1,1-Dichloroethylene (1,1-DCE); CASRN 75-35-4

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR 1,1-Dichloroethylene (1,1-DCE)

File First On-Line 01/30/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	08/13/2002*
Inhalation RfC (I.B.)	yes	08/13/2002*
Carcinogenicity Assessment (II.)	yes	08/13/2002*

*A comprehensive review of toxicological studies was completed (05/27/05) - please see sections I.A.6., I.B.6., and II.D.2. for more information.

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — 1,1-Dichloroethylene (1,1-DCE)
CASRN — 75-35-4
Last Revised — 08/13/2002

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without

an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

This summary replaces the summary dated 04/01/1989. This RfD differs from the previous EPA value of 0.009 mg/kg-day. The previous EPA evaluation used the same study but considered the lowest exposure of 9 mg/kg-day in female rats as a LOAEL for minimal hepatocellular fatty change and minimal hepatocellular swelling and applied a total uncertainty factor (UF) of 1000 (10 for LOAEL-to-NOAEL extrapolation, 10 for interspecies extrapolation, and 10 for human variability). EPA no longer considers hepatocellular swelling, in the absence of other effects such as increased liver enzymes in the serum, as biologically significant in this bioassay. The increased incidence of midzonal fatty change at 9 mg/kg-day in female rats is not statistically significant. The NOAEL in this bioassay is 9 mg/kg-day. In addition, the present evaluation uses benchmark dose (BMD) methodology and calculates a $BMDL_{10}$ for midzonal fatty change in female rats.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver toxicity (fatty change) **Rat chronic drinking water study** **Quast et al. (1983)**	NOAEL: 9 mg/kg-day LOAEL: 14 mg/kg-day $BMDL_{10}$: 4.6 mg/kg-day	100	1	5E-2 mg/kg-day

*Conversion Factors and Assumptions — The authors provided the exposure data from the bioassay based on measured drinking water consumption.

I.A.2. Principal and Supporting Studies (Oral RfD)

Quast et al. (1983) conducted a 2-year chronic toxicity and carcinogenicity study of 1,1-DCE in Sprague-Dawley rats (6–7 weeks old). The control group comprised 80 rats of each sex, and each exposed group comprised 48 rats of each sex. The 1,1-DCE was incorporated in the drinking water of the rats at nominal concentrations of 0, 50, 100, or 200 ppm. The time-weighted average exposure over the 2-year period was 7, 10, or 20 mg/kg-day for males and 9, 14, or 30 mg/kg-day for females. Rampy et al. (1977) also reported some of the data. Humiston et al. (1978) reported more detailed data. No significant differences were observed among the groups in appearance and demeanor, mortality, body weight, food consumption, water consumption, hematology, urinalysis, clinical chemistry determinations, organ weights, or organ to body weight ratios. After 1 year on study, there was no depletion of the nonprotein sulfhydryl levels in the liver or the kidneys (Rampy et al., 1977).

The only treatment-related effect observed in rats was minimal hepatocellular midzonal fatty change and hepatocellular swelling. At the termination of the study, male rats showed increased incidence of minimal hepatocellular fatty change (control, 14/80; 50 ppm, 5/48; 100 ppm, 13/48; 200 ppm, 19/47) and minimal hepatocellular swelling (control, 0/80; 50 ppm, 1/48; 100 ppm, 2/48; 200 ppm, 3/47). The changes were statistically significant ($p<0.05$) only in the 200 ppm group. At the termination of the study, female rats showed an increased incidence of minimal hepatocellular fatty change (control, 10/80; 50 ppm, 12/48; 100 ppm, 14/48; 200 ppm, 22/48; statistically significant [$p<0.05$] at 100 and 200 ppm) and minimal hepatocellular swelling (control, 3/80; 50 ppm, 7/48; 100 ppm, 11/48; 200 ppm, 20/48; statistically significant [$p<0.05$] in all groups). No exposure-related neoplastic changes occurred at any exposure. No hepatocellular necrosis was evident at any exposure. Based on the minimal nature of the hepatocellular swelling reported by the authors and no change in liver weight, no change in clinical chemistry measurements diagnostic for liver damage, and no other indication of abnormal liver function, the hepatocellular swelling is not considered biologically significant or an adverse effect in this study. The statistically significant hepatocellular midzonal fatty change, however, is considered a minimal adverse effect in this study. Accordingly, the NOAEL in male rats is 10 mg/kg-day and the LOAEL is 20 mg/kg-day; the NOAEL in female rats is 9 mg/kg-day and the LOAEL is 14 mg/kg-day. A BMD analysis was conducted for the results in female rats. In female rats, the BMD_{10} is 6.6 mg/kg-day and the $BMDL_{10}$ is 4.6 mg/kg-day.

A three-generation study by Nitschke et al. (1983), described in Section I.A.4, corroborated the results of Quast et al. (1983).

The National Toxicology Program conducted 104-week chronic toxicity and carcinogenicity studies of 1,1-DCE in male and female F344 rats (200 of each sex, 9 weeks old) by gavage in

corn oil at 0, 1, or 5 mg/kg-day (NTP, 1982). There were no significant differences in survival, clinical signs, or body weight as compared with controls for any group, suggesting that the maximum tolerated dose was not achieved. The results of histopathological examination indicated chronic renal inflammation in male rats (26/50, 24/48, 43/48) and female rats (3/49, 6/49, 9/44). The increase was statistically significant only in males. As this lesion commonly occurs in male rats (Kluwe et al., 1984, 1990), it is not considered biologically significant in this study. The NOAEL in this study 5 is mg/kg-day (the highest exposure tested).

NTP also conducted 104-week chronic toxicity and carcinogenicity studies of 1,1-DCE in male and female B6C3F$_1$ mice (50 of each sex in each group, 9 weeks old) by gavage in corn oil at 0, 2, or 10 mg/kg (NTP, 1982). There were no significant differences in survival, clinical signs, or body weight in any group. The only noncancer effect observed by histopathological examination was necrosis of the liver (male: 1/46; 3/46; 7/49; female: 0/47; 4/49; 1/49). The effect was not statistically significant at either exposure (p=0.6 and 0.06 at the mid- and high-exposure levels in males using a two-tailed test, respectively). In male and female mice the NOAEL is 10 mg/kg-day (the highest exposure tested). The BMD_{10} is 7.8 mg/kg-day and the $BMDL_{10}$ is 4.1 mg/kg-day. This study was not used to derive the RfD because the gavage route of exposure will affect the pharmacokinetics of 1,1-DCE and the exposure-response relationship.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — 100

The critical effect is liver toxicity (fatty change) in rats, with a $BMDL_{10}$ of 4.6 mg/kg-day. Although this minimal effect might not be considered adverse—as there is no evidence of a functional change in the liver in rats exposed and glutathione levels are not reduced in this bioassay—the $BMDL_{10}$ was used to derive the RfD, because limiting exposure to the $BMDL_{10}$ will protect the liver from more serious damage (fatty liver or necrosis) that could compromise liver function. Individual UFs of 10 each were used for interspecies extrapolation and intraspecies variability because there were no applicable data to justify departure from the default values. Derivation of the RfD from the $BMDL_{10}$ for the minimal fatty change in the liver does not require an effect-level extrapolation. This conclusion is based on the minimal nature of the fatty change and its questionable biological significance because of the absence of any observable functional deficit in the liver. A subchronic-to-chronic extrapolation factor was not applied because the study exposed the animals for 2 years. A database UF is not applied because the database is considered complete. A number of long-term bioassays in rodents by the oral or inhalation route show that liver toxicity is the critical effect. There is no chronic bioassay in a nonrodent mammal. However, there are 90-day bioassays in several species (rats, mice, dogs, guinea pigs, rabbits, and monkeys) that suggest similar exposure-

response relationships across species. Therefore, the lack of a chronic bioassay in a nonrodent mammal is not considered a data gap. There are no focused studies on neurotoxicity, but there is no indication from chronic, reproductive, and developmental bioassays in rats and mice by oral or inhalation exposure that neurotoxicity in an important toxic endpoint. No long-term studies have evaluated immunotoxicity in laboratory animals by any route of exposure. The existing bioassays, however, provide no suggestion that immunotoxicity is a critical effect. EPA does not consider these data gaps compelling enough to require application of a database UF.

MF = 1.

I.A.4. Additional Studies/Comments (Oral RfD)

NTP (1982) conducted a study in male and female F344 rats (10 of each sex, 9 weeks old) administered 1,1-DCE by gavage in corn oil at 0, 5, 15, 40, 100, or 250 mg/kg. Animals were exposed five times per week for 13 weeks. Representative tissues from animals receiving 250 mg/kg and from control animals were examined microscopically. Livers from all groups were examined. Three female rats receiving 250 mg/kg died during the first week of the study. No other rats died. The mean body weight was depressed 13% for male rats receiving 250 mg/kg as compared with controls. Mean body weight in other groups was comparable. Only the liver showed effects attributed to 1,1-DCE. At 250 mg/kg, the three female rats that died showed severe centrilobular necrosis. Minimal to moderate hepatocytomegaly was seen in the rest of the rats at 250 mg/kg. Minimal to mild hepatocytomegaly was seen in 6/10 male rats and 3/10 female rats that received 100 mg/kg. No biologically significant changes were observed in rats that received 40 mg/kg or less. The NOAEL in this study is 40 mg/kg (equivalent to 28.5 mg/kg-day); the LOAEL is 100 mg/kg (equivalent to 71.4 mg/kg-day).

NTP (1982) conducted a study in male and female $B6C3F_1$ mice (10 of each sex, 9 weeks old) administered 1,1-DCE by gavage in corn oil at 0, 5, 15, 40, 100, or 250 mg/kg. Animals were exposed five times per week for 13 weeks. Representative tissues from mice receiving 100 and 250 mg/kg and from control animals were examined microscopically. Livers from all groups were also examined. Survival was 20/20, 19/20, 19/20, 19/20, 15/20, and 1/20 at 0, 5, 15, 40, 100, and 250 mg/kg, respectively. At 100 mg/kg there was a decrease in mean body weight in males (14%) but not in females. No change in mean body weight was observed at lower exposures. Only the liver showed effects attributed to 1,1-DCE. Centrilobular necrosis of the liver was observed in 5/10 males and 5/10 females that received 250 mg/kg and 2/10 males and 2/10 females that received 100 mg/kg. No biologically significant changes in the liver occurred in mice receiving 40 mg/kg or less. The NOAEL in this study is 40 mg/kg (adjusted to a continuous daily exposure of 28.6 mg/kg-day); the LOAEL is 100 mg/kg (adjusted to a continuous daily exposure of 71.4 mg/kg-day).

Quast et al. (1983) conducted a study in beagle dogs (four per group, 8 months old) administered 1,1-DCE by gavage in peanut oil at 0, 6.25, 12.5, or 25 mg/kg-day for 97 days. No significant differences were observed among groups in appearance and demeanor, mortality, body weight, food consumption, hematology, urinalysis, clinical chemistry determinations, organ weights, and organ-to-body-weight ratios. No exposure-related gross or histopathological changes were present in tissues. There was no depletion of the nonprotein sulfhydryl levels in the liver or kidneys. The NOAEL in this study is 25 mg/kg-day (the highest exposure tested).

Reproductive and Developmental Studies

Nitschke et al. (1983) evaluated the reproductive and developmental toxicity of 1,1-DCE in Sprague-Dawley rats. Three generations of the test animals were exposed to drinking water containing nominal 1,1-DCE concentrations of 0 (initially 15 males and 30 females), 50, 100, or 200 ppm (initially 10 males and 20 females at each exposure). The authors provided no information on water consumption. This study was a companion study to Quast et al. (1983) and used the same concentrations of 1,1-DCE in drinking water; in Quast et al. (1983) the average exposure to females was 9, 14, or 30 mg/kg-day. After 100 days of exposure, the rats were mated.

In this three-generation study, there were no biologically significant changes in fertility index, in average number of pups per litter, in average body weight of pups, or in pup survival at any exposure. Neonatal survival was decreased from concurrent control values in the f_2 and f_{3a} litters of dams ingesting 1,1-DCE from drinking water. The survival indices, however, were within the range of control values for this strain of rats in this laboratory. The authors attributed the decreased survival index in f_2 to increased litter size at birth in dams exposed to 1,1-DCE. The apparent effect seen in the f_{3a} litters was not repeated in subsequent matings of the same adults to produce either the f_{3b} or the f_{3c} litters. The authors attributed the decreased survival in the f_{3a} litters as being due to chance.

Histopathological examination of tissues of rats exposed to 1,1-DCE in the drinking water in utero, during lactation, and postweaning revealed slight hepatocellular fatty change and an accentuated hepatic lobular pattern of a reversible nature in the adult rats (data not reported, but the observation is consistent with that reported by Quast et al. [1983] in a chronic bioassay). These effects were observed in the 100 and 200 ppm groups in the F_1 generation and in all groups of the F_2 generation. The authors did not present incidence data and did not report statistical analysis. Exposure to 1,1-DCE in drinking water at concentrations causing mild, dose-related changes in the liver did not affect the reproductive capacity of rats through three generations that produced six sets of litters. The NOAEL for reproductive and

developmental toxicity in this study is 200 ppm for exposure to 1,1-DCE in drinking water (the highest exposure tested and about 30 mg/kg-day).

Murray et al. (1979) evaluated the developmental toxicity of 1,1-DCE administered in drinking water at 0 (27 animals) or 200 ppm (26 animals) to pregnant Sprague-Dawley rats (body weight 250 g). Rats were exposed on gestation days 6–15 at 40 mg/kg-day. No teratogenic effects were seen in the embryos using standard techniques for soft and hard tissue examination, and there was no evidence of toxicity to the dams or their offspring. The NOAEL for developmental toxicity in this study is 40 mg/kg-day (the highest exposure tested).

Dawson et al. (1993) evaluated the ability of 1,1-DCE administered in drinking water at 110 ppm or 0.15 ppm to female Sprague-Dawley rats (body weight 250 g) to induce fetal cardiac changes. Rats were administered 110 ppm 1,1-DCE for 61 days before mating or for 48 days before mating and for 20 days during gestation. Other rats were administered 0.15 ppm 1,1-DCE for 82 days before mating or for 56 days before mating and for 20 days during gestation. The dams were killed on gestational day 22 and the gravid uterus was removed and examined. There was no effect on maternal weight gain, average resorption sites (sites where development began but resorption later occurred), or average implantation sites (sites that did not appear to develop beyond implantation and contained a metrial gland only). No increase in the incidence of cardiac changes occurred when dams were exposed only before mating. There was, however, a statistically significant increase ($p<0.01$) in the percent of fetuses with cardiac changes (atrial septal, mitral valve, and aortic valve changes) when the dams were exposed before mating and during gestation. The incidence was control, 7/232 (3%); 0.15 ppm, 14/121 (12%); and 110 ppm, 24/184 (13%).

This statistical analysis was based on total occurrence of affected fetuses. Because the exposure was to the dam and not to individual fetuses, a nested statistical analysis is preferred. Such an analysis takes into account the correlation among fetuses within a litter and the possible nesting of effects within litters. This analysis has not been conducted because all the necessary data are not available. The author provided additional data to resolve typographical errors in the exposure information for each group and to clarify the number of affected litters and number of fetuses per litter affected (letter from Brenda Dawson, University of Auckland, New Zealand, to Robert Benson, U.S. EPA, January 24, 2001). The exposure to dams before and during pregnancy was 0, 0.02, or 18 mg/kg-day in the control, 0.15 ppm, and 110 ppm groups, respectively. The number of affected litters was 5/21 (24%), 8/11 (73%), and 13/17 (76%). The mean number of affected fetuses per litter for affected litters only was 1.40 (13% of the fetuses in the litter), 1.75 (16% of the fetuses in the litter), and 1.85 (17% of the fetuses in the litter). The mean number of affected fetuses per litter for all litters was 0.33 (3% of the

fetuses in the litter), 1.27 (12% of the fetuses in the litter), and 1.41 (13% of the fetuses in the litter).

Dawson et al. (1993) did a much more thorough evaluation of alterations in cardiac development than is done in standard developmental toxicity testing protocols. There is no experience with the background rates or the functional significance of such alterations from other studies or laboratories. The incidence of alterations in control fetuses (3% of all fetuses, 24% of all litters, and 1.40 affected fetuses per affected litter) suggests a high background incidence. The authors reported that examinations were done blind to the treatment group, so the data are presumed not to be affected by observer bias.

There is no demonstrated exposure-response relationship in Dawson et al. (1993). A 900-fold increase in exposure did not produce a significant, increase in response in any measure of effect. The cardiac changes are of questionable biological significance, as there were no biologically significant effects reported on growth and survival in the three-generation study (Nitschke et al., 1983). No cardiac effects were reported in a prenatal developmental study (Murray et al., 1979); however, in this study exposure to 1,1-DCE did not occur throughout pregnancy. The pharmacokinetics of 1,1-DCE make it biologically implausible that the cardiac changes were causally associated with exposure to 1,1-DCE. The exposures used in Dawson et al. (1993) are below the level of saturation of CYP2E1 in the rat liver. Essentially all of the 1,1-DCE administered to the dams will be metabolized in the liver and will react with glutathione or macromolecules in the liver. (See the discussion and references in Section 3.) Therefore, it is extremely unlikely that any significant amount of 1,1-DCE or any toxic metabolite will be in the fetal compartment. CYP2E1 is not expressed in fetal liver but begins to be expressed shortly after birth (Cresteil, 1998).

EPA is not aware of any information on the expression of CYP2E1 in fetal cardiac tissue. Cardiac tissue, however, is not generally considered to be a tissue with significant potential for metabolism of xenobiotics. For these reasons EPA cannot conclude that the cardiac changes are caused by exposure to 1,1-DCE. It would be helpful if more definitive studies with a greater range of exposures were conducted to determine the cause and biological significance of the cardiac changes apparently associated with exposure to 1,1-DCE during the period of cardiac organogenesis.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. Confidence in the Oral RfD

Study — High
Database — Medium
RfD — Medium

The overall confidence in this RfD assessment is medium. The principal study (Quast, 1983) was well conducted, with an adequate number of animals and appropriate evaluation of a wide variety of endpoints. This study is supported by an additional bioassay in rats (NTP, 1982) and a three-generation reproductive and developmental study showing consistent effects in the liver. A three-generation reproductive study and several bioassays show that reproductive and developmental toxicity are not critical effects. One developmental study, however, shows variations in cardiac morphology that have appear to have little or no physiological consequence. There are no focused studies on neurotoxicity, but there are no indications from chronic, reproductive, or developmental bioassays in rats and mice by oral or inhalation exposure that neurotoxicity is an important toxic endpoint. No long-term studies have evaluated immunotoxicity in laboratory animals by any route of exposure. The existing bioassays, however, provide no suggestion that immunotoxicity is a critical effect. Accordingly, the database is given a medium confidence, but no additional UF is considered necessary.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — Toxicological Review of 1,1-Dichloroethylene (2002)

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of 1,1-Dichloroethylene. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Other EPA Documentation — This assessment replaces previous assessments (U.S. EPA, 1985a,b).

Agency Consensus Date — 06/07/2002

A comprehensive review of toxicological studies published through May 2005 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing RfD for 1,1-Dichloroethylene (1,1-DCE) and a change in the RfD is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — 1,1-Dichloroethylene (1,1-DCE)
CASRN — 75-35-4
Last Revised — 08/13/2002

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is generally expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

The previous EPA evaluation did not derive an RfC.

I.B.1. Inhalation RfC Summary

Critical Effect	Experimental Doses*	UF	MF	RfC
Liver toxicity (fatty change) **Rat chronic inhalation study Quast et al. (1986)**	$NOAEL_{HEC}$: 17.7 mg/m^3 $LOAEL_{HEC}$: 53.2 mg/m^3 $BMCL_{10HEC}$: 6.9 mg/m^3	30	1	2E-1 mg/m^3

*Conversion Factors and Assumptions — The NOAEL from the chronic bioassay is 25 ppm, where the exposure was for 6 hrs/day, 5 days/wk. The conversion factor is 1 ppm = 3.97 mg/m^3. The human equivalent concentration (HEC) was calculated using the equation for a category 3 gas (U.S. EPA, 1994). The blood:gas partition coefficient in the rat is 5 (D'Souza and Andersen, 1988). No useable data are available on the blood:gas coefficient in humans. Accordingly the default value of 1 is used for the ratio of these coefficients.
$NOAEL_{HEC} = NOAEL_{adj} \times (H_{b/g})_A/(H_{b/g})_H = 25 \text{ ppm} \times 6/24 \times 5/7 \times 1 \times 3.97 = 17.7 \text{ mg/m}^3$
$BMCL_{HEC} = BMCL_{adj} \times (H_{b/g})_A/(H_{b/g})_H = 9.8 \text{ ppm} \times 6/24 \times 5/7 \times 1 \times 3.97 = 6.9 \text{ mg/m}^3$

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Quast et al. (1986) and Rampy et al. (1977) reported results from studies that exposed male and female Sprague-Dawley rats (Spartan substrain, 86 animals/group) to 1,1-DCE by inhalation 6 hrs/day, 5 days/wk, for up to 18 months. Interim sacrifices occurred at 1, 6, and 12 months. Rats were exposed to 1,1-DCE concentrations of 10 ppm and 40 ppm for the first 5 weeks of the study. Because of the absence of observable treatment-related effects among rats sacrificed after 1 month of exposure, the concentrations were increased to 25 and 75 ppm. Exposures were continued at these concentrations through the 18th month of the study. The surviving animals were then held without exposure to 1,1-DCE until 24 months. Cytogenetic evaluations were performed on a separate group of animals (four/sex) exposed to 0, 25, or 75 ppm for 6 months. A separate 90-day study using 20 rats/sex/treatment group was conducted at 0, 25, and 75 ppm, with an interim sacrifice of 8 rats/group at 30 days. There were no exposure-related changes in mortality, appearance and demeanor, body weight, clinical chemistry determinations, hematologic evaluations, urinalysis, or cytogenetic evaluation of bone marrow preparations.

Minimal hepatocellular fatty change in the midzonal region of the hepatic lobule was observed in both male and female rats in the 25 ppm and 75 ppm groups at the 6-month interim sacrifice (male: control, 0/5; 25 ppm, 1/5; 75 ppm, 4/5; female: control, 0/5; 25 ppm, 2/5; 75 ppm, 4/5). The fatty change was also observed at the 12-month sacrifice, but there was no indication of progression of severity (male: control, 0/5; 25 ppm, 3/5; 75 ppm, 5/5; female: control, 0/5; 25 ppm, 5/5; 75 ppm, 5/5). At the 18-month sacrifice the incidence of this change was no longer increased in male rats (control, 0/27; 25 ppm, 0/25; 75 ppm, 1/27). However, the change persisted in female rats (control, 0/16; 25 ppm, 6/29; 75 ppm, 7/20). The effect was statistically significant ($p<0.05$) only at the higher exposure. During the last 6 months of the study, after exposure had been discontinued, this effect was no longer discernible (male: control, 0/46; 25 ppm, 1/47; 75 ppm, 0/51; female: control, 0/49; 25 ppm, 0/46; 75 ppm, 1/48).

Although the incidences of several tumors and/or tumor types were found to be statistically increased or decreased compared with controls, none of these differences were judged to be attributable to 1,1-DCE. The tumor incidence data for both control and treated rats in this study were comparable to historical control data for the Sprague-Dawley rats (Spartan substrain) used by this laboratory for several studies of similar design and duration.

Although the minimal hepatocellular midzonal fatty change was reversible and did not result in altered organ weight, clinical chemistry changes diagnostic for liver damage, or any obvious decrement in liver function, the fatty change in liver is considered a minimal adverse effect. Accordingly, the NOAEL in male rats in this study is 75 ppm (the highest exposure tested). The NOAEL for female rats in this study is 25 ppm; the LOAEL is 75 ppm. A benchmark dose analysis was conducted. In female rats the BMC_{10} is 15.1 ppm and the $BMCL_{10}$ is 9.8 ppm, equivalent to 1.8 ppm adjusted for continuous exposure (9.8 ppm × 6/24 × 5/7).

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF = 30.

The critical effect is liver toxicity (fatty change) in rats with a $BMCL_{10HEC}$ of 6.9 mg/m^3. Although this minimal effect might not be considered adverse—as there is no evidence of a functional change in the liver in rats exposed at this level and glutathione levels are not reduced—it is used to derive the RfC, because limiting exposure to this level will protect the liver from more serious damage (fatty liver or necrosis) that could compromise liver function. The total UF is 30 and the modifying factor is 1. A UF of 3 is used for interspecies extrapolation because a dosimetric adjustment was used.

There is some suggestion that the effects in the kidney of male mice might occur at an exposure lower than the level that produced effects in the liver of rats. Thus, there is some uncertainty as to whether the most sensitive species has been used to derive the RfC. A UF of 10 is used for intraspecies variability because there were no applicable data to depart from the default value. Derivation of the RfD from the $BMDL_{10}$ for the minimum fatty change in the liver does not require an effect-level extrapolation. This conclusion is based on the minimal nature of the fatty change and its questionable biological significance because of the absence of any observable functional deficit in the liver. Although the animals were exposed for 18 months, rather than the full lifetime, there was no indication that the fatty change was progressing. In contrast, the evidence indicated the fatty change was decreasing in incidence with continued exposure. EPA, therefore, did not apply a subchronic-to-chronic extrapolation factor. A database UF is not applied because the database is considered complete.

A number of long-term bioassays in rodents by the oral or inhalation route show that liver toxicity is the critical effect. There is no chronic bioassay in a nonrodent mammal. However, there are 90-day bioassays in several species (rats, mice, dogs, guinea pigs, rabbits, and monkeys) that suggest similar exposure-response relationships across species. Therefore, the lack of a chronic bioassay in a nonrodent mammal is not considered a data gap. There are no focused studies on neurotoxicity, but there are no indications from chronic, reproductive, and developmental bioassays in rats and mice by oral or inhalation exposure that neurotoxicity is an important toxic endpoint. No long-term studies have evaluated immunotoxicity in laboratory animals by any route of exposure. The existing bioassays, however, provide no suggestion that immunotoxicity is a critical effect. EPA does not consider these data gaps compelling enough to require application of a database UF.

MF = 1.

I.B.4. Additional Studies/Comments (Inhalation RfC)

Prendergast et al. (1967) evaluated the toxicity of 1,1-DCE in Long-Evans or Sprague-Dawley rats, Hartley guinea pigs, beagle dogs, New Zealand albino rabbits, and squirrel monkeys. The test animals (15 rats/group, 15 guinea pigs/group, 3 rabbits/group, 2 dogs/group, or 3 or 9 monkeys/group) were exposed continuously for 90 days to 1,1-DCE vapors at 189 ± 6.2, 101 ± 4.4, 61 ± 5.7, or 20 ± 2.1 mg/m^3. The concurrent controls included 304 rats, 314 guinea pigs, 48 rabbits, 34 dogs, and 57 monkeys. The age of the animals was not specified. The exposed animals were evaluated for visible signs of toxicity, mortality, and hematologic, biochemical, pathologic, and body weight changes. There was apparent exposure-related mortality in guinea pigs and monkeys. In guinea pigs the mortality was 2/314, 2/45, 3/15, 3/15, and 7/15 and in monkeys it was 1/57, 1/21, 0/9, 2/3, and 3/9 in the 0, 20, 61, 101, or 189 mg/m^3 exposure groups, respectively. The guinea pigs died between days 3 to 9 of exposure; the monkeys died

on days 26, 39, 47, 60, and 64 of exposure. There were no visible signs of toxicity in any surviving animals.

At the highest exposure in monkeys, but not in guinea pigs, there was some histopathological evidence of liver damage (see below). In guinea pigs at the highest exposure, there was an increase in serum glutamic-pyruvic transaminase and liver alkaline transaminase (see below). Because visible signs of toxicity were not observed and only minor liver damage is apparent in this study, the mortality data in guinea pigs and monkeys are given no weight.

Varying degrees of growth depression were found in all exposures, but were significant in all species only at 189 mg/m^3. The test animals exhibited no significant hematologic alterations, and serum urea nitrogen levels were within control limits in all exposures in which determinations were made. Significant elevations of serum glutamic-pyruvic transaminase and liver alkaline phosphatase activities were found in rats (a threefold and 1.75-fold increase, respectively) and guinea pigs (sevenfold and 2.4-fold increase, respectively) exposed to 189 mg/m^3 (other species not tested) but not at 20 mg/m^3 (enzyme levels at intermediate exposures not tested). Histopathological examination of liver from dogs, monkeys, and rats revealed damage at 189 mg/m^3 (other species not examined). The effects observed included fatty metamorphosis, focal necrosis, hemosiderosis deposition, lymphocytic infiltration, bile duct proliferation, and fibrosis. The changes were most severe in dogs. Sections of kidney from all rats showed nuclear hypertrophy of the tubular epithelium. No detectable liver or kidney damage was observed in any species exposed to 101 mg/m^3 or less. The NOAEL in this study is 101 mg/m^3 (equivalent to 25 ppm); the LOAEL is 189 mg/m^3 (equivalent to 47 ppm).

Short et al. (1977) evaluated developmental toxicity of 1,1-DCE administered by inhalation to pregnant CD-1 rats (Charles River). Animals were exposed to 0 (58 animals), 15 ppm (18 animals), 57 ppm (20 animals), 300 ppm (18 animals), or 449 ppm (18 animals) for 22-23 hours/day on gestation days 6 to 16. Dams were sacrificed on gestation day 20. Maternal toxicity was exhibited as severe maternal weight loss (> 28 grams/dam) at 15 ppm and higher and by maternal mortality at 57 ppm and higher. There was a statistically significant increase in the mean number of fetuses per litter with hydrocephalus at 15 and 57 ppm, with malaligned sternebrae at 15 ppm, and with unossified sternebrae at 57 ppm. Because of the severe maternal toxicity at 15 ppm (60 mg/m^3) and higher, this study is not useful for evaluating developmental toxicity.

Short et al. (1977) evaluated developmental toxicity of 1,1-DCE administered by inhalation to pregnant CD-1 mice (Charles River). Animals were exposed to 0 (65 animals), 15 ppm (23 animals), 30 ppm (19 animals), 57 ppm (21 animals), 144 ppm (18 animals), or 300 ppm (15 animals) for 22–23 hrs/day on gestation days 6 to 16. Dams were sacrificed on gestation day 17. At 30 ppm and higher there was maternal toxicity, as shown by statistically significant

decreases in maternal weight gain. At 144 and 300 ppm there was an increase in maternal mortality. At 30 ppm and higher there was severe fetal toxicity, with complete early resorption of the litters. At 15 ppm there was no evidence of maternal toxicity, no decrease in fetal body weight, and no decrease in the percentage of viable fetuses. At 15 ppm, there was an increase in the mean number of fetuses per litter with hydrocephalus, occluded nasal passages, micropthalmia, cleft palate, small liver, and hydronephrosis. None of these changes, however, were statistically significant when compared to controls. Also at 15 ppm there was a statistically significant increase in the mean number of fetuses with an unossified incus and with incompletely ossified sternebrae. This study provides evidence of fetal toxicity at 15 ppm, the only exposure without significant maternal toxicity. In this study the LOAEL for developmental toxicity is 15 ppm (60 mg/m^3), the lowest exposure tested.

Short et al. (1977) also evaluated developmental neurotoxicity of 1,1-DCE administered by inhalation to CD-1 rats (Charles River). Pregnant rats were exposed to 0 (24 animals), 56 ppm (20 animals), or 283 ppm (19 animals) for 22–23 hrs/day on gestation days 8 to 20. Maternal toxicity was observed at both exposures, as shown by weight loss of 7 g per dam at 56 ppm and 15 grams per dam at 283 ppm. There was complete resorption of three litters at 283 ppm. There was a statistically significant decrease in average pup weight as compared to control at both exposures on post-natal day 1. The difference in pup weight between control and exposed groups decreased with time and disappeared by postnatal day 21. There was no evidence of developmental neurotoxicity at either exposure in pups tested at various times from postnatal day 1 to day 21 in a battery of behavioral tasks, including surface righting, pivoting, auditory startle, bar holding, righting in air, visual placing, swimming ability, physical maturation, and activity. This study shows evidence of maternal and fetal toxicity at both exposures but no evidence of developmental neurotoxicity at either exposure. Accordingly, the NOAEL for developmental neurotoxicity in this study is 283 ppm (1124 mg/m^3), the highest exposure tested.

Murray et al. (1979) evaluated developmental toxicity of 1,1-DCE administered by inhalation to pregnant Sprague-Dawley rats (body weight 250 g). Animals were exposed to 0 (20 or 47 animals), 20 ppm (44 animals), 80 ppm (30 animals), or 160 ppm (30 animals) for 7 hrs/day on gestation days 6–15. At 20 ppm there was no maternal toxicity and no effect on embryonal or fetal development. At 80 and 160 ppm, there was toxicity to the dams (statistically significant depression in weight gain at gestation day 6–9, more severe at 160 ppm). At 80 and 160 ppm, there were also statistically significant increased incidences of wavy ribs and delayed ossification of the skull, which are regarded as embryotoxic effects. Both effects were more severe at 160 ppm. No teratogenic effects were seen at any exposure. The NOAEL for developmental toxicity in this study is 20 ppm; the LOAEL is 80 ppm. Under the Guidelines for Developmental Toxicity (U.S. EPA, 1994), these values are not adjusted to continuous exposure.

Murray et al. (1979) evaluated the developmental toxicity of 1,1-DCE administered by inhalation to New Zealand white rabbits (body weight 3.4–4.7 kg). Animals were exposed to 0 (16 animals), 80 ppm (22 animals), or 160 ppm (18 animals) for 7 hrs/day on gestation days 6–18. At 80 ppm there was no maternal toxicity and no effect on embryonal or fetal development. Toxicity to both the dams and their developing embryos was observed at 160 ppm. There was a marked increase in the incidence of resorptions per litter (0.3 ± 0.6 vs. 2.7 ± 3.9). A significant change occurred in the incidence of several minor skeletal variations in their offspring, including an increase in the occurrence of 13 pairs of ribs and a increased incidence of delayed ossification of the fifth sternebra (data not reported). No teratogenic effects were seen at any exposure. The NOAEL for developmental toxicity in this study is 80 ppm; the LOAEL is 160 ppm. Under the Guidelines for Developmental Toxicity (U.S. EPA, 1991), these values are not adjusted to continuous exposure.

See also studies showing liver toxicity and the reproductive and developmental studies summarized in the RfD section.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.B.5. Confidence in the Inhalation RfC

Study — High
Database — Medium
RfC — Medium

The overall confidence in this RfC assessment is medium. The principal study (Quast, 1986) was a well-conducted inhalation bioassay with adequate numbers of animals and appropriate evaluation of a wide variety of endpoints. The result is supported by several other 90-day inhalation studies in a variety of species (Prendergast et al. 1967). These inhalation studies are supported by an additional bioassay in rats and a 90-day study in dogs, both by the oral route of exposure showing NOAELs (see the summary of these studies in the RfD section). There is no evidence from the inhalation bioassays that the respiratory tract is a target tissue of low-dose exposure. Several studies by the inhalation route of exposure show that developmental toxicity is not a critical effect. A three-generation reproductive study by the oral route of exposure showed no significant reproductive effects, and several bioassays showed no developmental toxicity. However, one developmental study by the oral route of exposure shows variations in cardiac morphology that appear to have little or no physiological consequence. There are no focused studies on neurotoxicity, but no indication from chronic, reproductive, and developmental bioassays in rats and mice by oral or inhalation exposure that neurotoxicity is an important toxic endpoint. No long-term studies have evaluated

immunotoxicity in laboratory animals by any route of exposure. The existing bioassays, however, provide no suggestion that immunotoxicity is a critical effect. Accordingly, the database is given medium confidence, but no additional UF is considered necessary.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — Toxicological Review of 1,1-Dichloroethylene (2002)

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to the Toxicological Review of 1,1-Dichloroethylene. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF).***

Other EPA Documentation — None.

Agency Consensus Date — 06/07/2002

A comprehensive review of toxicological studies published through May 2005 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing RfC for 1,1-Dichloroethylene (1,1-DCE) and a change in the RfC is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (email address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — 1,1-Dichloroethylene (1,1-DCE)
CASRN — 75-35-4
Last Revised — 08/13/2002

Section II provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per µg/L drinking water or risk per µg/cu.m air breathed. The third form in which risk is presented is a concentration of the chemical in drinking water or air associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

This IRIS Summary replaces the summary dated 03/31/1987. The assessment of carcinogenicity by the inhalation route of exposure under the draft revised guidelines for carcinogen risk assessment (U.S. EPA, 1999) differs from the previous EPA evaluation (U.S. EPA, 1985a, b). EPA's previous evaluation considered the incidence of kidney adenocarcinomas (Maltoni et al., 1985) as providing sufficient evidence of carcinogenicity to justify deriving an inhalation unit risk for quantifying the potential human cancer risk. As noted in Sections 4.4.3 and 4.6 of the Toxicological Review of 1,1-Dichloroethylene, the new data suggesting that the kidney adenocarcinomas could be a sex- and species-specific response reduce the weight-of-evidence for carcinogenicity by the inhalation route of exposure. Accordingly, the present evaluation does not derive an inhalation unit risk. This conclusion is consistent with the evaluation by the International Agency for Research on Cancer (IARC) (IARC, 1999).

In addition, this assessment of carcinogenicity by the oral route of exposure under the draft revised guidelines for carcinogen risk assessment (U.S. EPA, 1999) differs from the previous EPA evaluation (U.S. EPA, 1985a, b). The previous EPA evaluation derived an oral slope factor from the highest of four slope factors calculated from two studies (NTP, 1982; Quast et al., 1983) that did not show statistically significant increases in tumor incidence attributable to

oral exposure. The highest slope factor was based on the adrenal pheochromocytomas in male rats (NTP, 1982). Under the 1999 draft revised guidelines for carcinogen risk assessment, EPA emphasizes the importance of using data that show a statistically significant increase in tumor incidence for calculating a slope factor. As there is no statistically or biologically significant increase in tumor incidence at any site in the relevant oral bioassays, the present evaluation characterizes the weight-of-evidence as *inadequate* and accordingly does not derive an oral slope factor. This conclusion is consistent with the evaluation by IARC (1999).

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Under the 1986 cancer guidelines (U.S. EPA, 1986), 1,1-DCE is assigned to Group C, possible human carcinogen.

Under the draft revised guidelines for carcinogen risk assessment (U.S. EPA, 1999), EPA concludes 1,1-DCE exhibits *suggestive evidence* of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure in studies in rodents. Male mice developed kidney tumors at one exposure in a lifetime bioassay, a finding tempered by the absence of similar results in female mice or male or female rats and by the enzymatic differences (i.e., CYP2E1) between male mice and female mice, male and female rats, and human kidney cells. Limited evidence of genotoxicity has been reported in bacterial systems with metabolic activation. The data for 1,1-DCE are *inadequate* for an assessment of human carcinogenic potential by the oral route, based on the absence of statistically or biologically significant tumors in limited bioassays in rats and mice balanced against the suggestive evidence in male mice in a single bioassay by inhalation and the limited evidence of genotoxicity. The human epidemiological results on the carcinogenicity of 1,1-DCE are too limited to draw useful conclusions. EPA concludes that the results of kidney tumors in one sex and one exposure in a single species of rodents are too limited to support an exposure-response assessment.

Bioassays for cancer by the oral route of exposure have been conducted in rats (Maltoni et al., 1985; NTP, 1982; Ponomarkov and Tomatis, 1980; Quast et al., 1983) mice (NTP, 1982), and trout (Hendricks et al., 1995). Some of these bioassays were conducted at an exposure below the maximum tolerated dose. The bioassay conducted by Maltoni et al. (1985) exposed the animals for only 1 year. The bioassay conducted in rats by Quast et al. (1983) and the bioassay conducted in mice by NTP (1982) were well conducted and both showed some toxicity in the liver at the highest exposure. Neither of these bioassays provides any significant evidence that 1,1-DCE is a carcinogen by the oral route of exposure. The genotoxicity studies are incomplete, but most studies in mammalian cells indicate a lack of genotoxicity.

Bioassays for cancer by the inhalation route of exposure have been conducted in rats (Lee et al., 1977, 1978; Viola and Caputo, 1977; Hong et al., 1981; Maltoni et al., 1985; Quast et al., 1986; Cotti et al., 1988), mice (Lee et al., 1977, 1978; Hong et al., 1981; Maltoni et al., 1985), and hamsters (Maltoni et al., 1985). None of these bioassays was conducted by a protocol that meets current standards. The major defects in most of these bioassays include exposure of the animals for 1 year and exposure at less than the maximum tolerated dose. The only bioassay that showed some evidence of carcinogenicity was the study in Swiss-Webster mice (Maltoni et al., 1985). This study was conducted at or near the maximum tolerated dose, as animals exposed at 50 ppm died after a few exposures. Although the animals were exposed for only 1 year and then observed until natural death, this study showed an increased incidence of kidney adenocarcinomas in male mice at 25 ppm but not at 10 ppm. The incidence of mammary carcinomas in female mice and pulmonary adenomas in male and female mice did not increase with increased exposure. The responses were actually lower at 25 ppm than at 10 ppm, but survival and other toxicities were comparable.

There is evidence that the induction of kidney adenocarcinomas is a sex- and species-specific response related to the expression of CYP2E1 in the kidney of male mice (Speerschneider and Dekant, 1995; Amet et al., 1997; Cummings et al., 2000). The data presented by these researchers, however, are not sufficient to justify a conclusion that the kidney tumors in male mice have no relevance for a human health risk assessment. This conclusion is made with the knowledge that compounds similar in structure to 1,1-DCE (e.g., tetrachloroethylene, trichloroethylene, and 1,2-dichloroethylene) produce varying degrees of kidney tumors in animal bioassays.

The genotoxicity studies are incomplete, but most studies in mammalian cells indicate a lack of genotoxicity. Accordingly, EPA concludes that the data on the increased incidence of kidney adenocarcinomas in male mice (Maltoni et al., 1985) provide *suggestive evidence* of carcinogenicity by the inhalation route of exposure. EPA also concludes, considering the evidence of a potential sex- and species-specific response, that the results of this bioassay showing an increase in tumors in one sex and one exposure in a single species of rodents are too limited to support an exposure-response assessment.

1,1-DCE causes gene mutations in microorganisms in the presence of an exogenous activation system. Although most tests with mammalian cells show no evidence of genetic toxicity, the test battery is incomplete because it lacks an in vivo test for chromosomal damage in the mouse lymphoma system.

There are a number of uncertainties in the assessment of the carcinogenicity of 1,1-DCE. As noted above, many of the bioassays by the inhalation route of exposure were not conducted at the maximum tolerated dose or for the full lifetime of the animals. EPA has acknowledged this

uncertainty in the weight-of-evidence classification. In addition, our knowledge of the metabolic pathways for 1,1-DCE in the human is incomplete. Although it is likely that the initial oxidation of 1,1-DCE in humans occurs via CYP2E1, there could be other CYP isoforms that could activate 1,1-DCE. Thus, there is some potential for a species-specific carcinogenic response in humans similar to the apparent sex- and species-specific response observed by Maltoni et al. (1985) in the kidney of male mice.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. Human Carcinogenicity Data

Ott et al. (1976) investigated the health records of 138 employees occupationally exposed to 1,1-DCE in processes not involving vinyl chloride. The individuals included in the study had worked in experimental or pilot plant polymerization operations, in a monomer production process as tankcar loaders, or in a production plant that manufactured a monofilament fiber. Time-weighted-average concentrations (8 hours) of 1,1-DCE in the workplace were estimated from job descriptions and the results of industrial hygiene sampling. The subjects were grouped into three exposure categories: less than 10 ppm, 10–;24 ppm, and greater than 25 ppm. The researchers estimated career exposure by taking into account average duration of employment. Results of the most recent health inventory for individuals in the cohort were compared with findings of matched controls. Analysis of mortalities among the cohort indicated no statistically significant findings. Overall, there were no significant differences between the exposed cohort and the controls in hematology and clinical chemistry parameters. Based on power considerations, this study is inadequate for assessing cancer risk in humans.

II.A.3. Animal Carcinogenicity Data

Oral

Rats. Ponomarkov and Tomatis (1980) treated 24 female BD IV rats by gavage with 1,1-DCE dissolved in olive oil (150 mg/kg body weight) on the 17th day of gestation. Their offspring (81 males and 80 females) were treated weekly with 1,1-DCE at 50 mg/kg body weight by gavage from the time of weaning for 120 weeks or until the animal was moribund. A control group of offspring (49 males and 47 females) received only olive oil. Liver and meningeal tumors were more frequently observed in treated than in untreated animals, but the difference

was not statistically significant. The total number of tumor-bearing animals was not statistically different between treated and untreated animals.

NTP (1982) conducted chronic toxicity and carcinogenicity studies of 1,1-DCE for 104 weeks in male and female F344 rats (200 of each sex, 9 weeks old) by gavage in corn oil at 0, 1, or 5 mg/kg-day. No significant differences were observed in survival, clinical signs, or body weight as compared with controls for any group, suggesting that the maximum tolerated dose was not achieved. All of the increased tumor incidences that were statistically significant by the Fisher exact test or by the Cochran-Armitage linear trend test (adrenal pheochromocytoma, pancreatic islet cell adenoma or carcinoma, and subcutaneous fibroma in males and pituitary adenoma in females) were not significant when life-table analyses were used. This difference occurs because life table analyses adjust for intercurrent mortality, and thus minimize the impact of animals dying before the onset of late-appearing tumor. This adjustment was particularly critical for the analyses of tumor incidences in male rats, because 12 controls and 10 low-dose animals were accidentally killed during week 82 of the study. Accordingly, NTP concluded that no increased incidence of tumors was found at any site in these bioassays. Under the conditions of this bioassay, 1,1-DCE administered by gavage was not carcinogenic for F344 rats.

Quast et al. (1983) conducted a 2-year chronic toxicity and carcinogenicity study of 1,1-DCE in Sprague-Dawley rats (6–7 weeks old). There were 80 of each sex rats in the control group and 48 rats of each sex in each exposed group. The 1,1-DCE was incorporated in the drinking water of the rats at nominal concentrations of 0, 50, 100, or 200 ppm. The time-weighted-average exposure over the 2-year period was 7, 10, or 20 mg/kg-day for males and 9, 14, or 30 mg/kg-day for females. No significant differences were found among the groups in appearance and demeanor, mortality, body weight, food consumption, water consumption, hematology, urinalysis, clinical chemistry determinations, organ weights, or organ-to-body-weight ratios. The only treatment-related effect observed in rats was a minimal amount of midzonal fatty change and hepatocellular swelling. No exposure-related neoplastic changes occurred at any exposure.

Maltoni et al. (1985) conducted a carcinogenicity and toxicity study of 1,1-DCE in Sprague-Dawley rats. Animals (9 or 10 weeks old) were exposed by gavage in olive oil to 0, 0.5, 5, 10, or 20 mg/kg, 4–5 days/wk for 52 weeks. There were two control groups, one with 150 animals (75 of each sex) and the other with 200 animals (100 of each sex). The exposed groups had 100 animals (50 of each sex). Following the 52-week exposure, animals were observed until spontaneous death (total duration 147 weeks). Body weight was measured every 2 weeks during the 52 week exposure and every 8 weeks thereafter. Full necropsy and histopathological examination were performed. No biologically significant changes were

observed in mortality or body weight. There were no biologically significant noncancer or cancer effects in any organ.

Mice. NTP (1982) conducted 104 weeks of chronic toxicity and carcinogenicity studies on 1,1-DCE in male and female B6C3F_1 mice (200 of each sex, 9 weeks old) by gavage in corn oil at 0, 2, or 10 mg/kg. No significant differences in survival, clinical signs, or body weight were in any group, suggesting that the maximum tolerated dose was not achieved. The only observed significant increase (p<0.05) in tumor incidence occurred in low-dose females for lymphoma (2/48, 9/49, 6/50) and for lymphoma or leukemia (7/48, 15/49, 7/50). These increases were not considered to be related to 1,1-DCE administration because similar effects were not found in the high-dose females or in males. Under the conditions of this bioassay, 1,1-DCE administered by gavage was not carcinogenic for B6C3F_1 mice.

Trout. Hendricks et al. (1995) conducted an 18-month carcinogenicity study of 1,1-DCE in rainbow trout (8 weeks old) at 4 mg/kg-day. Tissues examined for neoplasms included liver, kidney, spleen, gill, gonads, thymus, thyroid, heart, stomach, pyloric ceca, duodenum, rectum, pancreas, and swimbladder. 1,1-DCE produced no neoplasms and no increase in liver weight. There was no evidence of any other chronic toxic effects.

Inhalation

Rats. Lee et al. (1977, 1978) exposed 2-month-old Charles River CD rats (36 males and 35 females) to 55 ppm 1,1-DCE for 6 hrs/day, 5 days/wk, for 12 months. No significant changes were observed in survival, body weight, hematology, clinical blood chemistry, pulmonary macrophage count, cytogenetic analysis of bone marrow, x-ray examination of extremities, collagen contents in liver and lung, serum aminolevulinic acid (ALA) synthetase, urinary ALA level, and serum alpha-fetoprotein. A mild to markedly severe focal, disseminated vacuolization was observed in livers of most of the rats. No hemangiosarcomas were found in the liver or lung. The incidence of hemangiosarcomas in mesenteric lymph node or subcutaneous tissue was 2/36 in males and 0/35 in females.

Viola and Caputo (1977) exposed 2-month-old Sprague-Dawley rats (30 males and 30 females per group) to 0, 75 ppm, or 100 ppm 1,1-DCE for 22–24 months (hours of daily exposure not reported). The incidence of tumors observed at necropsy (males and females combined) was 15/60; 10/36 and 20/60 at 0, 75 ppm, and 100 ppm, respectively. The tumors observed were classified as subcutaneous fibromas or abdominal lymphomas. The histopathological results from this study have not been published. No other data are reported for this study.

Viola and Caputo (1977) also exposed 2-month-old albino Wistar rats (37 males and 37 females) to 1,1-DCE for 4 hrs/day, 5 days/wk, for 12 months. The exposure was at 200 ppm

for the first 6 months and at 100 ppm for the rest of the study. A control group of 60 animals received air only. The incidence of tumors (described as reticulum cell sarcomas of a nonsincytial type, primarily in the abdominal cavity) was 15/60 and 17/74 in control and exposed groups, respectively. No other data are reported from this study.

Hong et al. (1981) evaluated mortality and tumor incidence in rats exposed to 1,1-DCE. Groups of 2-month-old CD rats of both sexes were exposed to 0 or 55 ppm 1,1-DCE 6 hrs/day, 4 days/wk for 1 month (four of each sex), 3 months (four of each sex), 6 months (four of each sex), or 10 months (16 of each sex). Following exposure, all animals were observed for an additional 12 months. In rats exposed for 10 months, there was an increase in mortality following the 12-month observation period (67% in exposed, 41% in controls). There was no significant increase in tumors at any site for any exposure period.

Maltoni et al. (1985) conducted a carcinogenicity and toxicity study of 1,1-DCE in Sprague-Dawley rats. Animals (16 weeks old) were exposed by inhalation to 0, 10, 25, 50, 100, or 150 ppm for 4 hrs/day, 4–5 days/wk for 52 weeks. The control group had 200 animals (100 of each sex); the 10, 25, 50, and 100 ppm groups had 60 animals (30 of each sex), and the 150 ppm group had 120 animals (60 of each sex). Following the 52-week exposure, animals were observed until spontaneous death (total duration 137 weeks). Body weight was measured every 2 weeks during the 52-week exposure and every 8 weeks thereafter. Full necropsy and histopathological examination were performed. No biologically significant changes were seen in mortality or body weight. There were no biologically significant noncancer effects in any organ in either sex and no increase in tumors in males at any site. There was a statistically significant increase ($p<0.05$) in each treatment group as compared with controls in the number of females with mammary fibromas and fibroadenomas. The incidence was 44/56 (78.6%), 24/24 (100%), 20/20 (100%), 21/22 (95.4%), 21/23 (91.3%), and 38/43 (88.4%) in the control, 10, 25, 50, 100, and 150 ppm groups, respectively. The latency time and the number of tumors per tumor-bearing animal were similar among all groups. The incidence of mammary carcinoma in exposed groups was consistently less than that of controls. The incidence was 16/56 (28.6%), 5/24 (20.8%), 4/20 (20%), 1/21 (4.5%), 3/21 (13.0%), and 9/38 (20.9%) in the control, 10, 25, 50, 100, and 150 ppm groups, respectively.

Quast et al. (1986) and Rampy et al. (1977) reported results from studies that exposed male and female Sprague-Dawley rats (Spartan substrain, 86 animals/group) to 1,1-DCE by inhalation 6 hrs/day, 5 days/wk, for up to 18 months. Interim sacrifices occurred at 1, 6, and 12 months. Rats were exposed to 1,1-DCE concentrations of 10 ppm and 40 ppm for the first 5 weeks of the study. Based on the absence of observable treatment-related effects among rats sacrificed after 1 month of exposure, the concentrations were increased to 25 and 75 ppm. Exposures were continued at these concentrations through the 18th month of the study. The surviving animals were then held without exposure to 1,1-DCE until 24 months. Cytogenetic

evaluations were performed on a separate group of animals (four per sex) exposed to 0, 25, or 75 ppm for 6 months. There were no exposure-related changes in mortality, appearance and demeanor, body weight, clinical chemistry determinations, hematologic evaluations, urinalysis, or cytogenetic evaluation of bone marrow preparations. Although the incidences of several tumors and/or tumor types were found to be statistically increased or decreased as compared with controls, none of these differences were judged to be attributable to 1,1-DCE. The tumor incidence data for both control and treated rats in this study were comparable to historical control data for the Sprague-Dawley rats (Spartan substrain) used by this laboratory for several studies of similar design and duration.

Cotti et al. (1988) exposed Sprague-Dawley rats to 1,1-DCE at 0 or 100 ppm for 4–7 hrs/day, 5 days/wk. The exposures were to 13-week-old females for 104 weeks (60 control animals and 54 exposed animals) and to 12-day embryos for 15 or 104 weeks (158 males and 149 females as controls, 60 males and 60 females exposed for 15 weeks, and 62 males and 61 females exposed for 104 weeks). Animals were observed until spontaneous death. In males and females exposed for 104 weeks and in male offspring exposed for 15 weeks, a slight decrease in body weight (data not reported) was observed. An increased percentage of rats bearing malignant tumors (30.9% vs. 17.3 % in controls) and an increased number of malignant tumors per 100 animals (34.1% vs. 17.9% in controls) were observed in male and female offspring exposed for 104 weeks (statistical analysis not presented). An increase in leukemia in offspring, which appeared to be related to length of exposure (4.2% for controls, and 8.3% and 11.4% for exposure of 15 and 104 weeks, respectively), was also observed. Tumors at other sites (total benign and malignant tumors, total benign and malignant mammary tumors, malignant mammary tumors, and pheochromocytomas) showed no change or a decreased incidence. Data from this study are also reported in Maltoni et al. (1985).

Mice. Lee et al. (1977, 1978) exposed 2-month-old CD-1 mice (18 males and 18 females) to 0 or 55 ppm 1,1-DCE for 6 hrs/day, 5 days/wk, for up to 12 months. No deaths occurred in the control or exposed groups. Weight gain was comparable between groups. There was no change in hematology, clinical blood chemistry, cytogenetic analysis of bone marrow, x-ray examination of extremities, or serum alpha-fetoprotein. The livers showed no increase in mitotic figures using ^{14}C-thymidine incorporation. The incidence of bronchioalveolar adenoma (males and females combined) for 1–3 months exposure, 4–6 months exposure, 7–9 months exposure, and 10–12 months exposure was 0/24, 1/8, 2/10, and 3/28, respectively. The incidence of hemangiosarcomas in liver (males and females combined) for 6 months exposure, 7–9 months exposure, and 10–12 months exposure was 0/16, 1/10, and 2/28, respectively. No hemangiosarcomas were found in other tissues.

Hong et al. (1981) evaluated mortality and tumor incidence rates in mice exposed to 1,1-DCE. Groups of 2-month-old albino CD-1 mice of both sexes were exposed to 0 or 55 ppm for 6

hrs/day, 4 days/wk, for 1 month (8 of each sex), 3 months (8 of each sex), or 6 months (12 of each sex). Following exposure, all animals were observed for an additional 12 months. In mice exposed for 6 months, there was a slight increase in mortality following the 12-month observation period (46% in exposed, 39% in controls). There was no significant increase in tumors at any site for any exposure period.

Maltoni et al. (1985) conducted a carcinogenicity and toxicity study of 1,1-DCE in Swiss mice. Animals (9 or 16 weeks old) were exposed by inhalation to 0, 10, or 25 ppm. Animals were exposed for 4 hrs/day, 4–5 days/wk, for 52 weeks. There were two control groups, one with 180 animals (90 of each sex) and the other with 200 animals (100 of each sex). The 10-ppm group had 60 animals (30 of each sex). Two groups were exposed to 25 ppm: one with 60 animals (30 of each sex) and the other with 240 animals (120 of each sex). Following the 52-week exposure, animals were observed until spontaneous death (total duration 126 weeks). Body weight was measured every 2 weeks during the 52-week exposure and every 8 weeks thereafter. Full necropsy and histopathological examination were performed.

No biologically significant changes occurred in body weight. The exposed animals had a somewhat higher survival than controls. There was a statistically significant increase ($p<0.01$) as compared with controls in kidney adenocarcinomas in male mice at 25 ppm but not in male mice at 10 ppm or in female mice at either exposure. The incidence was 0/126 (0%), 0/25 (0%), and 28/119 (23.5%) in male mice in the combined controls, 10 ppm, and combined 25 ppm groups, respectively.

There was a statistically significant increase ($p<0.01$) as compared with controls in mammary carcinomas in female mice at both exposures, but there was no clear exposure-response relationship. The incidence was 3/185 (1.6%), 6/30 (20%), and 16/148 (11%) in females in the combined controls, 10 ppm, and combined 25 ppm groups, respectively. There was also a statistically significant increase ($p < 0.01$) compared with control in pulmonary adenomas in both exposed groups, but there was no clear exposure-response relationship. The incidence was 12/331 (3.6%), 14/58 (24.1%), and 41/288 (14.2%) in male and female mice combined in the combined controls, 10 ppm, and combined 25 ppm groups, respectively. There were no pulmonary carcinomas in any mice. The incidence data are reported as the number of tumor-bearing animals as compared with the number of animals alive when the first tumor was observed in that organ (kidney adenocarcinoma, 55 weeks; mammary tumor, 27 weeks; pulmonary adenoma, 36 weeks)

Hamsters. Maltoni et al. (1985) conducted a carcinogenicity and toxicity study of 1,1-DCE in Chinese hamsters. Animals (28 weeks old) were exposed by inhalation to 0 or 25 ppm. Animals were exposed for 4 hrs/day, 4-5 days/wk, for 52 weeks. The control group had 35 animals (18 male and 17 female); the 25 ppm group had 60 animals (30 of each sex).

Following the 52-week exposure, animals were observed until spontaneous death (total duration 157 weeks). Body weight was measured every 2 weeks during the 52-week exposure and every 8 weeks thereafter. Full necropsy and histopathological examination were performed. There were no biologically significant changes in mortality or body weight. No biologically significant noncancer or tumor effects were seen in any organ.

Dermal. Van Duuren et al. (1979) evaluated the carcinogenicity of 1,1-DCE in male and female noninbred Ha:ICR Swiss mice. Carcinogenicity was assessed in three types of tests: a dermal initiation-promotion assay, a repeated dermal application assay, and a subcutaneous injection assay. Vehicle, no-treatment, and positive control groups were included in the tests. In the initiation-promotion assay, 1,1-DCE was tested as a tumor-initiating agent with phorbol myristate acetate as the promoter. Thirty female mice were treated with 121 mg 1,1-DCE. A significant increase ($p<0.005$) was observed in skin papillomas (nine in eight mice). In the repeated dermal application assay, exposures of 40 and 121 mg/mouse were used. 1,1-DCE was applied to the back of the shaved animals (30 females/dose). No sarcomas were observed at the treatment site. Although 19 mice in the high-dose group and 12 in the low-dose group had lung tumors and 2 mice in the high-dose group had stomach tumors, the tumor incidence at both sites was not significantly different from that of controls (30 lung tumors and 5 stomach tumors). In the subcutaneous injection assay, the test animals were given weekly injections of 2 mg of 1,1-DCE. After 548 days on test, none of the injected animals developed sarcomas at the injection site. 1,1-DCE showed initiating activity in the two-stage carcinogenesis experiments but was inactive as a whole-mouse dermal carcinogen and after subcutaneous injection.

II.A.4. Supporting Data for Carcinogenicity

Reitz et al. (1980) investigated the ability of 1,1-DCE to cause DNA alkylation, DNA repair, and DNA replication in liver and kidney of rats and mice. Male Sprague-Dawley rats (body weight 200–250 g) and male CD-1 mice (body weight 18–20 g) were exposed by inhalation for 6 hours. There was only a minimal increase in DNA alkylation in both rats and mice at 50 ppm. Similarly, DNA repair in kidneys of mice was only minimally increased at 50 ppm. However, tissue damage (kidney nephrosis at 50 ppm, minimal effect at 10 ppm), an increase in DNA replication (sevenfold increase in ^{3}H-thymidine incorporation at 10 ppm, 25-fold increase at 50 ppm), and an increase in mitotic figures occurred. There was no observed histopathological damage or increased DNA replication in the liver of mice at 10 or 50 ppm. In rats there was a small increase in DNA replication (twofold increase in ^{3}H-thymidine incorporation) in the kidney but no increase in liver at 10 ppm.

1,1-DCE induced mutations in *Salmonella typhimurium* and *Escherichia coli* in the presence of an exogenous metabolic system. In *Saccharomyces cerevisiae,* 1,1-DCE induced reverse

mutation and mitotic gene conversion in vitro and in a host-mediated assay in mice. In a single study in *Saccharomyces cerevisiae*, it induced aneuploidy in the presence and absence of metabolic activation. In vitro, gene mutations were increased in mouse lymphoma cells but not in Chinese hamster lung cells with or without an exogenous metabolic system. In a single study, 1,1-DCE induced sister chromatid exchanges in Chinese hamster lung cells in the presence of an exogenous metabolic system but not in its absence. In single studies in vivo, 1,1-DCE did not induce micronuclei or chromosomal aberrations in bone marrow or in fetal erythrocytes of mice, nor dominant lethal mutations in mice or rats.

1,1-DCE causes gene mutations in microorganisms in the presence of an exogenous activation system. Although most tests with mammalian cells show no evidence of genetic toxicity, the test battery is incomplete because it lacks an in vivo assessment of chromosomal damage in the mouse lymphoma assay, a test that EPA considers to be an important component of a genotoxicity battery.

Speerschneider and Dekant (1995) investigated the metabolic basis for the species- and sex-specific nephrotoxicity and tumorigenicity of 1,1-DCE. In kidney microsomes from male mice, the rate of oxidation of 1,1-DCE depended on the hormonal status of the animals. Oxidation of 1,1-DCE was decreased by castration and restored when the castrate was supplemented with exogenous testosterone. In kidney microsomes from naive female mice, the rate of oxidation of 1,1-DCE was significantly lower than in males, but it could be increased by administration of exogenous testosterone. Using an antibody to rat liver CYP2E1, the researchers showed expression of a cross-reacting protein in male mouse kidney microsomes that was regulated by testosterone and correlated with the ability to oxidize 1,1-DCE and other substrates for CYP2E1 (e.g., p-nitrophenol and chlorozoxazone).

The researchers also showed that different strains of mice express different levels of CYP2E1, and the strains most sensitive to the effects of 1,1-DCE express greater levels of CYP2E1. Nephrotoxicity in Swiss-Webster mice after inhalation of 1,1-DCE was observed in males and in females treated with exogenous testosterone, but not in naive females. In kidney microsomes obtained from both sexes of rats and in six samples of human kidney from male donors, no p-nitrophenol oxidase activity was detected. Other research groups have also reported the absence of detectable CYP2E1 in human kidney tissue (Amet et al., 1997; Cummings et al., 2000).

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

Not applicable. 1,1-DCE shows equivocal evidence of carcinogenicity by the oral route of exposure.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

Not applicable. 1,1-DCE shows suggestive evidence of human carcinogenicity by the inhalation route of exposure. The weight-of-evidence, however, is not sufficient to justify deriving an inhalation unit risk.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Document — Toxicological Review of 1,1-Dichloroethylene (2002)

This assessment was peer reviewed by external scientists. Their comments have been evaluated carefully and incorporated in finalization of this IRIS Summary. A record of these comments is included as an appendix to Toxicological Review of 1,1-Dichloroethylene. ***To review this appendix, exit to the toxicological review, Appendix A, Summary of and Response to External Peer Review Comments (PDF)***.

Other EPA Documentation — This assessment replaces previous assessments (U.S. EPA, 1985a,b).

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Consensus Date — 06/07/2002

A comprehensive review of toxicological studies published through May 2005 was conducted. No new health effects data were identified that would be directly useful in the revision of the existing carcinogenicity assessment for 1,1-Dichloroethylene (1,1-DCE) and a change in the assessment is not warranted at this time. For more information, IRIS users may contact the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — 1,1-Dichloroethylene (DCE)
CASRN — 75-35-4

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VII. Revision History

Substance Name — 1,1-Dichloroethylene (DCE)
CASRN — 75-35-4
Primary Synonym — Vinylidene Chloride

Date	Section	Description
03/31/1987	II.	Carcinogenicity Section added
08/13/2002	I-VIII	New RfD, RfC, and cancer assessment
10/28/2003	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.
06/22/2005	I.A.6., I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been removed and replaced by comprehensive literature review conclusions.

VIII. Synonyms

Substance Name — 1,1-Dichloroethylene
CASRN — 75-35-4
Last Revised — 08/13/2002

- 1,1-Dichloroethene
- 1,1-DCE
- Dichloroethene, 1,1-
- Ethylene, 1,1-dichloro-
- NCI-C54262
- RCRA Waste Number U078
- Sconatex
- UN 1303
- Vinylidene chloride
- Vinylidene dichloride

- Vinylidine chloride
- Chlorure de vinylidene
- VDC