

## IRIS External Peer Review Draft

0039

1, 1-Dichloroethylene (1,1-DCE); CASRN 75-35-4; 00/00/00

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices, Regional Offices, and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

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

File First On-Line 01/30/1987

<u>Category (section)</u>	<u>Status</u>	<u>Last Revised</u>
Oral RfD Assessment (I.A.)	On-line	00/00/00
Inhalation RfC Assessment (I.B.)	On-line	00/00/00
Carcinogenicity Assessment (II.)	On-line	00/00/00

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## **I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS**

### **I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)**

1,1-Dichloroethylene (1,1-DCE)

CASRN -- 75-35-4

Last Revised -- 00/00/0000

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.



### I.A.1. ORAL RfD SUMMARY

This summary replaces the summary dated 04/01/1989.

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

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\*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-dichloroethylene (DCE) in Sprague-Dawley rats (6-7 weeks old). There were 80 rats of each sex 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. Rampy et al. (1977) also reported some of the data. Humiston et al. (1978) reported more detailed data. There were no significant differences 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 nonprotein sulfhydryl levels in the liver or the kidneys (Rampy et al., 1977). The only treatment-related effects observed were minimal hepatocellular midzonal fatty change and hepatocellular swelling. In the male rats at the termination of the study, there was an 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 only in the 200-ppm group. In female rats at the termination of the study, there was 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 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 in all groups). No exposure-related neoplastic changes occurred at any exposure. No significant hepatocellular necrosis was evident at any exposure. In addition, there was no change in liver weight, no change in clinical chemistry measurements diagnostic for liver damage, and no other indication of abnormal liver function. The minimal hepatocellular swelling is not considered 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 no-observed-adverse-effect level (NOAEL) in male rats is 10 mg/kg-day and the lowest-observed-adverse-effect level (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 benchmark dose analysis was conducted for the results in female rats. In female rats, the benchmark dose (BMD<sub>10</sub>) is 6.6 mg/kg-day and the benchmark dose limit (BMDL<sub>10</sub>) is 4.6 mg/kg-day. Any effect occurring at or below the BMDL<sub>10</sub> is not considered an adverse effect.

NTP (1982) 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. There were no significant differences in survival, clinical signs, or body weight 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 is 5 mg/kg-day (the highest exposure tested).

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

### I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100.

The critical effect is liver toxicity (fatty change) in rats with a BMDL<sub>10</sub> of 4.6 mg/kg-day. Individual uncertainty factors (UFs) of 10 each were used for interspecies extrapolation and intraspecies variability because there were no applicable data to depart from the default values. A LOAEL-to-NOAEL extrapolation was not used because EPA concludes that any effect occurring at or below the BMDL<sub>10</sub> is not adverse. A subchronic-to-chronic extrapolation factor was not applied because the study exposed the animals for 2 years. A database uncertainty factor 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) suggesting 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 or developmental neurotoxicity. There are no studies evaluating immunotoxicity. EPA does not consider these data gaps compelling enough to require application of a database uncertainty factor.

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 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).

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. There were no significant differences 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 male and 30 female), 50, 100, or 200 ppm (initially 10 male and 20 females at each exposure). The time-weighted 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, on average number of pups per litter, on average body weight of pups, or on pup survival at any exposure. Histopathological examination of tissues of rats exposed to 1,1-DCE in 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). These effects were observed in the 100 and 200 ppm groups in the F<sub>1</sub> generation and in all groups of the F<sub>2</sub> generation. 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 30 mg/kg-day (the highest exposure tested).

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 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 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). There was no increase in the incidence of cardiac changes 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 (11.6%); and 110 ppm, 24/184 (13%). This statistical analysis was based on total occurrence of affected fetuses. The author (Dawson, personal communication, January 24, 2001) provided additional data to clarify the number of affected litters and the number of fetuses per litter affected and to resolve typographical errors in the exposure information for each group. The number of affected litters was 5/21 (24%), 8/11 (73%), and 13/17 (76%); the mean number of affected fetuses per litter was 1.4 (12% 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); and 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.

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 3% rate of alterations in control fetuses suggests a high background incidence. The authors report that examinations were done blind to the treatment group, so the data are presumed not affected by observer bias.

There is no demonstrated exposure-response relationship in this study (a 900-fold increase in exposure did not produce a significant increase in response in any measure of effect) and the cardiac changes reported do not appear to be related to altered growth and survival. These results must be considered in light of other data from studies with longer and higher exposures that showed a lack of effect on average number of pups per litter, on average body weight of pups, and on pup survival in a three-generation study (Nitschke et al., 1983) and no reported effects in a prenatal developmental toxicity study (Murray et al., 1979). Thus, the changes reported by Dawson et al. (1993) must be assumed at this point to represent variations in cardiac morphology that have little or no physiological consequence.

#### 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 little or no physiological consequence. There are no adequate studies focusing on neurotoxicity or immunotoxicity by any route of exposure. The existing bioassays, however, provide no suggestion that neurotoxicity or immunotoxicity are critical effects. Accordingly, the database is given a medium confidence, but no additional uncertainty factor is considered necessary.

#### **\_\_I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD**

Source Document -- Toxicological Review of 1,1-Dichloroethylene

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.

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

Agency Consensus Date -- \_\_/\_\_/\_\_

#### **\_\_I.A.7. EPA CONTACTS (ORAL RfD)**

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (Internet address).

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#### **\_\_I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)**

1,1-Dichloroethylene (1,1-DCE)  
CASRN -- 75-35-4  
Last Revised -- 00/00/0000

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.

### I.B.1. INHALATION RfC SUMMARY

<u>Critical Effect</u>	<u>Experimental Doses*</u>	<u>UF</u>	<u>MF</u>	<u>RfC</u>
Liver toxicity (fatty change)	NOAEL <sub>HEC</sub> : none LOAEL <sub>HEC</sub> : 17.7 mg/m <sup>3</sup>	30	1	2E-1 mg/m <sup>3</sup>
Rat chronic inhalation study Quast et al., 1986	BMCL <sub>10HEC</sub> : 6.9 mg/m <sup>3</sup>			

\*Conversion Factors and Assumptions -- The LOAEL from the chronic bioassay is 25 ppm where the exposure was for 6 hours/day, 5 days/week. The conversion factor is 1 ppm = 3.97 mg/m<sup>3</sup>. The human equivalent concentration (HEC) is 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 data are available on the blood:gas coefficient in humans. Accordingly the default value of 1 is used for the ratio of these coefficients.

$$\text{LOAEL}_{\text{HEC}} = \text{LOAEL}_{\text{adj}} \times (\text{H}_{\text{b/g}})_{\text{A}} / (\text{H}_{\text{b/g}})_{\text{H}} = 25 \text{ ppm} \times 6/24 \times 5/7 \times 1 \times 3.97 = 17.7 \text{ mg/m}^3$$

$$\text{BMCL}_{\text{HEC}} = \text{BMCL}_{\text{adj}} \times (\text{H}_{\text{b/g}})_{\text{A}} / (\text{H}_{\text{b/g}})_{\text{H}} = 9.8 \text{ ppm} \times 6/24 \times 5/7 \times 1 \times 3.97 = 6.9 \text{ mg/m}^3$$

### 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 hours/day, 5 days/week 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). 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 is 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 LOAEL for female rats in this study is 25 ppm (the lowest exposure tested). A benchmark dose analysis was conducted. In female rats the BMC<sub>10</sub> is 15.1 ppm and the BMCL<sub>10</sub> is 9.8 ppm, equivalent to 1.8 ppm adjusted for continuous exposure (9.8 ppm × 6/24 × 5/7). EPA concludes that any effect occurring at or below the BMCL<sub>10</sub> is not adverse.

### 1.B.3. UNCERTAINTY AND MODIFYING FACTORS (INHALATION RfC)

UF = 30.

The total uncertainty factor is 30 and the modifying factor is 1. A UF of 3 is used for interspecies extrapolation because a dosimetric adjustment is used. A UF of 10 is used for intraspecies variability because there were no applicable data to depart from the default value. A LOAEL-to-NOAEL extrapolation was not used because EPA concludes that any effect occurring at or below the BMCL<sub>10</sub> is not adverse. A subchronic-to-chronic extrapolation factor was not applied because the study exposed the animals for 18 months. 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) suggesting 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 or developmental neurotoxicity. There are no studies evaluating immunotoxicity. 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 to 1,1-DCE vapors continuously for 90 days to  $189 \pm 6.2$ ,  $101 \pm 4.4$ ,  $61 \pm 5.7$ , or  $20 \pm 2.1$  mg/m<sup>3</sup>, respectively. 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. Exposure-related increased mortality occurred in guinea pigs and monkeys. Increased incidence of mortality was observed in guinea pigs and monkeys at 189 mg/m<sup>3</sup> (2/45 in controls versus 7/15 in guinea pigs and 1/21 in controls versus 3/9 in monkeys). The deaths occurred early in the study (guinea pigs between day 4 and day 9 of exposure; monkeys on days 26, 60, and 64). The surviving animals exhibited no visible signs of toxicity. Varying growth depression was found in all exposures, but was significant in all species only at 189 mg/m<sup>3</sup>. 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 3-fold and 1.75-fold increase, respectively) and guinea pigs (7-fold and 2.4-fold increase, respectively) exposed to 189 mg/m<sup>3</sup> (other species not tested). Histopathological examination of liver from dogs, monkeys, and rats revealed damage at 189 mg/m<sup>3</sup>. 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 animals exposed to 101 mg/m<sup>3</sup> or below. The NOAEL in this study is 101 mg/m<sup>3</sup> (equivalent to 25 ppm); the LOAEL is 189 mg/m<sup>3</sup> (equivalent to 47 ppm).

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 hours/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 was also a statistically significant increased incidence of wavy ribs and delayed ossification of the skull, regarded as an embryotoxic effect. 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 hours/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 ( $0.3 \pm 0.6$  versus  $2.7 \pm 3.9$ ). There was also a significant change in the incidence of several minor skeletal variations in their offspring, including an increase in the occurrence of 13 pairs of ribs and an 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.

#### **\_\_\_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, 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. There are several studies by the inhalation route of exposure showing that developmental toxicity is not a critical effect. By the oral route of exposure there is a three-generation reproductive study showing no significant reproductive effects and several bioassays showing no developmental toxicity. One developmental study by the oral route of exposure, however, shows variations in cardiac morphology that have little or no physiological consequence. There are no adequate studies focusing on neurotoxicity or immunotoxicity by any route of exposure. The existing bioassays, however, provide no suggestion that neurotoxicity or immunotoxicity are critical effects. Accordingly, the database is given medium confidence but no additional UF is considered necessary.

## I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document -- Toxicological Review of 1,1-Dichloroethylene

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.

Other EPA Documentation -- None.

Agency Consensus Date -- \_\_/\_\_/\_\_

## I.B.7. EPA CONTACTS (INHALATION RfC)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (Internet address).

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## II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

1,1-Dichloroethylene (1,1-DCE)

CASRN -- 75-35-4

Last Revised -- 00/00/0000

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 : g/L drinking water or risk per : g/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.

### II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

#### II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

This summary replaces the summary dated 02/01/1998.

There is one epidemiological study (Ott et al., 1976) following occupational exposure. This study included only 138 people and is too limited to draw useful conclusions about the carcinogenicity of 1,1-DCE in humans.

Bioassays for cancer by the oral route of exposure have been conducted in rats (Ponomarkov and Tomatis, 1980; NTP, 1982; Quast et al., 1983; Maltoni et al., 1985), mice (NTP, 1982), and trout (Hendricks et al., 1995). None of these bioassays provide any evidence that 1,1-DCE is a carcinogen by the oral route of exposure. However, none of these bioassays was conducted at the maximum tolerated dose as no significant toxicity was observed in any study. In addition, one bioassay (Maltoni et al., 1985) exposed the animals for only one year.

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). The only bioassay showing some evidence of carcinogenicity was the study in Swiss-Webster mice (Maltoni et al., 1985). Although the animals were exposed for only 1 year, this study showed an increased incidence of kidney adenocarcinomas in male mice at 25 ppm, but not at 10 ppm, an increased incidence of mammary carcinomas in female mice at 10 ppm and 25 ppm, and an increased incidence of pulmonary adenomas in male and female mice combined at 10 ppm and 25 ppm. The incidence of mammary carcinomas and pulmonary adenomas did not increase with increased exposure. The responses were actually lower at 25 ppm than at 10 ppm, but survival and other toxicity was comparable. There is some evidence that the kidney adenocarcinomas constitute a sex- and species-specific response related to the expression of CYP2E1 (Speerschneider and Dekant, 1995; Amet et al., 1977; 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.

The one dermal study (Van Duuren et al., 1979) shows no evidence of carcinogenicity.

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.

Under the 1986 cancer guidelines (U.S. EPA, 1986), 1,1-DCE is assigned to Group C, possible human carcinogen. Under the 1996 proposed guidelines for carcinogen risk assessment (U.S. EPA, 1996), 1,1-dichloroethylene shows no evidence of human carcinogenicity by the oral or dermal routes of exposure. 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.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 manufacturing 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 the 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 17<sup>th</sup> 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. There were no significant differences in survival, clinical signs, or body weight compared with controls for any group, suggesting that the maximum tolerated dose was not achieved. No increased incidence of tumors was found at any site. 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. There were no significant differences 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/week 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. There were no biologically significant changes 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<sub>1</sub> mice (200 of each sex, 9 weeks old) by gavage in corn oil at 0, 2, or 10 mg/kg. There were no significant differences in survival, clinical signs, or body weight in any group, suggesting that the maximum tolerated dose was not achieved. The only observed significant ( $p < 0.05$ ) increase 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<sub>1</sub> 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 hours/day, 5 days/week 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) exposed 2-month-old albino Wistar rats (37 males and 37 females) to 1,1-DCE for 4 hours/day, 5 days/week 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 nonsyncytial 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 hours/day, 4 days/week for 1 month (4 of each sex), 3 months (4 of each sex), 6 months (4 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 hours/day, 4-5 days/week 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. There were no biologically significant changes 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 compared with control 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 hours/day, 5 days/week 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 upon 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. 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 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 hours/day, 5 days/week. 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 was also observed in offspring that 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). 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 hours/day, 5 days/week 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 <sup>14</sup>C-thymidine incorporation. The incidence of broncioloalveolar 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 hours/day, 4 days/week 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 hours/day, 4-5 days/week 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). There were two groups 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 121 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 body weight. The exposed animals had a somewhat higher survival than controls. There was a statistically significant increase ( $p < 0.01$ ) 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 ( $p < 0.01$ ) 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 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 hours/day, 4-5 days/week 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. There were no biologically significant noncancer or tumor effects 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 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 animals injected with 1,1-DCE 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  $^3\text{H}$ -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  $^3\text{H}$ -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 EPA considers 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 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 no 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

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.

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

##### **II.D.2. EPA REVIEW (CARCINOGENICITY ASSESSMENT)**

Agency Consensus Date -- \_\_/\_\_/\_\_

### **\_\_II.D.3. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)**

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX), or RIH.IRIS@EPAMAIL.EPA.GOV (Internet address).

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1,1-Dichloroethylene (DCE)

CASRN -- 75-35-4

Last Revised -- 00/00/0000

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## **\_VII. REVISION HISTORY**

1,1-Dichloroethene (DCE)

CASRN -- 75-35-4

<u>Date</u>	<u>Section</u>	<u>Description</u>
[insert from substance file 0039] 00/00/00	I-VIII	New RfD, RfC, and cancer assessment

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## **\_VIII. SYNONYMS**

1,1-Dichloroethylene

CASRN -- 75-35-4

Last Revised -- \_\_/\_\_/\_\_

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