 1.6E-6 $(\mu g/m^3)^{-1}$, respectively. Cancer potency is based on mammary gland adenocarcinomas observed in the female Osborne-Mendel rats, the most sensitive of the species and sexes tested by NCI (1978). Because survival of female rats was poor, the potency was derived using a time-to-tumor analysis and "expedited Proposition 65 methodology" with cross route extrapolation. The unit risk factor was derived from the cancer potency factor using a human reference body weight of 70 kg and an inhalation rate of 20 m^3/day. Cancer assessments for 1,1-dichloroethane are included in the Drinking Water Criteria Document (U.S. EPA, 1983) and the HEA (U.S. EPA, 1984), in which a classification of Group D (not classifiable) was proposed for 1,1-dichloroethane. The HEAST (U.S. EPA, 1997) contains only a reference to the assessment on IRIS. An assessment for 1,1-dichloroethane is not available from the International Agency for Research on Cancer (IARC, 2006).

Literature searches were conducted from 1983 to June 2003 in TOXLINE (supplemented with BIOSIS and NTIS updates), MEDLINE, CANCERLIT, GENETOX, HSDB, EMIC/EMICBACK, DART/ETICBACK, RTECS and TSCATS for relevant studies. Additional literature searches from June 2003 through September 2004 were conducted by NCEA-Cincinnati using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF PERTINENT DATA

Human Studies

Oral Exposure. No studies were located regarding toxicity or carcinogenicity in humans following oral exposure to 1,1-dichloroethane.

Inhalation Exposure. Little information is available regarding the health effects of 1,1-dichloroethane following inhalation exposure in humans. 1,1-Dichloroethane was used in the past as an inhalation 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). The medical use of 1,1-

dichloroethane was discontinued because it was found to induce cardiac arrhythmias at anesthetic doses (Browning, 1965).

Animal Studies

Oral Exposure. In a range-finding experiment for a cancer bioassay, NCI (1978) exposed Osborne Mendel rats (5/sex/dose) and B6C3F1 mice (5/sex/dose) to 1,1-dichloroethane doses of 0, 562 (rats only), 1000, 1780, 3160, 5620, or 10,000 (mice only) mg/kg-day by gavage in corn oil, 5 days/week for 6 weeks followed by a 2 week observation period. Deaths occurred at doses of 3160 mg/kg-day in rats and 5620 mg/kg-day in mice. Reductions in body weight were seen at all doses in rats, but in none of the mouse groups. No other endpoints were monitored.

In the ensuing bioassay, NCI (1978) exposed Osborne Mendel rats (50/sex/dose) and B6C3F1 mice (50/sex/dose) to 1,1-dichloroethane by gavage in corn oil, 5 days/week for 78 weeks. Corn oil vehicle and untreated control groups, each consisting of 20 animals/sex/species, were included. Due to toxicity, the administered doses were adjusted during the course of the study and were given in a cyclic pattern (no dosing for one week, followed by 4 weeks of administration at the previously administered dose) from study week 32 until the end of the exposure period. High and low time-weighted average doses were 764 and 382 mg/kg-day for male rats, 950 and 475 mg/kg-day for female rats, 2885 and 1442 mg/kg-day for male mice, and 3331 and 1665 mg/kg-day for female mice. Following the exposure period, rats and mice were held for observation for 33 and 13 weeks, respectively, prior to sacrifice. Survival in male and female rats and several mouse groups was poor. Mortality in all groups of rats and mice was treatment-related. Survival at the end of the study in the untreated control, vehicle control, low dose, and high dose groups was 30, 5, 4, and 8% in male rats; 40, 20, 16, and 18% in female rats; 35, 55, 62, and 32% in male mice; and 80, 80, 80, and 50% in female mice, respectively. Pneumonia occurred in 80% of the rats in the study and was the major cause of death in that species; cause of death in mice was not reported. Body weights were generally comparable to the vehicle controls. The type and incidence of nonneoplastic lesions in dosed animals were similar to those observed in the control groups. The sensitivity of this study was reduced by the high mortality rate, and a reliable NOAEL could not be determined.

A statistically significant positive dose-related trend in incidence of hemangiosarcomas (0/19 for matched vehicle controls, 0/50 for the low-dose group, and 4/50 for the high-dose group) was observed in the female rats (NCI, 1978). The incidence of mammary gland adenocarcinomas (1/20 for the untreated group, 0/19 for the vehicle control group, 1/50 for low-dose, and 5/50 for high-dose groups) showed a statistically significant dose-related positive trend in those female rats surviving at least 52 weeks, based on tumor incidence of 0/16, 1/28 and 5/31 for vehicle control, low- and high-dose groups, respectively. (Tumor incidence at termination for the untreated control females surviving at least 52 weeks was not reported.) No hemangiosarcomas or mammary gland adenomas were observed in the dosed male rats. An increased incidence of hepatocellular carcinoma in male mice was not statistically significant by either pair-wise or trend test using the uncensored data (2/17 in the untreated control group, 1/19 in the vehicle control group, 8/49 in the low-dose and 8/47 in the high-dose group). However, there was a statistically significant positive trend for hepatocellular carcinoma in male mice surviving at least 52 weeks in comparison to a pooled vehicle control group consisting of vehicle

control mice from this and other concurrent experiments in the same laboratory, based on incidences of 1/19, 6/72, 8/48, and 8/32 in the matched vehicle control group, pooled vehicle control group, low-, and high-dose groups, respectively. In female mice, liver carcinomas were reported in only the vehicle control (1/19) and low-dose groups (1/47): no liver tumors were seen in the untreated controls or the high-dose group. A statistically significant increase in benign uterine endometrial stromal polyps (4/46) was observed in high-dose females; these were not observed in any other group.

The experiments in both rats and mice were limited by high early mortality in many of the groups. The low survival rates precluded the appearance of possible late-developing tumors and decreased the statistical power of this bioassay. The researchers concluded that this study provided no evidence of carcinogenicity in male rats or mice, and only equivocal evidence of carcinogenicity in female rats and mice (NCI, 1978; NTP, 2006).

In another study conducted primarily to investigate potential carcinogenicity, Klaunig et al. (1986) exposed groups of 35 male B6C3F1 mice to 1,1-dichloroethane in drinking water at concentrations of 0, 835, or 2500 mg/L for 52 weeks. Ten mice from each group were sacrificed after 24 weeks, and the remainder at the end of the exposure period. Body weight and drinking water consumption were monitored throughout the exposure period. All animals were necropsied at sacrifice and examined for gross lesions. Liver, kidneys, and lungs were weighed and examined for tumors by histopathology. Exposure to 1,1-dichloroethane did not significantly affect water intake, body weight or survival in treated mice. No nonneoplastic lesions in the liver, kidney, or lung were reported in 1,1-dichloroethane-treated mice. Based on an estimated weekly intake of 3.8 mg/g calculated by the study authors, the mice received a dose of approximately 543 mg/kg-day at the high concentration.

A more comprehensive, subchronic study was reported by Muralidhara et al. (2001), who treated male Sprague-Dawley rats (15/dose) with 1,1-dichloroethane doses of 0, 500, 1000, 2000, or 4000 mg/kg-day by gavage in corn oil, 5 days/week for 13 weeks. Body weights were recorded weekly. Urine was collected every two weeks from half of the animals in each dose group for measurement of protein, glucose, and selected enzyme markers of toxicity (acid phosphatase [ACP], N-acetylglucosaminidase [NAG], alkaline phosphatase [ALP], and maltase [MAL]). Blood was collected from the remaining half of the animals in weeks 0, 4, 8, and 12 for measurement of serum enzyme markers of toxicity (alanine aminotransferase [ALT], sorbitol dehydrogenase [SDH], ornithine-carbamyl transferase [OCT], and blood urea nitrogen [BUN]). At study termination, the liver and kidney were weighed and assayed for nonprotein sulfhydryl content, and samples from these organs and the lung, brain, adrenal, stomach, spleen, testes, and epididymis were collected for histological examination.

Rats in the 4000 mg/kg-day group exhibited protracted narcosis each day after dosing (Muralidhara et al., 2001). As a result, body weight gain in this group was significantly and progressively reduced throughout the study. The first death in this group occurred in week 1, and additional deaths were recorded through week 11, when the seven surviving rats in this group were sacrificed. In the 2000 mg/kg-day group, rats showed moderate CNS depression after dosing each day and one animal died in the sixth week. Body weights in this group were significantly reduced compared to controls and the lower dose groups after week 4 of the study.

No gross evidence of CNS depression (sensitive, objective tests not conducted), no deaths, and no effect on body weight were seen in the 500 or 1000 mg/kg-day groups. No effects on serum SDH, OCT, or BUN levels or urinary glucose or protein excretion were found at any time point in any group (data not shown). ALT results were not discussed. Urinary activities of ACP and NAG were significantly increased in the 1000, 2000, and 4000 mg/kg-day groups at 8 weeks. ACP was also significantly increased in the 2000 and 4000 mg/kg-day groups at 6 weeks. By 12 weeks, levels of ACP in all surviving treated groups (500, 1000, and 2000 mg/kg-day groups) had decreased and were significantly lower than controls. Urinary ALP and MAL results were not discussed. Relative liver weights were similar to controls in all treatment groups. Kidney weight data were not discussed. Histopathological examination of the liver revealed a slight change in hepatocyte histology (mild condensation and change in cytoplasmic staining consistent with glycogen mobilization) in the rats from the 4000 mg/kg-day group sacrificed at 11 weeks, but no changes in lower dose groups. Nephropathy and pulmonary inflammation were seen to a similar or greater extent in control rats than in treated rats, and so were not considered to be chemical-related. No effects were seen in the other tissues examined. Based on the transitory and reversible increase in urinary enzymes (ACP) indicative of renal injury at 8 weeks, the 1000 mg/kg-day dose can be considered a NOAEL and the 2000 mg/kg-day dose a LOAEL in this study.

Acute studies and studies by other routes provide some support for identification of the kidney as a sensitive target for 1,1-dichloroethane. Dow Chemical (1960) reported that single oral doses of 2 g/kg induced no adverse reactions in rats, although autopsy showed some kidney injury. In single exposure studies of male rats to 1,1-dichloroethane vapors, dose- and time-related lethality was observed at concentrations of 8,000 to 64,000 ppm of 1,1-dichloroethane (32,380 - 259,036 mg/m^3, assuming 25°C and 760 mm Hg) for 0.1-7 hours (Dow Chemical, 1960). Autopsy of the animals that died revealed lung injury with slight liver and kidney pathology. Hofmann et al. (1971) observed serum enzyme changes (increased BUN and serum creatinine) and histopathology (renal tubular dilatation and degeneration) indicative of renal toxicity in cats and exposed by inhalation to 1000 ppm of 1,1-dichloroethane for 13 weeks immediately following 13-week exposure to 500 ppm.

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 of 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.

Inhalation Exposure. Groups of 10 Sprague-Dawley rats, 10 Pirbright-White guinea pigs, 4 "colored" rabbits and 4 cats were exposed to 0 or 500 ppm of 1,1-dichloroethane (2024 mg/m^3, assuming 25°C and 760 mm Hg) for 6 hours/day, 5 days/week for 13 weeks (Hofmann et al., 1971). 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, serum ALT, AST, and creatinine, and BUN were monitored in rats, rabbits and cats. Sulfobromophthalein 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. The animals of the treated groups were then exposed to 1000 ppm (4047 mg/m^3) for an additional 10-13 weeks, while the control animals were maintained without exposure for the same period. 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 BUN and serum creatinine levels relative to controls. In the cats at 1000 ppm, BUN levels were elevated immediately and rose steadily until week 11 (week 24 of the whole study), at which time they reached a peak level that was approximately three-fold greater than the control level. Blood creatinine levels showed a parallel but less dramatic increase. No increases were noted in the activities of serum ALT or AST. 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. 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. Identification of NOAEL and LOAEL values for renal effects in the cat study is problematic because the kidneys were not examined during the 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. The exposure of 1000 ppm (4047 mg/m^3) was a NOAEL for rats, guinea pigs and rabbits.

The results of another multispecies subchronic inhalation study were reported only as unpublished summaries (Dow Chemical, 1990; AIHA, 1986). 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, ALT, BUN) 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 dogs (1/gender/group) exposed to 0 or 1000 ppm of 1,1-dichloroethane 7 hours/day for a total of 75 exposures over a 6-month period. The results, however, are of questionable significance because 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.

Schwetz et al. (1974) exposed mated female Sprague-Dawley rats (20/concentration) to 3800 or 6000 ppm of 1,1-dichloroethane (15,382 or 24,287 mg/m^3, respectively) for 7 hours/day on gestation days 6-15 in two successive experiments. Nonpregnant rats were exposed concurrently and were used for evaluation of serum ALT and liver weight during and after exposure. Control animals (total of 47 in the two experiments) were concurrently exposed to filtered room air. Maternal toxicity, frequency of fetal anomalies, hepatotoxicity, liver weights, ALT activity, and resorptions were evaluated for compound-related effects. Maternal food consumption and weight gain were significantly decreased starting after the initiation of exposure on day 6 of gestation and continuing throughout the exposure period for food consumption and throughout gestation for body weight in rats exposed to 3800 or 6000 ppm of 1,1-dichloroethane. Clinical signs, conception rate, number of implantations, litter size, ALT activity, and gross appearance of the liver were unaffected by treatment. Liver weight was unaffected by exposure in the pregnant rats. In the nonpregnant rats, absolute and relative liver weights were similar to controls at the end of the exposure period; relative, but not absolute, liver weight was significantly increased 6 days later. Exposure of pregnant females to 3800 or 6000 ppm of 1,1-dichloroethane had no effect on fetal resorption, fetal body measurements, or on the incidence of gross or soft tissue anomalies. The overall incidence of skeletal anomalies was also unaffected. There was a statistically significant increase in the number of litters with pups showing delayed ossification of sternebrae, a minor skeletal variation, at 6000 ppm when compared with concurrent controls. However, this may reflect an unusually low incidence of this variation in this control group (11%), which was significantly lower than the control group for the low dose group (61%), rather than an exposure-related effect in the 6000 ppm group, which had an incidence (42%) similar to the 3800 ppm group (44%). This study found no clear evidence of maternal or developmental toxicity at concentrations up to 6000 ppm.

Acute studies and studies by other routes provide some support for identification of the kidney as a sensitive target for 1,1-dichloroethane. 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 of 1,1-dichloroethane (32,380 - 259,036 mg/m^3, 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. Dow Chemical (1960) reported that single oral doses of 2 g/kg induced no adverse reactions in rats, although autopsy showed some kidney injury. Muralidhara et al. (2001) observed temporary significant increases in the urinary activities of acid phosphatase (ACP) and N-acetylglucosaminidase (NAG), two enzyme markers for renal toxicity, in male rats treated with 1000 mg/kg-day or more of 1,1-dichloroethane by gavage in corn oil, 5 days/week for 13 weeks.

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 of 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.

Other Studies

Studies in animals indicate that 1,1-dichloroethane is readily absorbed by the gastrointestinal tract following oral dosing (ATSDR, 1990). Absorbed 1,1-dichloroethane is poorly metabolized in rats and mice and the majority of the administered dose is rapidly excreted in expired air. Studies with liver microsomes indicate that acetic acid is the primary metabolite in the small fraction of the administered dose that is metabolized. Hydroxylation of the C-1 carbon is hypothesized to produce an unstable alpha haloalcohol that rearranges to form reactive acyl chlorides that can react with cellular constituents leading to dysfunction. Conjugation with glutathione is a possible detoxification mechanism.

Klaunig et al. (1986) exposed groups of 35 male B6C3F1 mice to 1,1-dichloroethane in drinking water at 0, 835, or 2500 mg/L for up to 52 weeks following a 4-week treatment with either drinking water containing 10 mg/L diethyl nitrosamine (DENA-initiated groups) or with deionized water (noninitiated groups). The investigators estimated that the approximate weekly dose of 1,1-dichloroethane was 3.8 mg/g/week (corresponding to 543 mg/kg-day) for the groups exposed to 2500 mg/L. Upon sacrifice at the end of either 24 weeks (10 mice/group) or 52 weeks (25 mice/group) of promotion, all tissues were examined for gross pathologic lesions and histologic sections of the liver, kidneys and lungs were examined. Neither the initiated nor the noninitiated 1,1-dichloroethane-treated groups showed a significant increase in the incidence of liver or lung tumors compared with initiated or noninitiated controls, respectively. The authors concluded that 1,1-dichloroethane was not carcinogenic to mice and did not act as a tumor promoter following initiation with DENA. These conclusions may not be entirely justified, since the duration of the study and dose may have been inadequate for the development of tumors in noninitiated 1,1-dichloroethane-treated animals. In addition, the incidence of liver tumors in DENA-initiated controls was 70% at 24 weeks and 100% at 52 weeks, and the number of tumors/mouse in DENA-initiated controls at these times was 3.00 and 29.30, respectively. Hence, an increase in tumors or decrease in latency in 1,1-dichloroethane-treated DENA-initiated animals would have had to be marked in order to be detectable.

Milman et al. (1988) and Story et al. (1986) investigated the chlorinated ethanes and ethylenes to detect their potential tumor initiating or promoting effects in a gavage liver foci assay in Osborne-Mendel rats. In this assay, 1,1-dichloroethane did not give positive results for initiation (with phenobarbital as promoter), or as a complete carcinogen when administered in the absence of initiation or promotion. Positive results for were seen for promotion with DENA as initiator. The assumption that the liver foci seen in this type of assay are precancerous has not been validated.

The genotoxicity of 1,1-dichloroethane has been assessed in a number of *in vitro* assays, and results have been mixed. 1,1-Dichloroethane was mutagenic in *Salmonella typhimurium*

strains TA1535, TA98, and TA100 (but not TA1537) with or without metabolic activation when tested by plate incorporation in a desiccator (Mitoma et al., 1984; Milman et al., 1988). However, results were negative for mutagenicity in strains TA97, TA98, TA100, TA1535, and TA1537 with or without metabolic activation when tested following preincubation in capped tubes to prevent evaporation of the test material (Zeiger et al., 1992). Because both of these studies were conducted under methods appropriate for volatile chemicals, loss of 1,1-dichloroethane from the test system is unlikely to explain the conflicting results obtained. Other assays were also conducted using methods for volatile chemicals. 1,1-Dichloroethane induced chromosome malsegregation in *Aspergillus nidulans* in a test featuring preincubation in capped tubes (Crebelli et al., 1988). Positive results were also obtained in a DNA repair assay in cultured primary rat and mouse hepatocytes performed in a sealed glass incubation chamber (Williams, 1977; Milman et al., 1988). Results were negative for BALB/c-3T3 cell transformation in the absence of metabolic activation (Tu et al., 1985; Milman et al., 1988), but positive for viral transformation in Syrian hamster embryo cells (Hatch et al., 1983) in tests conducted in sealed test systems. 1,1-Dichloroethane covalently bound to DNA to form adducts in both *in vitro* and *in vivo* assays, with a Covalent Binding Index that classified it as a weak initiator (Colacci et al., 1985; Lattanzi et al., 1988).

Treatment of mice and rats with the isomer 1,2-dichloroethane resulted in induction of tumors at multiple sites and included some of the same tumor types observed in the cancer bioassays of 1,1-dichloroethane (U.S. EPA, 2006). The incidences of forestomach squamous cell carcinomas and hemangiosarcomas were significantly increased in male rats and the incidence of mammary adenocarcinomas was increased in female rats and mice orally exposed to 1,2-dichloroethane. In addition, alveolar and bronchiolar adenomas were reported in male and female mice, endometrial stromal polyps and sarcomas were reported in female mice, and hepatocellular carcinomas were reported in male mice orally exposed to 1,2-dichloroethane. The 1,2 isomer is classified as a Group B2 probable human carcinogen (U.S. EPA, 2006).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC RfDs FOR 1,1-DICHLOROETHANE

The subchronic oral exposure study by Muralidhara et al. (2001) identified the kidney as a sensitive target for 1,1-dichloroethane in male rats. NOAEL and LOAEL values of 1000 and 2000 mg/kg-day, respectively, were estimated, based on increased urinary enzyme markers for renal damage and CNS depression. Other oral studies provided limited data, but renal effects of 1,1-dichloroethane have been found by other routes of exposure (Hofmann et al., 1971; Dow Chemical, 1960; Plaa and Larson,1965).

The NOAEL of 1000 mg/kg-day, administered for 5 days/week, is adjusted to 714.3 mg/kg-day for continuous exposure. The provisional subchronic RfD is derived by dividing the NOAEL of 714.3 mg/kg-day in male Sprague-Dawley rats by a combined uncertainty factor (UF) of 300 (Muralidhara et al., 2001). The combined UF includes factors of 10 for interspecies extrapolation, 10 for human variability, and 3 for database deficiencies (including lack of reproductive and developmental toxicity tests by the oral route). The provisional **subchronic oral RfD of 2 mg/kg-day** is calculated as follows:

subchronic p-RfD = NOAEL / UF
= 714.3 mg/kg-day / 300
= 2.4 mg/kg-day or 2E+00 mg/kg-day

The provisional chronic oral RfD is derived by dividing the NOAEL of 714.3 mg/kg-day established by the study of Muralidhara et al. (2001) by a combined UF of 3000. The combined UF includes factors of 10 for extrapolation from a subchronic study, 10 for interspecies extrapolation, 10 for human variability, and 3 for database deficiencies. The provisional **chronic oral RfD of 0.2 mg/kg-day** is calculated as follows:

p-RfD = NOAEL / UF
= 714.3 mg/kg-day / 3000
= 0.2 mg/kg-day or 2E-01 mg/kg-day

Confidence in the principal study is medium. The study examined relevant endpoints in adequate numbers of male Sprague-Dawley rats exposed to an appropriate array of doses of 1,1-dichloroethane by gavage for 13 weeks. However, the study tested male rats only and reporting of results was only marginally adequate, as data were not presented for many endpoints and several endpoints listed in the methods were not discussed at all in the results. Confidence in the database is low. The database is lacking human data, supporting subchronic or chronic animal studies by the oral route, and studies of developmental, reproductive effects, or neurological effects of exposure to 1,1-dichloroethane by the oral route. The principal study reported clinical signs of CNS effects at the higher doses tested, but the potential neurological or neurobehavioral effects of 1,1-dichloroethane have not been quantified. Overall, confidence in the provisional RfD for 1,1-dichloroethane is low.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfCs FOR 1,1-DICHLOROETHANE

The available inhalation toxicity data for 1,1-dichloroethane are inadequate for derivation of provisional subchronic or chronic RfC values. Hofmann et al. (1971) identified renal effects in the cat as the most sensitive species for 1,1-dichloroethane in a subchronic study. However, the study included only 2 cats of each sex, did not include investigation of portal of entry (i.e., respiratory) effects, and tested only two concentrations of 1,1-dichloroethane - in succession in the same group of test animals. Because of the unusual study design, the kidneys were not examined for histopathology after the 500 ppm exposure. 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. Therefore, the data are inadequate to identify the 500 ppm level as either a LOAEL or a NOAEL. No effects on the kidneys or other organs were found in other species tested in this study or in other repeated exposure inhalation studies (Dow Chemical, 1990; AIHA, 1986; Union Carbide, 1947), although there is some support for the kidney as a target of 1,1-dichloroethane from acute studies and studies by other routes (Dow

Chemical, 1960; Plaa and Larson, 1965; Muralidhara et al., 2001). A developmental toxicity study (Schwetz et al., 1974) found no clear evidence of maternal or developmental toxicity at concentrations up to 6000 ppm.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 1,1-DICHLOROETHANE

Weight-of-evidence Classification

As listed in IRIS (U.S. EPA, 2006), 1,1-dichloroethane is classified in Weight-of-Evidence Group C. This classification is based on lack of human data and limited evidence of carcinogenicity in rats and mice, as shown by increased incidences of hemangiosarcomas and mammary gland adenocarcinomas in female rats and increased incidences of hepatocellular carcinomas and benign uterine polyps in mice exposed by gavage in corn oil. Mixed results in initiation/promotion studies and genotoxicity assays are consistent with this classification. The close structural relationship between this chemical and 1,2-dichloroethane, which is classified as a B2 probable human carcinogen and produces tumors at many of the same sites where marginal tumor increases were observed for 1,1-dichloroethane, supports the suggestion that the 1,1-isomer could potentially be carcinogenic to humans. In accordance with the cancer guidelines (U.S. EPA, 2005), 1,1-dichloroethane is considered to show *suggestive evidence of carcinogenic potential*.

Quantitative Estimates of Carcinogenic Risk

A provisional oral slope factor or inhalation unit risk value for 1,1-dichloroethane is not derived because the available data are insufficient to support derivation of quantitative risk values. This is in accordance with the U.S. EPA (2005) cancer guidelines, which state that it is generally not appropriate to derive quantitative estimates of cancer risk for chemicals where the weight-of-evidence for carcinogenicity provides only *suggestive evidence of carcinogenic potential*.

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