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Provisional Peer-Reviewed Toxicity Values for

1,2-Dichloroethane
(CASRN 107-06-2)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
UF	uncertainty factor
UF_A	animal-to-human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete-to-complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 1,2-DICHLOROETHANE (CASRN 107-06-2)

BACKGROUND

HISTORY

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

1) EPA's Integrated Risk Information System (IRIS)
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in EPA's Superfund Program
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR);
   - California Environmental Protection Agency (CalEPA) values; and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

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

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

DISCLAIMERS

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

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

QUESTIONS REGARDING PPRTVS

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

INTRODUCTION

The compound 1,2-dichloroethane (1,2-DCA), also known as ethylene dichloride (EDC), is a chlorinated solvent and degreaser with a molecular weight of 98.96 g/mol (Hazardous Substances Data Bank [HSDB], 2008). Figure 1 shows its chemical structure.

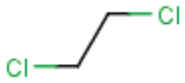

Figure 1. Chemical Structure of 1,2-Dichloroethane

IRIS (U.S. EPA, 2008) does not include RfD or RfC values for 1,2-DCA. No RfD or RfC values are listed in the HEAST (U.S. EPA, 1997). Relevant documents on the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994a) include a Health Effects Assessment (HEA) (U.S. EPA, 1984), a Health and Environmental Effects Profile (HEEP) (U.S. EPA, 1985a), and a Health Assessment Document (HAD) (U.S. EPA, 1985b). None of these documents attempted to derive RfD or RfC values because 1,2-DCA had been demonstrated to be carcinogenic. A drinking water Quantification of Toxicological Effects (QTE) (U.S. EPA, 1985c) presented interim RfD derivations based on an oral multigeneration study by Lane et al. (1982) and on inhalation data. However, a subsequent Drinking Water Health Advisory (U.S. EPA, 1987) concluded that no appropriate data were available for determining an RfD, and no RfD value appears on the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006).

ATSDR (2001) derived an intermediate-duration oral minimal risk level (MRL) of 0.2 mg/kg-day from a 13-week drinking water study in rats (National Toxicology Program [NTP], 1991) in which a lowest-observed-adverse-effect level (LOAEL) of 58 mg/kg-day for increased kidney weight was identified. Uncertainty factors (UFs) used in the MRL derivation

were 3 for use of a minimal LOAEL, 10 for interspecies extrapolation, and 10 for human variability. No chronic oral MRL was derived due to the lack of adequate data. ATSDR (2001) derived an MRL of 0.6 ppm for chronic-duration inhalation exposure (>365 days) to 1,2-DCA based on a no-observed-adverse-effect level (NOAEL) of 50 ppm from a study with rats exposed for 7 hours/day, 5 days/week for 2 years (Cheever et al., 1990). The UF comprised factors of 3 for interspecies extrapolation after dosimetric adjustment, 10 for human variability, and 3 for database deficiencies. Although only one dose was tested in the source study, other studies in the database support the NOAEL.

California EPA (CalEPA, 2000, 2008a,b) lists a chronic inhalation recommended exposure limit (REL) of 0.4 mg/m^3 (0.1 ppm) for 1,2-DCA based on a NOAEL of 10 ppm and LOAEL of 50 ppm for hepatotoxicity (increased serum liver enzymes) in rats exposed 7 hours/day, 5 days/week for 12 months (Spreafico et al., 1980). The World Health Organization (WHO, 1987, 1995) has published environmental health criteria documents for 1,2-DCA and a companion health and safety guide (WHO, 1991); the health and safety guide concludes that it was not possible to derive a NOEL for noncarcinogenic effects on the basis of available human data, but that a NOEL of 400 mg/m^3 could be established on the basis of animal toxicity data. No oral values for drinking water were derived by WHO (1991).

There are occupational exposure limits for 1,2-DCA. The American Conference of Governmental Industrial Hygienists (ACGIH, 2007) posts a threshold limit value-time weighted average (TLV-TWA), dating from 1977, of 10 ppm to protect against liver damage and nausea, with an A4 designation (not classifiable) for human carcinogenicity. In contrast, the National Institute of Occupational Safety and Health (NIOSH, 2008) lists 1,2-DCA as an occupational carcinogen with a recommended exposure limit-time weighted average (REL-TWA) of 1 ppm (4 mg/m^3) and a short-term exposure limit of 2 ppm (8 mg/m^3). The Occupational Safety and Health Administration (OSHA, 2008) permissible exposure limit (PEL) is 50 ppm as TWA, 100 ppm as a ceiling, and 200 ppm as an acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift (not to exceed 5 minutes in any 3 hours).

IRIS (U.S. EPA, 2008) classifies 1,2-DCA as a Group B2 (probable human) carcinogen based on the induction of several tumor types in rats and mice treated by gavage and on observation of lung papillomas in mice after topical application. IRIS (U.S. EPA, 2008) posts an OSF of 9.1×10^{-2} per mg/kg-day derived from linearized multistage modeling of hemangiosarcomas in male Osborne-Mendel rats treated with 1,2-DCA by gavage (National Cancer Institute [NCI], 1978). This corresponds to a Drinking Water Unit Risk of 2.6×10^{-6} per µg/L and a risk level of 10^{-4} at a drinking water concentration of 0.040 mg/L. The latter level is included in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006). IRIS also posts an Inhalation Unit Risk Factor (IUR) of 2.6×10^{-5} per $\mu g/m^3$ based on extrapolation from the oral data for hemangiosarcoma in male rats (NCI, 1978).

NTP (2008) has assessed the toxicity (NTP, 1991: 13-week study) and carcinogenicity of 1,2-DCA (NCI, 1978), and this compound is included in the 11th Report on Carcinogens (NTP, 2005), which concludes that 1,2-DCA is *Reasonably Anticipated to Be a Human Carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (NCI, 1978). The International Agency for Research on Cancer (IARC, 1979, 1987, 1999, 2008) classifies 1,2-DCA as Group 2B (*Possible Human Carcinogen*) based on sufficient evidence of carcinogenicity in animals and inadequate evidence of carcinogenicity in humans. Oral studies

in mice[1] and rats[2] conducted by NCI (1978) were considered adequate. Inhalation studies with rats and mice were not considered to be adequate. CalEPA (2002) lists a cancer IUR factor of 2.1×10^{-5} $(\mu g/m^3)^{-1}$ and an OSF of 7.2×10^{-2} $(mg/kg\text{-}day)^{-1}$ for 1,2-DCA. Environment Canada (1994) categorized 1,2-DCA as Group II (*Probably Carcinogenic to Humans*), with estimates of carcinogenic potency ($TD_{0.05}$) ranging from 6.2 to 297 mg/kg-day. The present document does not contain a cancer assessment for 1,2-DCA, as one is available on IRIS (U.S. EPA, 2008).

Literature searches were conducted from 1960s through January 2010 in the following databases for studies relevant to the derivation of provisional toxicity values for 1,2-DCA: TOXLINE, MEDLINE, TSCATS1/2, RTECS, CCRIS, DART, HSDB, GENETOX, CCRIS, CHEMABS, BIOSIS, and Current Contents (last 6 months). An Organisation for Economic Co-operation and Development Screening Information Dataset (OECD SIDS) Initial Assessment Report (OECD, 2002) was also consulted for relevant information.

REVIEW OF PERTINENT DATA

HUMAN STUDIES

Oral Exposure

Information concerning the toxic effects of ingested 1,2-DCA in humans is largely limited to case reports of individuals who accidentally or intentionally ingested 1,2-DCA. These case reports generally describe findings in single individuals exposed acutely to 1,2-DCA and give only crude estimates of ingested dose, further limiting the value of the data. Available reviews (ATSDR, 2001; IARC, 1999; WHO, 1995) reported that symptoms of acute 1,2-DCA intoxication include cardiac arrhythmia, bronchitis, hemorrhagic gastritis and colitis, hepatocellular damage, renal tubular necrosis and calcification, and CNS depression. WHO (1995) reported the estimated lethal dose in humans to be 20−50 mL based on these case reports; these intakes correspond to doses of 25−62 g[3], or 350−890 mg/kg based on a reference body weight of 70 kg. Ecological epidemiological studies (Bove, 1996; Bove et al., 1995; Croen et al., 1997, all cited in ATSDR, 2001) have reported an association between 1,2-DCA in drinking water supplies and major birth defects, but lack of individual exposure information and concurrent exposures to other compounds limits the usefulness of these studies for establishing an association or evaluating the dose-response relationship. Both oral and inhalation exposures were likely in these studies.

Inhalation Exposure

Fatal and nonfatal outcomes have resulted from acute occupational exposure to 1,2-DCA (U.S. EPA, 1985b). In most occupational cases, the exposures were poorly characterized and consisted of a mixture of solvents. Generally, inhalation of 1,2-DCA vapor first affects the CNS (with symptoms of headache, dizziness, lethargy, feelings of drunkenness, unconsciousness) and causes irritation and inflammation of the respiratory tract, which is characteristic of chlorinated aliphatic hydrocarbon toxicity (U.S. EPA, 1985b). Other signs and symptoms of inhalation

[1]Significant increases in benign and malignant tumors of the lung, malignant lymphomas, hepatocellular carcinomas, and mammary and uterine adenocarcinoma.
[2]Forestomach carcinomas in males, benign and malignant mammary tumors in females, and hemangiosarcomas in both sexes.
[3]Assuming specific gravity of 1.235 (HSDB, 2008).

exposure included eye irritation, cyanosis, epigastric tenderness, hepatomegaly, and jaundice (U.S. EPA, 1985b; WHO, 1995). WHO (1995) reported damage to the liver, kidneys, and lungs. Quantitative data pertinent to the effects of repeated inhalation of 1,2-DCA by humans are limited and derived chiefly from foreign reports lacking controls and providing inadequate information about duration of exposure and/or number of subjects exposed (U.S. EPA, 1985b). Case reports of repeated exposures to unknown concentrations describe nervousness, irritability, tremors, depressed reflexes, and irritation of the skin and mucous membranes in exposed workers (U.S. EPA, 1985b). EPA (1985b) reviewed a number of older case reports and occupational health studies; selected case reports and studies (those providing semiquantitative information and/or clear identification of target organs) are described below, as are newer studies of inhalation exposure to 1,2-DCA in humans.

A case study reported by Nouchi et al. (1984) detailed the clinical effects, blood chemistry, and autopsy findings of a 51-year-old man who died after being exposed to 1,2-DCA vapor for 30 minutes while removing 1,2-DCA residue from the hold of an oil tanker. Exposure is likely to have occurred by both the inhalation and dermal routes. No estimate of the exposure concentration was available, although exposure conditions were described as a "thick vapor of dichloroethane." An autopsy revealed congestion of the lungs, degenerative changes in the myocardium, liver necrosis, renal tubular necrosis, and smaller nerve cells in the brain.

In a summary of studies of 100 Russian workers from different (unspecified) industries who were exposed to ≤25 ppm (~100 mg/m^3) of 1,2-DCA for 6 months to 5 years, Rosenbaum (1947; as cited in U.S. EPA, 1985a,b) reported that the following signs and symptoms occurred in "many" of the workers: heightened responses of the autonomic nervous system, improved muscular tonus, bradycardia, increased perspiration, and increased frequency of fatigue, irritability, and sleeplessness.

Agricultural workers in Poland were exposed to 1,2-DCA during its transportation, distribution, and application (use as a fumigant on agricultural fields) (Brzozowski et al., 1954; as cited in U.S. EPA, 1984). The exposure was believed to be primarily via dermal contact, but air concentrations were estimated to range from 4−60 ppm (~16−240 mg/m^3) depending on the activity. Among 118 of these workers, 90 had clinical findings, including conjunctival congestion (82/118), weakness (54/118), reddening of the pharynx (50/118), bronchial symptoms (43/118), metallic taste (40/118), dermographism (37/118), nausea (31/118), cough (30/118), liver pain (29/118), irritation of the conjunctiva (24/118), rapid pulse (21/118), and dyspnea after effort (21/118).

Cetnarowicz (1959) studied a small number of Polish oil refinery workers exposed to vapor from a solvent containing 80% 1,2-DCA and 20% benzene for ~6 months. All 10 centrifuge workers exposed to levels of 1,2-DCA ranging from 250 to 800 mg/m^3 reported eye irritation and lacrimation, and 6 complained of dryness of the mouth, gastrointestinal disturbances (nausea, vomiting, loss of appetite), dizziness, and fatigue. Of the 10, 3 complained of epigastric pain. Upon clinical examination, palpation revealed liver tenderness with slight enlargement in 4/10 workers. Only 1/6 workers exposed to lower concentrations (40 to 150 mg/m^3) of 1,2-DCA complained of symptoms similar to those reported by the centrifuge-exposure subgroup. Additional physical examination of all 16 workers revealed no eye or upper or lower respiratory tract damage but provided additional evidence of liver effects (altered liver function tests) and gastrointestinal effects (X-ray observable gastritis in 6/16, with

pyloric spasms in 3/16); distribution of these additional findings among the two subgroups was not reported. This study is limited by coexposure to benzene and the lack of a control group.

Kozik (1957) reported the results of a study of Russian aircraft industry employees (glue shop workers) exposed to 1,2-DCA. In this study, morbidity and temporary loss of working capacity was examined during the period from 1951 to 1955. No information on the length of employment or the duration of exposure was reported. For 70−75% of the work shift, the ambient concentration of 1,2-DCA was ≤50 mg/m^3; for the remaining 25−30%, the levels ranged up to 150 mg/m^3. Upon reviewing the data on the ambient air concentrations, NIOSH (1976) estimated that the TWA concentration in the breathing zone was about 61 mg/m^3 (15 ppm[4]). The incidences of morbidity and the number of days lost from work due to acute gastrointestinal diseases, liver and gallbladder disease, neuritis and radiculitis, and other disorders were higher in the glue shop workers than in other workers in the plant, but a statistical analysis of the data was not reported. Respiratory tract disease or irritation was not mentioned. Examination of 83 of the gluers revealed that 19 had liver and gallbladder diseases, 13 had neuritis, 11 had hypotension, and 10 had goiter and hyperthyroidism. Examination of unexposed workers was not performed. The authors noted that diseases of the muscles, tendons, and ganglia were considered to be associated with the many repetitive motions the workers had to make when applying the glue. Results of neurobehavioral testing in a group of 17 gluers revealed impaired visual-motor reactions on 2/3 tests when compared with a group of 10 controls (machinists in the same factory). The test methods were poorly described but involved the determination of reaction time and error rate in the performance of a simple reaction, complex reaction (differentiation of color), and "alternation of the complex reaction." The mean rates for all three reactions (speed of reaction) before and after work were not significantly different between the two groups. The number of workers making errors and the percentage error were higher in gluers than in controls for the complex reaction and the alternation of complex reaction. Errors occurred only at the end of the work day. The authors reported that 4/10 machinists made errors, while 15/17 gluers made errors (p = 0.01 by Fisher's exact test performed for this review). This study has several limitations, including the lack of statistical analysis of morbidity data, lack of medical examination of nonexposed workers, examination of a limited number of toxicity endpoints, and the lack of control of potentially confounding factors, such as alcohol intake. Because the only endpoint that was evaluated in both an exposed and a referent group was the neurobehavioral testing, these data are used to define effect levels. For the purpose of this review, the TWA exposure concentration of 61 mg/m^3 estimated by NIOSH (1976) is considered to represent a LOAEL based on neurobehavioral effects in gluers. This LOAEL is uncertain given the poor quality of the study and reporting, limited numbers of subjects, and lack of control for potential confounders.

A number of recent studies of hazardous waste workers exposed to 1,2-DCA report effects on memory and other neurobehavioral parameters (Dilks et al., 2005, 2007; Bowler et al., 2003; Novakovic-Agopian and Bowler, 2001). Dilks et al. (2005, 2007) reported that 61 hazardous waste workers (59 men and 2 women) exposed to 1,2-DCA for 2 years and examined 4 years later exhibited statistically significant memory impairments when compared

[4]In its summary of this study, NIOSH (1976) estimated a TWA of 15 ppm and provided some information on the basis for this estimate. In its derivation of the recommended standard, NIOSH (1976) gave the exposure estimate as a range from 10−15 ppm, without any reference to the basis for the range. For the purpose of this review, the TWA estimate of 15 ppm is used.

with 48 workers without exposure to petrochemicals. A follow-up study of 12 of the male workers showed that the memory impairments persisted 8 years after the end of exposure. This study is limited by the lack of information on the nature and magnitude of exposure to 1,2-DCA, lack of information on other exposures sustained by the hazardous waste workers, lack of control for potential confounders, strong potential for selection bias (if the hazardous waste workers believed themselves to be impaired), and poor reporting.

Bowler et al. (2003; Novakovic-Agopian and Bowler, 2001) examined neuropsychological effects in 221 hazardous waste workers exposed to 1,2-DCA. The clinical evaluations were conducted as part of a lawsuit and were funded by the plaintiffs; however, they were peer reviewed and published in a publically available journal. This study reported some details of the exposure setting, but did not include any information on the magnitude of exposures. Based on the description of the exposure setting (cleanup of a spill of 1,2-DCA from a damaged pipeline), both dermal and inhalation exposures were likely. Bowler et al. (2003) reported subjective symptoms, as well as the results of a battery of neuropsychological tests (including intelligence, memory, motor speed, grip strength, visual function, and mood). There was no control group. The authors reported that the workers exhibited lower processing speed, attention, cognitive flexibility, motor coordination and speed, and impairments of verbal memory, verbal fluency, visuo-spatial ability, vision, and mood. Lack of a control group, absence of exposure information, and potential selection bias (due to the litigation) limit the usefulness of this study.

Cheng et al. (1999) examined serum chemistry parameters (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma glutamyl transpeptidase [GGT]) indicative of liver toxicity in 251 male workers at four vinyl chloride manufacturing plants. The workers were exposed to both vinyl chloride and 1,2-DCA. Using job descriptions and measurements of vinyl chloride and 1,2-DCA in various jobs, the authors defined three exposure groups: low 1,2-DCA (median of 0.32−0.44 ppm, range from 0.16 to 0.72 ppm) with moderate vinyl chloride (median of 0.44−1.63 ppm, range from 0.15 to 41.04 ppm); moderate 1,2-DCA (median of 0.77−1.31 ppm, range from 0.17 to 333.7 ppm) with low vinyl chloride (median of 0.18−0.27 ppm, range from 0.18 to 0.34 ppm); and low 1,2-DCA (median from 0.26−0.35 ppm; range from 0.17 to 0.52 ppm) with low vinyl chloride (median from 0.29−0.39 ppm; range from 0.25−2.46 ppm). Each exposure is presented as a median and range because multiple jobs were included in each category. The average duration of employment in the workers was 13.1 years. Using a logistic regression analysis in which abnormal AST was defined as a serum concentration >37 IU/L (international units per liter) and abnormal ALT was defined as >41 IU/L, the authors observed statistically significant increases in the odds of having abnormal AST (OR = 2.2, 95% CI = 1.0−5.4, $p < 0.05$) and ALT (OR = 2.1, 95% CI = 1.1−4.2, $p < 0.05$) levels in workers exposed to moderate levels of 1,2-DCA and low levels of vinyl chloride, compared with low 1,2-DCA and low vinyl chloride. Moderate vinyl chloride and low 1,2-DCA was not significantly associated with abnormal AST or ALT. No association between 1,2-DCA exposure and changes in GGT was seen in any exposure group. This study is limited by strong potential for exposure misclassification, as the median exposures to both 1,2-DCA and vinyl chloride were similar among all groups. Potential confounding by coexposure to vinyl chloride, a potent hepatotoxicant, also limits the utility of this study.

Zhao et al. (1989) conducted a retrospective survey of the reproductive history of 98 workers (44 males, 54 females) that had contact with 1,2-DCA at a synthetic fiber factory or a

Beijing chemical plant that produced 1,2-DCA (98.5% purity). The control group comprised 349 workers (136 males, 213 females) from a clothing factory or a computer factory having no 1,2-DCA contact but having similar medical and living conditions as the 1,2-DCA-exposed group. The 1,2-DCA concentrations were estimated based on the records of periodic tests performed at the plants during previous years. A large variation range of 1.5−1,534 mg/m^3 was reported for 1,2-DCA concentrations in the factories. The results of the survey indicated that female workers from the 1,2-DCA contact group and the wives of male workers in the contact group had statistically significant higher rates of premature births than the control group ($p < 0.05$). The rates of pregnancy, miscarriages, and fetal deaths prior to or at birth were comparable between the 1,2-DCA-contact and control groups. There were no physical deformities and no obvious effects on the body weights of the newborns. Because 1,2-DCA-contact workers were exposed to other chemicals concurrent with their 1,2-DCA exposure, no conclusions regarding the reproductive effects of 1,2-DCA could be reached.

ANIMAL STUDIES

Oral Exposure

Subchronic Studies—There are three subchronic studies in the literature: two in rats, and one in mice and rats. In the first study, Van Esch et al. (1977) exposed Wistar rats of both sexes (10/sex/dose) to 1,2-DCA (99% pure) via gavage administration at 0, 10, 30, or 90 mg/kg-day, 5 days/week for 90 days. The dose selections were based on the results of a range-finding study in which groups of six male rats were dosed with 3, 10, 30, 100, or 300 mg/kg-day, 5 days/week for 2 weeks. In the range-finding study, all high-dose rats died; histology on these animals revealed fatty degeneration of the liver. In the 90-day subchronic study, body weights and food consumption were measured (frequency not reported). At 4 and 8 weeks of exposure, blood was collected for serum chemistry (ALT, alkaline phosphatase [ALP]; eight males/dose group), and glucose-6-phosphatase, aryl hydrocarbon hydroxylase (AH), and aminopyrene demethylase (APDM) activity, and triglyceride levels were measured in the livers (four males/dose group). At the end of exposure, liver function was assessed using the bromosulphophthalein retention test on six animals/sex/group. Hematology parameters (hematocrit [Hct], hemoglobin [Hgb], red blood cells [RBC], total and differential white blood cells [WBC], mean cell volume [MCV], mean cell hemoglobin [MCH], and mean cell hemoglobin concentration [MCHC]) were assessed on blood collected at the end of exposure from all animals. Upon sacrifice at the end of exposure, organs (brain, heart, liver, spleen, kidneys, thymus, pituitary, thyroid, adrenals, ovaries, testes, and uterus) from all animals were weighed, and histopathology of these and 16 other tissues was assessed in control and high-dose animals. Liver and kidneys from low- and mid-dose groups were examined microscopically.

Additionally, in the subchronic study, Van Esch et al., 1977 observed slightly lower weight gain (3−7% less than controls) in females in all dose groups and in mid- and high-dose males; statistical analysis or data with which to perform statistical analyses were not reported (Van Esch et al., 1977). Increased relative kidney weight (14−17% higher than controls) occurred in both sexes at the high dose, and increased relative liver (13%) and brain (9%) weights were also seen in the females at this dose; absolute weights were not reported. Based on data reported in the paper, relative weights of other organs were not affected by treatment. Reduced body weights in the high-dose animals may have contributed to the increases in relative kidney, liver, and brain weights. Clinical chemistry parameters did not differ between exposed and control animals; based on data shown in the report, sporadic hematological changes were seen in females, but the changes were not dose-related. There were no treatment-related

histopathological lesions. The authors identified a no-effect level of 30 mg/kg-day. The increases in relative liver and kidney weights at 90 mg/kg-day are considered the LOAEL based on the following observation by the authors: liver toxicity at higher doses (fatty degeneration at 300 mg/kg-day in the range-finding study), the consistent finding of increased kidney weights in other studies of rats and mice exposed orally to 1,2-DCA (NTP, 1991; Daniel et al., 1994), and the observation of renal histopathology in mice and some strains of rats exposed to higher doses of 1,2-DCA (NTP, 1991; Daniel et al., 1994). The NOAEL is 30 mg/kg-day.

In the second subchronic study, which was chosen as the critical study, groups of F344/N rats, Sprague-Dawley rats, Osborne-Mendel rats, and B6C3F1 mice (10 animals/sex) were exposed to drinking water containing 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm of 1,2-DCA (>99% pure) for 13 weeks (NTP, 1991). The high concentration was close to the solubility limit for 1,2-DCA in water. The authors estimated the daily doses in mg/kg-day shown in Table 1 based on drinking water consumption and average body weights.

Table 1. Estimated Average Daily Doses (mg/kg-day) of 1,2-DCA in Animals Exposed via Drinking Water for 13 Weeks[a]

Concentration in Water (ppm)	Rats						Mice	
	F344/N		Sprague-Dawley		Osborne-Mendel		B6C3F1	
	Male	Female	Male	Female	Male	Female	Male	Female
500	49	58	60	76	54	82	249	244
1,000	86	102	99	106	88	126	448	647
2,000	147	182	165	172	146	213	781	1,182
4,000	259	320	276	311	266	428	2,710	2,478
8,000	515	601	518	531	492	727	4,207	4,926

[a]NTP (1991)

Additional groups of F344/N rats (10/sex) were administered 1,2-DCA (>99% pure) in corn oil by gavage on 5 days/week for 13 weeks to compare toxicity resulting from bolus administration with that of the continuous exposure in drinking water (NTP, 1991). Gavage doses were 0, 30, 60, 120, 240, or 480 mg/kg-day in the male rats and 0, 18, 37, 75, 150, or 300 mg/kg-day in the female rats. In all groups (drinking water and gavage), signs of toxicity were assessed twice daily, while body weight and food and water consumption were recorded weekly. Separate groups of 10 male rats/strain were exposed to 0, 2,000, 4,000, or 8,000 ppm in drinking water or 0, 120, 240, or 480 mg/kg-day by gavage and used for evaluation of hematology (RBC, WBC, Hgb, Hct, MCV, MCH, MCHC, differential leukocyte count, platelets, reticulocytes, and erythrocyte morphology) and serum chemistry (sorbitol dehydrogenase [SDH], creatine kinase, ALT, ALP, and blood urea nitrogen [BUN]) on Days 3, 7, 14, 45, and 90. Hematology and serum chemistry parameters were also evaluated on animals of the core groups at study termination. Upon sacrifice at the end of exposure, organ weights (liver, right kidney, brain, heart, thymus, lung, and right testis) were recorded, and gross necropsy was performed. Histological examinations were completed on control and high-dose animals of all species and strains, as well as on 4,000-ppm female mice, male rats exposed by gavage to 120 or 240 mg/kg-day, and on female rats exposed by gavage to 150 mg/kg-day.

None of the rats given 1,2-DCA in drinking water died, and no treatment-related clinical signs were observed (NTP, 1991). Dose-related decreases in water consumption, likely reflecting poor palatability of the compound, occurred in all treated groups; decreases were 4−44% in F334/N males, 5−42% in F334/N females, 14−56% in male Sprague-Dawley males, 25−70% in Sprague-Dawley females, 17−60% in Osborne-Mendel male rats, and 21−58% in Osborne-Mendel female rats. Dose-related reductions in body weight in most groups were considered by the researchers to result from dehydration. Several hematology and serum chemistry changes, including increases in RBC, Hct, or Hgb, mild decreases in MCV, and increases in BUN (all observed in males) were also attributed by the researchers to dehydration resulting from decreased water consumption. Sporadic, statistically significant ($p < 0.05$) decreases in ALP and ALT levels were observed in treated male animals evaluated for serum chemistry; the toxicological significance of these changes is uncertain. Creatine kinase activity was unaffected in male rats of all three strains. SDH activity was significantly increased at 8,000 ppm on Days 14 and 45 in F344/N males and at 8,000 ppm on Day 14 in Sprague-Dawley males (statistical significance of ($p < 0.05$) but was unaffected in Osborne-Mendel males.

In all three strains, absolute and/or relative kidney and liver weights were increased by exposure; Tables 2 and 3 show the organ-weight changes in males and females, respectively (NTP, 1991). Absolute kidney weights were significantly ($p < 0.01$) increased at ≥1,000 ppm in male F344/N rats; absolute kidney weights were not affected by treatment in male Sprague-Dawley or Osborne-Mendel rats. Relative kidney weights were significantly increased at ≥1,000 ppm in F344/N males, at ≥4,000 ppm in Osborne-Mendel males, and at 1,000, 4,000, and 8,000 ppm in Sprague-Dawley males ($p < 0.05$). Absolute kidney weights were significantly ($p < 0.05$) increased at all drinking water exposure levels in female rats of all strains; relative kidney weights were also increased at all exposure concentrations in female Sprague-Dawley and Osborne-Mendel rats, and at ≥1,000 ppm in female F344/N rats. In male rats of all strains, absolute liver weight changes were either not statistically significant or not dose-related; relative liver weights were increased at all exposure concentrations in male Sprague-Dawley rats and at ≥2,000 ppm in male F344/N rats but did not increase with dose. Neither absolute nor relative liver weights exhibited dose-related changes in male or female Osborne-Mendel rats. In female F344/N rats, there were sporadic increases in absolute liver weight, but the changes did not exhibit clear dose-dependence; relative liver weights were increased at ≥4,000 ppm. In female Sprague-Dawley rats, relative liver weight was increased at the highest drinking water concentration; there were no changes in absolute liver weight (see Table 3).

Table 2. Significant Changes in Male Rats Treated with 1,2-DCA in Drinking Water for 13 Weeks[a]

Parameter Evaluated	Concentration in Water (ppm)					
	Control	500	1,000	2,000	4,000	8,000
F344/N						
Dose (mg/kg-day)	0	49	86	147	259	515
Final body weight (g)	358 ± 4[b]	359 ± 7	358 ± 5	358 ± 3	329 ± 3[c]	302 ± 4[c]
Water consumption (g/day)	25	24	21	18	15	14
Organ weights						
Absolute kidney weight (mg)	1,232 ± 48	1,345 ± 38	1,433 ± 28[c]	1,523 ± 15[c]	1,451 ± 18[c]	1,377 ± 22[c]
Relative kidney weight (mg/g)	3.4 ± 0.16	3.8 ± 0.08	4.0 ± 0.09[c]	4.3 ± 0.04[c]	4.4 ± 0.06[c]	4.6 ± 0.07[c]
Absolute liver weight (mg)	15,450 ± 660	16,500 ± 540	16,960 ± 570	17,840 ± 250[d]	16,050 ± 330	14,760 ± 340
Relative liver weight (mg/g)	42.9 ± 2.17	46.5 ± 0.95	47.7 ± 1.37	50.2 ± 0.49[c]	49.1 ± 0.79[d]	49.2 ± 0.85[d]
Sprague-Dawley						
Dose (mg/kg-day)	0	60	99	165	276	518
Final body weight (g)	457 ± 11	452 ± 7	439 ± 6	436 ± 12	440 ± 8	418 ± 9[d]
Water consumption (g/day)	43	37	30	25	21	19
Organ weights						
Absolute kidney weight (mg)	1,871 ± 74	1,943 ± 59	1,954 ± 58	1,856 ± 74	2,000 ± 52	2,008 ± 55
Relative kidney weight (mg/g)	4.2 ± 0.14	4.4 ± 0.11	4.5 ± 0.08[d]	4.3 ± 0.11	4.6 ± 0.11[d]	4.9 ± 0.11[c]
Absolute liver weight (mg)	18,480 ± 790	20,080 ± 590	18,810 ± 570	20,100 ± 790	19,970 ± 490	19,230 ± 560
Relative liver weight (mg/g)	41.1 ± 1.03	45.0 ± 1.15[d]	43.6 ± 0.75[d]	46.5 ± 1.11[c]	45.9 ± 0.82[c]	46.5 ± 1.20[c]
Osborne-Mendel						
Dose (mg/kg-day)	0	54	88	146	266	492
Final body weight (g)	452 ± 15	482 ± 13	468 ± 17	435 ± 14	399 ± 12	382 ± 11[d]
Water consumption (g/day)	42	35	28	22	19	17
Organ weights						
Absolute kidney weight (mg)	1,506 ± 36 (n = 9)	1,600 ± 41	1,751 ± 40[c]	1,656 ± 59	1,613 ± 44	1,507 ± 68
Relative kidney weight (mg/g)	3.7 ± 0.28 (n = 9)	3.4 ± 0.09	3.8 ± 0.14	3.8 ± 0.09	4.1 ± 0.13[c]	4.0 ± 0.18[d]
Absolute liver weight (mg)	16,230 ± 810 (n = 9)	17,830 ± 610	21,080 ± 840[c]	19,310 ± 800	15,190 ± 510	15,900 ± 800
Relative liver weight (mg/g)	39.2 ± 2.01 (n = 9)	37.4 ± 0.85	45.4 ± 0.90[d]	44.6 ± 1.24[d]	38.8 ± 1.45	41.9 ± 1.59

[a]NTP (1991)
[b]Mean ± standard error; n = 10 per group unless noted otherwise
[c]$p < 0.01$
[d]Significantly different from control at $p < 0.05$

Table 3. Significant Changes in Female Rats Treated with 1,2-DCA in Drinking Water for 13 Weeks[a]

Parameter Evaluated	Concentration in Water (ppm)					
	Control	**500**	**1,000**	**2,000**	**4,000**	**8,000**
F344/N						
Dose (mg/kg-day)	0	58	102	182	320	601
Final body weight (g)	202 ± 2[b]	204 ± 3	207 ± 2	199 ± 3	195 ± 1	187 ± 2
Water consumption (g/day)	19	18	16	14	12	11
Organ weights						
Absolute kidney weight (mg)	739 ± 26	814 ± 16[c]	885 ± 16[d]	845 ± 17[d]	932 ± 15[d]	923 ± 15[d]
Relative kidney weight (mg/g)	3.8 ± 0.13	4.1± 0.07	4.2 ± 0.17[c]	4.3 ± 0.07[d]	4.8 ± 0.09[d]	5.0 ± 0.04[d]
Absolute liver weight (mg)	6,829 ± 154	7,268 ± 179	7,627 ± 177[d]	7,278 ± 165	7,551 ± 171[c]	7,134 ± 147
Relative liver weight (mg/g)	35.3 ± 0.85	36.6 ± 0.60	36.3 ± 1.57	37.2 ± 0.75	39.2 ± 0.94[d]	38.5 ± 0.61[d]
Histopathology (incidence)						
Renal tubular regeneration	0/10	0/10	1/10	2/10	3/10	9/10[e]
Sprague-Dawley						
Dose (mg/kg-day)	0	76	106	172	311	531
Final body weight (g)	281 ± 6	291 ± 8	290 ± 5	276 ± 5	270 ± 7	257 ± 5
Water consumption (g/day)	44	33	23	18	16	13
Organ weights						
Absolute kidney weight (mg)	1,030 ± 36	1,160 ± 27[c]	1,221 ± 28[d]	1,211 ± 33[d]	1,208 ± 50[d]	1,342 ± 16[d]
Relative kidney weight (mg/g)	3.8 ± 0.11	4.1 ± 0.09[c]	4.3 ± 0.13[c]	4.5 ± 0.11[d]	4.6 ± 0.16[d]	5.2 ± 0.10[d]
Absolute liver weight (mg)	11,140 ± 350	11,890 ± 530	12,200 ± 680	10,990 ± 310	11,500 ± 370	11,950 ± 450[f]
Relative liver weight (mg/g)	41.2 ± 1.07	42.0 ± 1.49	42.7 ± 2.60	40.6 ± 1.32	43.5 ± 1.37	46.6 ± 1.41[c,f]
Osborne-Mendel						
Dose (mg/kg-day)	0	82	126	213	428	727
Final body weight (g)	278 ± 12	277 ± 6	275 ± 5	261 ± 4	275 ± 7	258 ± 5
Water consumption (g/day)	43	34	26	23	22	18

Table 3. Significant Changes in Female Rats Treated with 1,2-DCA in Drinking Water for 13 Weeks[a]

Parameter Evaluated	Concentration in Water (ppm)					
	Control	**500**	**1,000**	**2,000**	**4,000**	**8,000**
Organ weights						
Absolute kidney weight (mg)	894 ± 28	1,017 ± 15[d]	1,041 ± 22[d]	1,020 ± 24[d]	1,096 ± 37[d]	1,094 ± 33[d]
Relative kidney weight (mg/g)	3.3 ± 0.11	3.7 ± 0.06[c]	3.9 ± 0.06[d]	4.0 ± 0.16[d]	4.1 ± 0.14[d]	4.2 ± 0.26[d]
Absolute liver weight (mg)	10,390 ± 450	11,580 ± 360	10,810 ± 230	10,390 ± 430	10,750 ± 300	10,100 ± 410
Relative liver weight (mg/g)	37.9 ± 1.04	41.5 ± 0.96	40.0 ± 0.81	41.0 ± 2.39	39.8 ± 0.73	38.6 ± 2.49

[a]NTP (1991)
[b]Mean ± standard error; $n = 10$ per group unless noted otherwise
[c]Significantly different from control at $p < 0.05$
[d]$p < 0.01$
[e]$p < 0.01$, Fisher's exact test performed for this review
[f]$n = 9$ per group

No lesions attributable to 1,2-DCA were observed in the livers of any strain or sex of rat. The only histopathology finding was minimal-to-mild renal tubular regeneration, which occurred at similar incidence and severity in all groups of treated and control male and female rats, except female F344/N rats. In female F344/N rats, there was a dose-related increase in the incidence of mild renal tubular regeneration; the increase was significantly different from control in the 8,000-ppm group. Information on possible functional renal deficits in this group was lacking, as serum chemistry analyses were only performed in male rats. A LOAEL of 58 mg/kg-day (500 ppm), the lowest dose tested, is identified for increased absolute kidney weight (>10%) in female F344/N rats. The increased kidney weight is considered to be an early stage adverse effect because a dose-related increase in the incidence of renal tubular regeneration (indicative of previous tubular injury with subsequent repair) was observed at higher doses in the same strain of rats. A NOAEL was not identified.

In the F344/N rat gavage study, all males exposed to 240 or 480 mg/kg-day and 9/10 females exposed to 300 mg/kg-day died; clinical signs preceding death included tremors, salivation, emaciation, abnormal postures, ruffled fur, and dyspnea (NTP, 1991). The deaths occurred throughout the exposure period. Pathology evaluation of moribund/dead animals showed necrosis in the thymus and cerebellum, as well as hyperplasia, inflammation, and mineralization in the forestomach mucosa. No deaths occurred at other doses, and there were no effects on growth at sublethal doses. Statistically significant differences from control values were observed in various hematological (decreased Hgb) and serum chemistry (increased ALT and SDH) measures in males dosed at 120 mg/kg-day, but these changes were not observed consistently throughout the study. Hematology and serum chemistry were not evaluated in females. As with the drinking water studies, both kidney and liver weights were affected by gavage treatment with 1,2-DCA (see Table 4) at sublethal doses. In male F344/N rats exposed via gavage, absolute kidney weights were significantly increased over controls at all doses, while relative kidney weights were higher at ≥60 mg/kg-day. In females, both absolute and relative kidney weights were significantly increased at ≥75 mg/kg-day. Absolute and relative liver weights were significantly increased in males at 120 mg/kg-day and in females at all doses. No liver lesions were reported in any group exposed via gavage. Renal tubular regeneration was observed in all dosed groups, but incidence was comparable to that of vehicle controls. These experiments identified a (Frank Effect Level) FEL of 240 mg/kg-day for mortality in male F344/N rats. A LOAEL of 75 mg/kg-day is identified based on increased absolute kidney weights in females. This determination is supported by the finding of renal histopathology in the same strain and sex of rat (female F344/N rats) exposed to higher doses of 1,2-DCA in the associated drinking water study (NTP, 1991). Increases in absolute and relative kidney weights were noted in males at lower doses in this study, but these changes were not associated with any histopathology in either this or the drinking water study. As such, the increases in kidney weights were not considered to be adverse in male rats. Increased liver weights were also noted at lower doses (i.e., ≥18 mg/kg-day in females); however, the increase in liver weight is considered to be nonadverse due to the lack of accompanying histopathology in this and other studies. Based on these considerations, the LOAEL for this study is 75 mg/kg-day based on increased kidney weight in females, and the NOAEL is 37 mg/kg-day.

Table 4. Significant Changes in F344/N Rats Treated with 1,2-DCA Via Gavage for 13 Weeks[a]

Parameter Evaluated	Dose (mg/kg-day)					
	Control	**30**	**60**	**120**	**240**	**480**
Males						
Final body weight (g)	333 ± 4[b]	346 ± 5	349 ± 9	338 ± 9	No survivors	No survivors
Organ weights						
Absolute kidney weight (mg)	1,324 ± 29	1,441 ± 26[c]	1,600 ± 54[d]	1,653 ± 47[d]		
Relative kidney weight (mg/g)	3.9 ± 0.06	4.1 ± 0.10	4.5 ± 0.08[d]	4.9 ± 0.07[d]		
Absolute liver weight (mg)	17,000 ± 440	17,960 ± 510 (*n* = 9)	18,270 ± 540	19,400 ± 660[c] (*n* = 9)		
Relative liver weight (mg/g)	50.2 ± 0.87	50.9 ± 0.97 (*n* = 9)	51.7 ± 0.92	57.4 ± 0.83[d] (*n* = 9)		
Females						
	Control	**18**	**37**	**75**	**150**	**300**
Final body weight (g)	193 ± 2	193 ± 2	197 ± 3	199 ± 3	194 ± 3	177
Organ weights						
Absolute kidney weight (mg)	800 ± 16	717 ± 70	798 ± 20	898 ± 23[d]	984 ± 9[d]	No data
Relative kidney weight (mg/g)	4.2 ± 0.08	3.8 ± 0.37	4.1 ± 0.09	4.6 ± 0.08[c]	5.1 ± 0.08[d]	No data
Absolute liver weight (mg)	7,345 ± 120	8,000 ± 201[c]	7,920 ± 191[c]	8,577 ± 197[d]	9,775 ± 151[d]	No data
Relative liver weight (mg/g)	38.7 ± 0.54	42.1 ± 0.87[d]	40.8 ± 0.61[c]	43.6 ± 0.69[d]	51.0 ± 1.08[d]	No data

[a]NTP, 1991
[b]Mean ± standard error; *n* = 10 per group unless noted otherwise
[c]Significantly different from control at $p < 0.05$
[d]$p < 0.01$

In the mouse drinking water study, 9/10 female mice exposed to 8,000 ppm died before the end of the study; there were no deaths in other treatment groups (NTP, 1991). No treatment-related clinical signs were observed at any dose, and water consumption, while variable, was similar between treated and control animals. Terminal body weights were lower in all treated groups of mice relative to controls (~5−10%); a decrease of 10% was observed only in males exposed to 8,000 ppm. Hematological and serum chemical analyses were not performed on mice. Table 5 shows organ-weight changes, limited to the kidney and liver. Significantly ($p < 0.05$) increased absolute and relative kidney weights occurred in males exposed to ≥1,000 ppm and in all treated females. The difference from controls increased with dose in males but not in females. Increased relative liver weight was observed in all treated males; absolute liver weight was increased only at ≥4,000 ppm in males. In females, relative liver weight was increased at ≥1,000 ppm, while absolute liver weight was significantly increased only at ≥4,000 ppm. A dose-related increase in the incidence of renal tubular regeneration (minimal-to-moderate) occurred in males (statistically significant versus controls in the 4,000- and 8,000-ppm groups, $p < 0.01$). Other renal lesions, including karyomegaly, dilatation, protein casts, and mineralization occurred in males at the highest dose but not in any other treated or control groups. Renal tubular regeneration was observed in 1/10 females at 4,000 ppm; no other renal lesions were reported in females. Treatment-related histopathology was not observed in other tissues. A NOAEL and LOAEL of 249 and 448 mg/kg-day (500 and 1,000 ppm), respectively, are identified for increased kidney weight in male mice. The increased kidney weight in male mice is considered to be an early stage adverse effect based on the dose-related increase in the incidence of renal histopathology observed at higher doses. Although increased kidney weights were observed in female mice exposed to 500-ppm 1,2-DCA, this change in females was not clearly adverse, as there was no further increase in kidney weight with dose and the weight change was not accompanied by histopathology at any dose.

In the third subchronic study, Daniel et al. (1994) exposed Sprague-Dawley rats (10/sex/dose) to 1,2-DCA (purity not reported; verified by gas chromatograph/mass spectrometry [GC/MS] to contain "no detectable impurities") in corn oil by gavage at doses of 0 (vehicle control), 37.5, 75, or 150 mg/kg-day for 90 consecutive days. Signs of toxicity were assessed daily, and body weight was measured weekly. Food and water intake were measured twice weekly. Ophthalmoscopy was evaluated before and after the exposure period. Urine samples collected during the last week of the study were analyzed for pH, protein, glucose, bilirubin, urobilinogen, and occult blood analyses. Prior to euthanization, blood was collected for hematology (WBC, RBC, Hgb, and Hct) and serum chemistry (BUN, creatinine, ALP, AST, ALT, lactate dehydrogenase, total bilirubin, total protein, albumin, calcium, sodium, and potassium). Comprehensive gross examinations were conducted at necropsy; the brain, liver, spleen, lungs, thymus, kidneys, adrenals, heart, and gonads were weighed. Comprehensive histopathology examinations were performed on control and high-dose animals, as well as on target tissues in other dose groups.

Table 5. Significant Changes in B6C3F1 Mice Treated with 1,2-DCA in Drinking Water for 13 Weeks[a]

Parameter Evaluated	Concentration in Water (ppm)					
	Control	500	1,000	2,000	4,000	8,000
Males						
Dose (mg/kg-day)	0	249	448	781	2,710	4,207
Final body weight (g)	31.4 ± .06[b]	28.9 ± 0.6	29.3 ± 0.5	29.4 ± 0.8	28.6 ± 0.7	25.9 ± 0.7
Organ weights						
Absolute kidney weight (mg)	305 ± 7	301 ± 8	323 ± 7[c]	358 ± 8[d]	385 ± 9[d]	379 ± 12[d]
Relative kidney weight (mg/g)	10.2 ± 0.22	10.8 ± 0.12	11.4 ± 0.12[d]	12.4 ± 0.33[d]	13.8 ± 0.40[d]	15.0 ± 0.54[d]
Absolute liver weight (g)	1,455 ± 55	1,490 ± 42	1,519 ± 55	1,571 ± 56	1,628 ± 54[c]	1,598 ± 78[c]
Relative liver weight (mg/g)	48.5 ± 1.06	53.6 ± 0.91[d]	53.4 ± 1.18[d]	54.3 ± 1.46[d]	57.6 ± 1.10[d]	62.8 ± 2.13[d]
Kidney histopathology[e]						
Tubular regeneration	0/10	1/10	2/10	2/10	8/10[d]	9/10[d]
Karyomegaly	0/10	0/10	0/10	0/10	0/10	10/10[d]
Dilatation	0/10	0/10	0/10	0/10	0/10	5/10[c]
Protein casts	0/10	0/10	0/10	0/10	0/10	8/10[d]
Mineralization	0/10	0/10	0/10	0/10	0/10	5/10[c]
Females						
Dose (mg/kg-day)	0	244	647	1,182	2,478	4,926
Final body weight (g)	25.9 ± 0.6	24.7 ± 0.5	23.2 ± 0.6	23.7 ± 0.5	23.8 ± 0.6	23.4[f]
Organ weights						
Absolute kidney weight (mg)	191 ± 4	225 ± 6[d]	211 ± 5[d]	212 ± 7[d]	215 ± 7[d]	217
Relative kidney weight (mg/g)	8.0 ± 0.23	9.4 ± 0.21[d]	9.4 ± 0.17[d]	9.3 ± 0.24[d]	9.3 ± 0.22[d]	9.4
Absolute liver weight (g)	1,258 ± 39	1,258 ± 52	1,263 ± 34	1,314 ± 56	1,383 ± 29[c]	1,391
Relative liver weight (mg/g)	52.5 ± 0.85	51.5 ± 0.95	56.0 ± 0.67[c]	56.1 ± 1.18[c]	59.7 ± 1.01[d]	60.5

[a]NTP (1991)
[b]Mean ± standard error; $n = 10$ per group unless noted otherwise
[c]Significantly different from control at $p < 0.05$
[d]$p < 0.01$
[e]Number affected/number examined
[f]Only one mouse survived to termination

There were no treatment-related deaths or clinical signs of toxicity in any groups (Daniel et al., 1994). Table 6 shows significant changes in body weight, hematology, and organ weights. Terminal body weight and food consumption were significantly decreased at 150 mg/kg-day in males (body weight was 17% less than controls; $p < 0.05$; food consumption data not shown) but comparable to controls in all other groups. No effects were observed upon ophthalmoscopic examination in any group. Hematology changes occurred in both male and female rats. In males, hemoglobin was significantly decreased (compared with controls) at the two highest doses ($p \leq 0.05$), while hematocrit was significant decreased at 75 mg/kg-day ($p \leq 0.05$) but increased at 150 mg/kg-day ($p \leq 0.05$). Platelets were also significantly ($p \leq 0.05$) increased in the high-dose group (see Table 6). In females exposed to the highest dose, red blood cells, lymphocytes, hemoglobin, and hematocrit were significantly ($p \leq 0.05$) decreased while platelets, white blood cells, neutrophils, and monocytes were significantly ($p \leq 0.05$) increased; however, the values reported are within reference ranges for these parameters (Wolford et al., 1986). Few serum chemistry changes were noted; in females, potassium levels were increased, and albumin levels decreased at ≥75 mg/kg-day, while in males, ALP was increased at these doses (data not shown in original manuscript). According to the authors, urinalysis data were unremarkable (data not shown). Changes in relative organ weights were observed at the mid- and high doses; absolute organ weights were not reported. In males, relative brain, kidney, and liver weights were significantly ($p \leq 0.05$) increased at doses of ≥75 mg/kg-day; increases in relative testes and adrenal weights occurred at 150 mg/kg-day, but were probably attributable to the body-weight decrements at this dose. In females, relative kidney weight was increased at ≥75 mg/kg-day (up to 22%) and relative liver weight at 150 mg/kg-day (32%); no other organ weight changes occurred in females. None of the few gross or microscopic lesions observed were considered by the researchers to be related to treatment (no further details reported). A LOAEL of 75 mg/kg-day is identified for these data based on increases in relative liver weights in males at this dose; the NOAEL is 37.5 mg/kg-day. Although the liver weight changes were not associated with any histopathology, Daniel et al. (1994) reported increased ALP levels in male rats, potentially indicative of hepatotoxicity, at doses of ≥75 mg/kg-day. Other changes at the LOAEL were increases in relative kidney weights, decreases in Hgb and Hct (and RBC in females), and increases in platelets in male and female rats.

Table 6. Significant Changes in Sprague-Dawley Rats Treated with 1,2-DCA by Gavage for 90 Days[a]

	Dose (mg/kg-day)			
	Control	**37.5**	**75**	**150**
Males				
No. animals examined	10	10	10	10
Terminal body weight	597 ± 30[b]	590 ± 30	562 ± 44	495 ± 39[c]
Hematology				
Hemoglobin (g/dL)	16.2 ± 0.6	16.0 ± 0.6	15.4 ± 0.5[c]	15.2 ± 0.7[c]
Hematocrit (%)	46.0 ± 2.1	45.4 ± 1.8	46.7 ± 1.1[c]	43.0 ± 2.0[c]
Platelets × 10^3	1,179 ± 188	1,219 ± 125	1,252 ± 91	1,394 ± 208[c]
Organ weights				
Brain (%)	0.40 ± 0.03	0.40 ± 0.02	0.43 ± 0.03[c]	0.49 ± 0.04[c]
Kidneys (%)	0.62 ± 0.06	0.66 ± 0.06	0.73 ± 0.05[c]	0.84 ± 0.07[c]
Liver (%)	2.59 ± 0.21	2.69 ± 0.16	3.10 ± 0.42[c]	3.40 ± 0.36[c]
Females				
No. animals examined	10	10	10	10
Terminal body weight	304 ± 31[b]	311 ± 33	284 ± 23	294 ± 35
Hematology				
Hemoglobin (g/dL)	15.9 ± 0.6	15.9 ± 0.7	15.2 ± 0.8	14.8 ± 0.7[c]
Hematocrit (%)	45.0 ± 1.7	45.2 ± 2.3	43.5 ± 1.7	41.6 ± 1.9[c]
Platelets × 10^3	1,119 ± 65	1,130 ± 115	1,235 ± 165	1,410 ± 156[c]
Red blood cells × 10^6	8.3 ± 0.03	8.4 ± 0.04	8.1 ± 0.3	7.7 ± 0.3[c]
White blood cells × 10^3	5.0 ± 2.0	5.6 ± 1.2	5.8 ± 1.0	7.9 ± 2.2 [c]
Neutrophils (%)	20.0 ± 13.2	21.4 ± 11.8	22.4 ± 8.8	26.6 ± 14.4[c]
Lymphocytes (%)	76.0 ± 28.4	76.8 ± 20.2	75.9 ± 16.6	68.4 ± 12.9[c]
Monocytes (%)	2.0 ± 1.8	0.0 ± 0.9	1.7 ± 1.9	2.2 ± 1.1 [c]
Organ Weights				
Kidneys (%)	0.67 ± 0.09	0.70 ± 0.06	0.77 ± 0.07[c]	0.82 ± 0.09[c]
Liver (%)	2.75 ± 0.17	2.85 ± 0.17	3.02 ± 0.35	3.64 ± 0.36[c]

[a]Daniel et al. (1994)
[b]Mean ± standard error
[c]Significantly different from control at $p \leq 0.05$

Chronic Studies—There are two chronic studies: one in rats, and one in rats and mice. In the first study, Alumot et al. (1976) conducted a 2-year study of dietary exposure to 1,2-DCA in which liver function was the primary evaluation. A preliminary study was conducted in which rats were fed dietary levels of 0, 300, or 600 ppm (about 30 or 60 mg/kg-day) 1,2 DCA (purity not specified) for 5 weeks or 1,600 ppm (about 160 mg/kg-day) 1,2-DCA for 7 weeks and liver weight, total liver fat content, and liver triglycerides were measured. Gross and histological examinations were not performed. In the group exposed to 1,600 ppm for 7 weeks, significant

($p < 0.05$) increases in total liver fat (13% higher than controls) and total liver triglycerides (75% higher) were observed, but liver weight was not different from control. Other groups did not exhibit differences from control values. In the 2-year study, groups of rats (18/sex/dose) of unspecified strain were fed a feed mash fumigated with 1,2-DCA (purity not reported) that resulted in measured feed concentrations of 0, 250, or 500 ppm (Alumot et al., 1976). The researchers estimated that 60−70% of the residue initially present in the feed was consumed. Body weight and food intake were recorded weekly for the first 3 months and biweekly thereafter. Based on typical body weights and food consumption, the authors estimated the doses consumed to be approximately 25 and 50 mg/kg-day. The animals were mated for evaluation of reproductive effects; these findings are discussed below under Reproductive and Developmental Studies. During mating periods of 10 days each, the animals were fed control diets. At sacrifice, blood was collected for analysis of total protein, albumin, glucose, urea, cholesterol, uric acid, ALT, and AST. Liver samples were analyzed for total fat, triglycerides, and phospholipids. No gross or microscopic examinations were performed. Survival of all groups, especially males, was affected by respiratory disease after 14 months; few males (≤22%) of any group (including controls) survived to study termination. The authors reported that there were no treatment-related effects on survival, growth, food consumption, or serum chemistry indices (data were shown for survival, body weight, and serum chemistry but not food consumption in the study report). In addition, the authors indicated that there were no fatty livers in the treated animals (no further information provided). Due to the uncertainty in dose estimates and limitations in the toxicological evaluations, effect levels were not determined.

In the second chronic study, which was used as the critical study, NCI (1978) carcinogenicity study, Osborne-Mendel rats (50/sex/group) were treated with 1,2-DCA (>90% pure) in corn oil by gavage at variable doses administered 5 days/week for 78 weeks. NCI (1978) estimated TWA doses (averaged over the 78-week treatment period, but not converted to equivalent continuous, 7-day per week doses) of 47 or 95 mg/kg-day for 78 weeks. B6C3F1 mice (50/sex/group) were also treated for 78 weeks with TWA doses of 97 or 195 mg/kg-day (males) and 149 or 299 mg/kg-day (females), 5 days/week. Untreated and vehicle controls (20/sex/group) of both species were maintained concurrently. Signs of toxicity, body weight, and food consumption were recorded weekly, and animals were palpated for tissue masses at the same time. Hematological and clinical chemistry determinations were not conducted. Observation continued for 13 weeks after the dosing period. Comprehensive gross and histological examinations were performed upon moribund condition, death, or sacrifice at the end of the bioassay.

In rats, mortality was significantly ($p < 0.001$) increased in both sexes exposed to 95 mg/kg-day when compared with controls but was not significantly affected in the low-dose group (NCI, 1978). Survival of male and female rats treated with 95 mg/kg-day was 50% at Weeks 55 and 57, respectively. For rats treated with 47 mg/kg-day, survival was reported as 52% at 82 weeks for male rats and 50% at 85 weeks in female rats. Of the vehicle controls, 50% of male and female rats survived at least 72 and 88 weeks, respectively, while 50 and 60% of untreated male and female control rats survived until the end of the study. The study authors attributed the high mortality in the rats to toxic effects and bronchopneumonia rather than to cancer. Several rats (number not reported) in both the 47- and 95-mg/kg-day dose groups had a hunched appearance and transient labored breathing beginning during the 6th week of treatment. Although one or two control rats (untreated or vehicle not specified) started to show these signs, the incidence was reported to be substantially higher in the treated groups than in the control

groups. Other treatment-related clinical signs observed during the first year included abdominal urine stains, cloudy or squinted eyes, and reddish crust on the eyes (incidence and affected doses not reported). Based on data shown in the report, there were no effects on body weight. The only treatment-related nonneoplastic lesion found upon microscopic examination was splenic hematopoiesis in female rats. Splenic hematopoiesis occurred in 0/20 untreated controls, 1/20 vehicle controls, and 0/50 low-dose and 16/50 high-dose females; the incidence at the high dose was statistically significantly different from controls ($p < 0.05$ by Fisher's exact test conducted for this review). A number of neoplasms were observed at increased incidence in male and/or female rats, including squamous cell carcinoma of the forestomach, hemangiosarcoma of the spleen and other sites, adenocarcinoma of the mammary gland, and subcutaneous fibroma. For noncancer effects, a LOAEL of 47 mg/kg-day, the lowest dose tested, is identified for clinical signs of labored breathing and hunched appearance in both sexes of rats. A NOAEL was not identified. However, the quality of this study was limited by dosage adjustments and poor survival; in addition, the clinical signs observed after Week 6 in this study were not seen in subchronic studies of rats exposed via gavage or drinking water to much higher doses (NTP, 1991).

Female mice treated with 299 mg/kg-day also had significantly increased mortality, but mortality was not affected in the other groups of mice (NCI, 1978). These deaths may have been tumor-related as 25/36 (69%) had one or more tumors. For male mice, there was no statistically significant association between 1,2-DCA dosage and mortality. Clinical signs in treated groups were unremarkable compared with controls. Body weight was not affected by treatment in male mice or low-dose female mice. Body weight in high-dose female mice became significantly depressed around 30 weeks and was reduced by >45% of control weight at 90 weeks. The incidence of chronic murine pneumonia was dose-related in mice; present in 0/17 untreated control, 0/19 vehicle control, 5/46 low-dose, and 11/47 high-dose males, and in 0/19 untreated control, 0/20 vehicle control, 1/50 low-dose and 6/48 high-dose females. However, only the incidence in high-dose males was statistically significantly different from controls ($p < 0.05$ by Fisher's exact test conducted for this review). No other treatment-related nonneoplastic lesions were found in mice. Increases in the incidences of hepatocellular carcinomas, alveolar/bronchiolar adenomas, mammary adenocarcinomas, endometrial tumors, and squamous cell carcinomas were observed in male or female mice. For noncancer effects, a NOAEL and LOAEL of 97 and 195 mg/kg-day, respectively, are identified for a significant increase in the incidence of chronic murine pneumonia in male mice.

Reproductive/Developmental Studies—There was one developmental and one multigenerational reproductive study in the literature. Reproductive function was assessed in the 2-year study conducted by Alumot et al. (1976). Groups of rats (18/sex/dose; strain not reported) were given feed fumigated with 1,2-DCA (purity not reported) to produce measured feed concentrations of 0, 250, or 500 ppm. The authors calculated doses of approximately 25 and 50 mg/kg-day based on typical body weight and food consumption. In addition to assessments of mortality, growth, and serum chemistry, the animals were mated periodically (first mating after 6 weeks of exposure) to assess reproductive function (pregnancy rate, birth rate, litter size, and pup survival and body weight at birth and at weaning). During mating periods of 10 days each, the animals were fed control diets; as a result, the overall doses received by the animals are somewhat uncertain. No differences were found in any of the parameters assessed (number of pregnancies and litters, litter size, mortality of young at birth and weaning, and the body weight

of young at birth and at weaning). Limitations in the reporting of this study and uncertainty in dose estimates preclude the determination of effect levels.

Mated female Sprague-Dawley rats (25−26/group) were given 0 (vehicle control), 1.2, 1.6, 2.0, or 2.4 mmol/kg-day 1,2-DCA (>99% pure) dissolved in corn oil (equivalent to 0, 119, 158, 198, or 238 mg/kg-day) by gavage on Gestation Days (GD) 6−20 (15 days) (Payan et al., 1995). Maternal body weights were measured on GD 0 and every 3 days during treatment. Dams were sacrificed on GD 21 for assessment of uterine weight and examination of uterine contents. Numbers of implantations, resorptions, and live and dead fetuses were noted. Live fetuses were weighed, sexed, and examined for external malformations. Half of the live fetuses were prepared for skeletal examination and the remainder for visceral examination. No maternal deaths occurred. A dose-related reduction in adjusted (for gravid uterine weight) maternal body-weight gain during treatment occurred, with statistical significance achieved at the two highest doses (30 and 49% reduction compared with controls, $p < 0.05$). Pregnancy rates were similar in all groups. However, three dams exposed to the highest dose of 1,2-DCA delivered their litters a day earlier than expected, and the litters were excluded from analysis due to the possibility that cannibalization of part of the litter may have occurred. Treatment with 1,2-DCA did not result in significant changes to the mean numbers of implantation sites and live fetuses, fetal sex ratio, or fetal weights. There was a slight but significant ($p < 0.05$) dose-related trend for increased resorptions (2.48 ± 0.89; 2.19 ± 0.84; 5.86 ± 2.55; 7.08 ± 1.49; and 13.30 ± 7.05 percent for control through high-dose); the difference from controls in pair-wise tests reached statistical significance ($p < 0.05$) only at ≥198 mg/kg-day. While the mean percentage of resorptions was increased at 238 mg/kg-day, the difference from controls was not statistically significant, apparently due to the smaller group size and larger variability. Incidences of external, visceral, and skeletal variations and malformations were similar in all groups. A developmental NOAEL and LOAEL of 158 and 198 mg/kg-day, respectively, are identified for increased resorptions. The maternal toxicity NOAEL and LOAEL are also 158 and 198 mg/kg-day, respectively for decreased body-weight gain during treatment.

In the multigeneration reproduction study, Lane et al., 1982 treated male and female ICR Swiss mice continuously with drinking water (ad libitum) containing 30, 90, or 290 ppm of 1,2-DCA (>99% pure), giving nominal daily doses of 0, 5, 15, or 50 mg/kg-day (Lane et al., 1982). Both vehicle (1% Emulphor) and untreated control groups were included. The parental (F0) generation was maintained on the exposure regimen for 35 days before the first mating period. Two weeks after the weaning of the F1A litters, the F0 parents were remated to produce the F1B litters. In a third mating of the F0 parents, the males were used in a dominant lethal study, while the females were used for a teratology study (F1C). Randomly selected pups from the F1B litters were mated at 14 weeks of age and then remated after weaning of the F2A litters, producing the final F2B litters. As with the F1C litters, the F2B litters were also used for dominant lethal and teratology studies. Among parents of the F0 and F1B generations, body weight was measured weekly, and fluid intake was recorded biweekly. After 24 or 25 weeks of dosing, the F0 and F1B parents were sacrificed and subjected to gross necropsy. Fertility and gestation indices were calculated from all matings. Litter observations included 21-day survival; litter size on Postnatal Days (PND) 0, 4, 7, 14, and 21; litter weights on PND 7 and 14; pup weights on PND 21; and viability and lactation indices. Pups from all generations were sacrificed and given gross necropsy after PND 21.

In the dominant lethal studies, treated males were mated with untreated females (Lane et al., 1982). After 14 days from the midpoint of the mating period, the females were sacrificed for examination of uterine contents. Numbers of implantations, early and late resorptions, and viable fetuses were counted. In the teratology studies, treated females were mated with untreated males and examined daily for a vaginal plug. On GD 18, the females were sacrificed, and uterine contents were examined; numbers of implantations, resorptions, and viable and nonviable male and female fetuses were recorded. Each fetus was weighed and evaluated for external malformations. If no external malformations were found, each third fetus was prepared for evaluation of visceral malformations, and the remainder were prepared for assessment of skeletal malformations. Due to a preparation error, the F1C fetuses were not examined for skeletal malformations.

No parental treatment-related effects were observed in F0 and F1B generations as judged by mortality rates, fluid intake, body-weight gain, and gross pathology (data shown; Lane et al., 1982). Furthermore, there were no significant differences between treated and control groups for gestation or fertility indices, weight gain, numbers of implantations, resorptions, or live fetuses, or on 4- and 21-day survival in any of the matings (data shown for all but weight gain). There was also no evidence of dominant lethality in treated males mated to untreated females. Finally, based on data shown in the report, no significant increase in gross, visceral, or skeletal anomalies or any fetotoxic effects were observed in the teratology studies. This study identifies a NOAEL of 50 mg/kg-day, the highest dose tested, for both parental and offspring toxicity.

Inhalation Exposure

Subchronic Studies—In the sole subchronic inhalation study, Nagano et al. (2006) conducted a subchronic dose range-finding study in preparation for a chronic toxicity/carcinogenicity bioassay of 1,2-DCA. Little information was provided on the range-finding study. Groups of F344/DuCrj rats and Crj:BDF1 mice of both sexes (number not reported) were exposed via inhalation to 1,2-DCA (>99% pure) for 13 weeks. Endpoints were limited to mortality, clinical signs, and body weight. The authors observed 100% mortality in rats exposed to 320 ppm (1,295 mg/m^3) 1,2-DCA, but no mortality, clinical signs, or body-weight changes at 160 ppm (648 mg/m^3). In the range-finding study of mice, 6/10 female mice exposed to 160 ppm (648 mg/m^3) 1,2-DCA died, while 7−9% body-weight reductions were observed in males and females exposed to 80 ppm (324 mg/m^3); no other mortality or signs of toxicity were reported. This study identifies FELs of 1,295 and 648 mg/m^3 (320 and 160 ppm) for rats and mice, respectively.

Chronic Studies—There are six chronic inhalation studies: three in rats, one in rats and mice, and two in multiples species. In the first chronic study, Heppel et al. (1946) exposed several species, including dogs, cats, guinea pigs, rabbits, rats, mice, and monkeys (strains not reported) to 420, 730, 1,540, or 3,900 mg/m^3 of commercial 1,2-DCA (purity not reported) 7 hours/day, 5 days/week for up to 8 months. Not all species were exposed to all concentrations. The duration of exposure varied with the exposure level and species, and group size and sex ratio were variable. Each exposure level was accompanied by control animals, but not all exposed species were represented by controls at each level. Toxicological evaluations varied with species and exposure level; mortality, clinical signs, and gross and microscopic pathology were evaluated in at least some animals in most experiments. Treatment-related mortality was observed in guinea pigs and rats exposed to ≥730 mg/m^3, in rabbits exposed to ≥1,540 mg/m^3,

and in dogs, cats, and monkeys exposed to 3,900 mg/m^3. Necropsy of animals that died often revealed pulmonary congestion, myocarditis, and/or fatty degeneration of the liver, kidney, and/or heart. Only rats, mice, and guinea pigs were exposed to the lowest concentration of 420 mg/m^3; the duration of exposure was 4 months. No compound-related deaths were observed at this level, but the guinea pigs of both control and exposed groups suffered from growth depression, disease, and some deaths unrelated to treatment. The female rats were bred, and the litter survival rates were characterized as "satisfactory" (data not shown). Evaluation of mice was limited to body weight, which was not affected at this exposure (data not shown). Gross and microscopic examinations (not specified) of selected rats and guinea pigs exposed to 420 mg/m^3 were unremarkable (data not shown). This study identified a FEL of 730 mg/m^3 (180 ppm) based on significant mortality in rats and guinea pigs. Limitations in study design (variable exposure protocols, group sizes, and toxicological evaluations) and reporting (strains and sexes not reported, results not reported quantitatively) preclude the identification of reliable effect levels from this study.

In the second chronic study, Spencer et al. (1951) exposed groups of Wistar rats (15/sex/group) for 212 days (30 weeks, up to 151 exposures), randomly bred guinea pigs (8/sex/group) for 162−246 days (23−35 weeks, up to 180 exposures), randomly bred rabbits (2 male and 1 female per group) for 232−248 days (33 to 35 weeks, up to 178 exposures), and rhesus monkeys (2/males/group) for up to 240 days (34 weeks, up to 178 exposures) to 0 (unexposed), 0 (chamber-exposed), 405, 810, or 1,620 mg/m^3 of 1,2-DCA (99.7% pure) 7 hours/day, 5 days/week. Rabbits and monkeys did not receive the mid-level exposures. Endpoints examined included body weight and food consumption, hematologic (not specified, but included prothrombin clotting time) and serum chemistry (BUN, nonprotein nitrogen, phosphatase) parameters, lipid content of liver (total, phospholipid, neutral fat, and free and esterified cholesterol), organ weights (lung, heart, liver, kidneys, spleen, and testes), and gross and histologic examination of the major organs and tissues (not specified). At 1,620 mg/m^3, the highest concentration, all rats, guinea pigs, and monkeys died or were killed in extremis within 56 (rats), 32 (guinea pigs), or 12 days (monkeys). Mortality was accompanied by weight loss (rats and guinea pigs), fatty livers (rats), fatty liver degeneration (guinea pigs and monkeys), cloudy swelling of the kidney tubular epithelium (guinea pigs), renal tubule degeneration with cast formation (monkeys), and increased liver and kidney weights (guinea pigs). There were no effects in rabbits at this concentration. At 810 mg/m^3, there was no mortality in either rats or guinea pigs (the only species tested). Rats exposed at this concentration exhibited no treatment-related effects on growth, organ weights, hematology, clinical chemistry, or histopathology. Both male and female guinea pigs showed poorer growth at 810 mg/m^3, but final body weight was significantly ($p = 0.001$) depressed only in males (16% less than controls). At 810 mg/m^3, half the guinea pigs of both sexes had parenchymatous liver degeneration with fat vacuoles. No effects on any of the parameters evaluated were observed in any of the four species exposed to 405 mg/m^3 of 1,2-DCA. A NOAEL and LOAEL of 405 and 810 mg/m^3, respectively, are identified for liver lesions (both sexes) and reduced body weight (males) in guinea pigs. The high concentration (1,620 mg/m^3) is a FEL for significant mortality in rats, guinea pigs, and monkeys.

In the third chronic study, Maltoni et al. (1980; Spreafico et al., 1980) exposed groups of male and female Sprague-Dawley rats and Swiss mice (90/sex/species/group) to concentrations of 5, 10, 50, or 150−250 ppm (20, 40, 202, or 607−1,012 mg/m^3) of 1,2-DCA (99.8% pure) 7 hours/day, 5 days/week for up to 18 months starting at age 11−12 weeks. Two control groups

of 180 rats (one chamber control and one untreated) and one group of 249 untreated mice were examined. After several days of exposure, the highest exposure level was decreased from 250 to 150 ppm because of severe toxicity (not further described). Body weights of all animals were recorded every 2 weeks during exposure. Interim sacrifices of 8−10 rats were made after 3, 6, or 18 months of exposure. At each interim sacrifice, hematology (Hgb, Hct, MCV, RBC, total and differential WBC, and platelet count) and serum chemistry (glucose, ALP, AST, ALT, GGT, albumin, bilirubin, cholesterol, lactic acid dehydrogenase [LDH], creatine phosphokinase, BUN, total proteins, uric acid, and electrolytes), and urinalysis (pH, proteins, bilirubin, glucose, Hgb, RBC, WBC, epithelial cells, casts, crystals, mucus, and microorganisms) were evaluated (rats only). Additional groups of 8−10 rats were started at age 14 months and exposed for 12 months to the same concentrations for evaluation of hematology and serum chemistry (only). Animals that were not sacrificed early were followed until natural death, whereupon gross necropsy was performed, along with microscopic examination of >18 tissues (including the lungs, liver, kidneys, and gonads).

Spreafico et al. (1980) reported methods and results of the blood analyses (most results reported only qualitatively), while Maltoni et al. (1980) reported the survival findings and neoplastic histopathology endpoints; nonneoplastic histopathology findings, if any, were not reported. No information was provided in either report on the nature or extent of the toxicity at 1,012 mg/m^3 that led to the reduction in exposure concentration to 607 mg/m^3 in the high-exposure group; it is not clear whether this toxicity included mortality. No concentration related effect on mortality was observed in the rats exposed to concentrations up to 607 mg/m^3. Sporadic statistically significant (statistical analyses and p value not reported by authors) changes in hematology, serum chemistry, and urinalysis parameters were observed in rats exposed to 1,2-DCA for 3, 6, or 18 months; however, evaluation of the data showed that these changes did not exhibit clear dose- or time-dependence. In rats that were exposed for 12 months beginning at age 14 months, some significant dose-related alterations in clinical chemistry values were observed, as shown in Table 7. Marked increases in ALT were observed in both sexes at the two highest concentrations (from 2- to 8-fold higher than controls). GGT was increased 96−111% over controls in females exposed to the two highest concentrations, although this change was not statistically significant. Serum uric acid and glucose (data not shown) were significantly higher than controls in rats exposed to 202−607 mg/m^3; however, these parameters were unusually low in control animals at this time point when compared with other time points, potentially inflating the difference associated with treatment. Nonneoplastic pathology data were not reported. The incidences of tumors were not different between the treatment and control groups. The clinical chemistry data from the rats exposed for 12 months beginning at age 14 months are suggestive of liver and possibly kidney toxicity and indicate a NOAEL and LOAEL of 40 and 202 mg/m^3 (10 and 50 ppm), respectively. The fact that these effects were not observed in younger rats exposed to the same concentrations suggests the possibility that aged animals may be more susceptible to the hepatic and/or renal toxicity of 1,2-DCA.

Table 7. Significant Serum Chemistry Changes in Sprague-Dawley Rats Treated with 1,2-DCA via Inhalation for 12 Months Beginning at 14 Months of Age[a]

Parameter Evaluated	Concentration (mg/m^3)				
	Control	20	40	202	607
Males					
ALT (milliunits/mL)	22.9 ± 2.3[b]	28.8 ± 3.6	23.2 ± 3.5	90.0 ± 9.3[c]	111.0 ± 13.4
Uric acid (mg %)	0.80 ± 0.1	1.05 ± 0.1	0.95 ± 0.1	1.50 ± 0.1[c]	1.90 ± 0.1[c]
Females					
ALT (milliunits/mL)	15.7 ± 1.0	23.4 ± 3.1	28.2 ± 4.5	143.0 ± 11.7[c]	110.1 ± 10.7[c]
GGT (milliunits/mL)	0.83 ± 0.3	0.63 ± 0.2	0.65 ± 0.4	1.63 ± 0.4	1.75 ± 0.2
Uric acid (mg %)	0.94 ± 0.1	1.08 ± 0.1	1.25 ± 0.1	1.63 ± 0.1[c]	3.41 ± 0.3[c]

[a]Spreafico et al. (1980)
[b]Presumed to be mean ± SD; report does not specify; number of animals was 8−10/group
[c]Significantly different from control at $p < 0.05$

The only toxicological information available on treated mice was survival and incidence of neoplasms (Maltoni et al., 1980; Spreafico et al., 1980); statistical analysis of survival rates was not reported. Body weight was reportedly measured, but no data were provided on this endpoint. Female high-concentration mice appeared to have slightly increased mortality during the first 80 weeks. Survival of high-concentration females at 78 weeks of age was 48.9% versus 56.8% in control females. Survival of other groups was comparable to controls. The incidences of tumors in mice were not different between the treatment and control groups. Effect levels cannot be determined from this study due to the limited toxicological evaluations performed.

In the fourth chronic study, groups of 50 male and 50 female Sprague-Dawley rats were exposed to 0 (chamber-filtered air exposed control) or 50 ppm (202 mg/m^3) of 1,2-DCA (>99% pure), 7 hours/day, 5 days/week for 2 years (Cheever et al., 1990). Signs of toxicity were noted twice daily, and body weight was measured weekly for 8 weeks and then monthly for the duration of the study. Food and water consumption were measured periodically during the study (frequency not reported). Hematology and clinical chemistry were not assessed. Organ weights (not specified) were recorded, and comprehensive gross and histological examinations (including the respiratory tract) were performed on animals found dead or sacrificed moribund or at the end of the exposure period. Survival, body weights, food consumption, and water consumption of exposed animals were comparable to control values, and clinical signs were unremarkable. Absolute and relative liver weights were not affected by treatment. Gross necropsy revealed a marginal increase in the incidence of testicular lesions in male rats (12/50 exposed versus 5/50 controls, $p = 0.054$ by Fisher's exact test conducted for this review). The lesions were not further described but may have been tumor-related in some animals (interstitial cell tumors of the testes were observed in three treated males and two control males). Histopathological examination did not reveal any differences in the testes between treated and control animals. Exposed female rats were reported to exhibit a slight increase in the incidence of unspecified basophilic focal cellular changes in the pancreas (data not shown, and no further detail provided). No other nonneoplastic lesions were reported. In addition, there were no exposure-related increases in the incidences of any tumors. The only exposure concentration tested, 202 mg/m^3 (50 ppm), is a NOAEL for systemic toxicity.

In the fifth chronic study, Nagano et al. (2006) conducted a chronic toxicity/carcinogenicity bioassay of 1,2-DCA (>99% pure) using F344/DuCrj rats and Crj:BDF1 mice exposed via inhalation. Exposure concentrations were selected on the basis of a subchronic dose range-finding study described earlier. In the chronic study, groups of 50 animals/sex were exposed to target concentrations of 0, 10, 40, or 160 ppm (rats) or 0, 10, 30, or 90 ppm (mice) continuously for 2 years. Daily observations for mortality and clinical signs were performed. Food intake and body weight were recorded weekly for the first 14 weeks and monthly for the remainder of the study. The toxicological evaluations were performed at the end of exposure and included hematology, serum chemistry, and urinalysis (parameters not specified), gross necropsy, selected organ weights (organs not specified), and comprehensive histopathology (tissues not specified). The authors reported that the study was "conducted with reference to" OECD Guideline 453 (Chronic Toxicity/Carcinogenicity Studies). Based on Guideline 453 (OECD, 2008), serum chemistry parameters likely included total protein; albumin; ALP, AST, and/or ALT; GGT; and ornithine decarboxylase. Average measured concentrations of 1,2-DCA were 0, 10.0 ± 0.1, 39.8 ± 0.6, and 159.7 ± 2.1 ppm for the exposed rats (0, 40, 162, or 648 mg/m^3), and 0, 10.0 ±0.2, 30.0 ± 0.4, and 89.8 ± 1.2 ppm for exposed mice (0, 40, 121, or 364 mg/m^3) (Nagano et al., 2006). As shown by data presented in the report, there were no significant treatment-related effects on survival or body weight in rats and mice. The study authors also reported that there were no significant treatment-related effects on food consumption, hematology, serum chemistry, urinalysis, or incidence of nonneoplastic histopathology changes (data not shown). Survival was significantly reduced ($p < 0.01$ compared with controls) in female mice exposed to 30 ppm; however, survival was not significantly different from controls at the high concentration. The authors attributed the deaths at 30 ppm to malignant lymphoma and reported that neither reduced survival nor the incidences of malignant lymphoma were related to exposure to 1,2-DCA. This study indicates a NOAEL of 648 mg/m^3 (160 ppm) for noncancer effects in rats. Although no treatment-related nonneoplastic changes were observed in mice exposed to concentrations up to 364 mg/m^3 (90 ppm), mortality from tumors in female mice exposed to 121 mg/m^3 limits the conclusions that can be drawn from the mouse study. The low concentration (40 mg/m^3) is considered a NOAEL for noncancer effects in mice.

Nagano et al. (2006) observed concentration-related increases in the incidences of subcutaneous fibroma (both sexes of rat), mammary gland fibroadenoma (both sexes of rat), mammary gland fibroma (female rats), mammary gland adenocarcinoma (female rats and mice), peritoneal mesothelioma (male rats), bronchiole-alveolar adenoma and carcinoma (female mice), endometrial stromal polyp (female mice), and hepatocellular adenoma (female mice).

In the sixth chronic study, Hofmann et al. (1971) exposed groups of randomly bred cats (2/sex/group), randomly bred "colored" rabbits (2/sex/group), Pirbright-White guinea pigs (5/sex/group), and Sprague-Dawley rats (5/sex/group) to 0, 100, or 500 ppm (0, 405, or 2,024 mg/m^3) of 1,2-DCA (>99% pure) 6 hours/day, 5 days/week for up to 17 weeks. The animals were observed for signs of toxicity, and their body weights were measured throughout exposure (frequency not reported). In all species but the guinea pigs, hematology (unspecified), urinalysis (unspecified), and serum chemistry (ALT, AST, urea, and creatinine) were analyzed repeatedly (frequency not reported). Liver function was assessed in rabbits and cats using the bromosulphophthalein test. Upon sacrifice, liver and kidney weights were recorded, and these and other "selected" organs were examined microscopically. At 2,024 mg/m^3, 3/4 rabbits died after 10−17 exposures, 9/10 guinea pigs after 4−14 exposures, and all rats after 1−5 exposures.

Necropsy of animals at this exposure level revealed dilatation of the heart (cats and rabbits), hyperemia with some edema of the lungs (rats and guinea pigs), fatty degeneration with necrosis of the myocardium and liver (rats and guinea pigs), and lipoid nephrosis and disgorgement of the adrenals (rats and guinea pigs). Increased serum urea was noted in cats exposed to 2,024 mg/m^3; no mortality was observed in this species. At 405 mg/m^3, there were no compound-related effects on clinical signs, body weight, clinical chemistry, liver or kidney weights, or histopathology. Hence, a NOAEL 405 (100 ppm) is identified for rabbits, guinea pigs, and rats. The high concentration (2,024 mg/m^3, or 500 ppm) is a FEL for mortality in rabbits, guinea pigs, and rats but is a NOAEL in cats.

Reproductive/Developmental Studies—There are six reproductive/developmental studies in the literature. In the first, groups of pregnant Sprague-Dawley rats (16−30/group) and New Zealand White rabbits (19−21/group) were exposed to 0 (control), 100, or 300 ppm (0, 405, or 1,214 mg/m^3) of 1,2-DCA (99.9% pure) for 7 hours/day on GDs 6−15 (rats) or GDs 6−18 (rabbits) (Rao et al., 1980). Maternal animals were examined daily, and their body weight recorded at intervals (unspecified) during treatment. The animals were sacrificed on GD 21 or 29 for rats or rabbits, respectively, corpora lutea were counted, and uteri were examined for resorption sites and live and dead fetuses. Fetuses were weighed, measured for length, sexed, and examined for external abnormalities, soft tissue alterations (1/3 of animals/group examined), and skeletal abnormalities.

In rats, maternal toxicity at 1,214 mg/m^3 was severe, with 10 deaths among 16 treated rats. Rao et al. (1980) did not report cause and timing of deaths. Prior to dying, rats showed lethargy, ataxia, decreased body weight and food consumption, and some evidence of vaginal bleeding. No fetuses survived from the 1,214 mg/m^3 group (there was only 1 litter at the high exposure level, and it was totally resorbed). No maternal signs of toxicity were observed at the 405 mg/m^3 1,2-DCA level. Exposure to 405 mg/m^3 of 1,2-DCA did not affect mean litter size, the incidence of resorptions, fetal body measurements, or sex ratio. Data provided in the report showed that the incidences of external, visceral, and skeletal malformations were not increased relative to controls at this exposure level. The incidence of a minor skeletal variation, bilobed thoracic centra, was significantly decreased relative to controls among litters from 405 mg/m^3 rats. A maternal and developmental NOAEL of 405 mg/m^3 (100 ppm) and FEL of 1,214 mg/m^3 (300 ppm) for maternal mortality and failure to produce offspring are defined in rats.

In rabbits, the maternal mortality incidence was 0/20, 4/21, and 3/19 among control, low-exposure, and high-exposure groups, respectively (Rao et al., 1980). The researchers considered these deaths to be treatment-related. Exposure did not affect the rate of pregnancy, number of implantation sites/doe, resorption incidence, litter size, sex ratio, or fetal measurements in surviving rabbits. Further, the incidences of external, visceral, and skeletal malformations were not increased among litters of treated rabbits compared with controls. A significant decrease in minor skeletal alterations (extra ribs or lumbar spurs) was reported among treated litters. The lowest exposure level, 405 mg/m^3 (100 ppm) is a FEL for maternal mortality in rabbits. The high exposure level of 1,214 mg/m^3 (300 ppm) is a NOAEL for developmental effects.

In the one-generation reproductive toxicity study, Rao et al. (1980) exposed groups of 20 Sprague-Dawley rats of each sex to 0 (control; 30/sex), 25, 75, or 150 ppm (0, 101, 304, or 607 mg/m^3) of 1,2-DCA (99.9% pure) 6 hours/day, 5 days/week for 60 days. Rats were mated

after a 60-day exposure period, one-to-one within the treatment groups, to produce the F1A generation. Exposure was continued during gestation (6 hours/day, 7 days/week), discontinued from GD 21 to PND 4 and resumed until the second breeding cycle. A week after the F1A litters were sacrificed (at age 21 days), the parental rats were remated to produce the F1B generation. Male rats were exposed from the start of the experiment, initially on a 5 days/week (for 60 days) schedule, then for 7 days/week. The rats were examined daily, and body weight and food consumption were recorded weekly. Upon delivery, live and dead pups were counted; pup survival was recorded again on PND 1, 7, 14, and 21. Litter weights were measured on PND 1, 7, 14, and 21, while individual pup weights were measured on PND 21. Parental animals were sacrificed and necropsied after weaning of the F1B litters. Liver and kidney weights of all parental animals were recorded, and these organs, along with the ovaries, uterus, and testes were examined microscopically in 10 rats/sex from the control and high-exposure groups. Pups from both litters were sacrificed and necropsied at PND 21. Liver and kidney weights were measured in five randomly selected pups/sex/group.

A few deaths occurred (one control female and one male and one female at 101 mg/m^3) but were not related to exposure (Rao et al., 1980). No treatment-related clinical signs or gross or microscopic pathology were observed among parents at any exposure level. Sporadic changes in food consumption were observed but were not attributed to treatment (data not shown). Data regarding fertility and reproduction from the F1A and F1B litters showed no concentration-related effects. Fetal survival through weaning was comparable between all treatment groups and controls. Exposure to 1,2-DCA did not affect neonatal body weight or growth to weaning in the F1A or F1B generations. There were no treatment-related changes in organ weights or histopathologic changes in the kidneys or livers of the F1 generations. In this study, the highest exposure level of 607 mg/m^3 (150 ppm) is a systemic and reproductive NOAEL for 1,2-DCA in rats.

In the second study, Payan et al. (1995) exposed pregnant Sprague-Dawley rats (26/group) for 6 hours/day to measured average concentrations of 0, 150, 194, 254, or 329 ppm (0, 607, 785, 1,028, or 1,332 mg/m^3) of 1,2-DCA (>99% pure) on GDs 6−20. Body weights of maternal animals were recorded on GDs 0, 6, 13, and 21, and the animals were sacrificed on GD 21 for examination of uterine contents. Numbers of implantations, resorptions, and live and dead fetuses were noted. Live fetuses were weighed, sexed, and examined for external and oral malformations. Half were then examined for visceral anomalies, and the remainder were examined for skeletal anomalies. Among the 26 females exposed to the highest concentration, two died during exposure; cause and timing of deaths were not reported. No deaths occurred in any of the other groups. At the high concentration of 1,332 mg/m^3, maternal body weight during GDs 6−21 was significantly less than that of the control group (reduced 24%, $p < 0.05$). At ≤1,028 mg/m^3 of 1,2-DCA, maternal body weight was unaffected. The pregnancy rate among females inhaling 1,028 mg/m^3 of 1,2-DCA was statistically significantly lower than control; however, no effect on pregnancy rate was observed at the highest exposure level, so the change is unlikely to be related to treatment. The data showed no significant differences between treated and control groups in reproductive parameters, fetal body weights or sex ratio, or in the incidences of external, skeletal, or visceral malformations or variations. A maternal NOAEL and LOAEL of 1,028 and 1,332 mg/m^3 (254 and 329 ppm), respectively, are identified for significantly reduced body weight and low mortality at the high concentration. The highest exposure level, 1,332 mg/m^3 (329 ppm), is a developmental NOAEL in rats.

In the third study, pregnant Wistar rats were exposed to 0, 6.1, or 51.3 ppm (0, 24.8, or 207.6 mg/m^3) of 1,2-DCA (98.5% purity) for 6 hours/day, from 2 weeks before mating until sacrifice on GD 20 (Zhao et al., 1989, 1997). The uteri were removed and implantation sites, resorptions, and dead fetuses were recorded. Live fetuses were sexed and weighed. Half of the fetuses were examined for external anomalies and the remaining for internal soft tissue abnormalities. There were no obvious differences in body-weight gain, impregnation rates, RBC counts, blood protein content, and urine protein in the treated dams compared to controls. ALT and AST were higher, but not significantly, in both treated groups compared to control. Preimplantation loss was significantly increased (31.0% compared to 10.2% in controls) in female rats (number unspecified) that were exposed to 51.3 ppm during the entire pregnancy period. Fetal survival rates in the treated groups were comparable to the control group. The body weight of male fetuses from the low-dose group was significantly lower than controls (3.9 g compared to 4.4 g in controls); however, no dose-relationship was evident, as no significant effect on body weight was reported in high-dose rats. The incidences of gross skeletal and visceral malformations in treated groups were not significantly different from the control group. In the two treated groups, male rat neonates showed a significant increase in open field measurements (times standing up and times of excretion) compared to the control group; however, the significance of this finding is unclear.

Male dominant lethality testing was also performed in rats (Zhao et al., 1989, 1997). Groups of male rats were exposed to 0, 6.2, or 198 ppm (0, 25, or 800 mg/m^3) of 1,2-DCA for 4 hours/day for 1, 2, 3, or 4 weeks prior to mating. The impregnation rate was significantly lower and the preimplantation loss significantly greater in females mated to high-dose males exposed for 2 weeks compared to concurrent controls. However, these differences were likely anomalies, as significant differences did not result in any other high-dose groups (1-, 3-, or 4-week exposures), and the impregnation rate and preimplantation loss in the 2-week controls comprised the high and low ends of their respective ranges within the four control groups. This study suggests a NOAEL and LOAEL of 6.1 and 51.3 ppm (24.8 and 207.6 mg/m^3), respectively, for reproductive effects in rats in the initial experiment (Zhao et al., 1989, 1997). However, confidence in these assessments is limited because the translation contained inconsistencies regarding species, group sizes were not reported, and the type of statistical test was not indicated. Furthermore, other studies with more reliable reporting (Rao et al., 1980; Payan et al., 1995) did not confirm the findings of Zhao et al., 1989, 1997.

In the fourth study, Zhao et al. (1984) exposed pregnant Swiss hybrid mice (15−19/group) to 0, 25, or 250 mg/m^3 of 1,2-DCA (98.5% pure) by breathing tube for 4 hours/day on GDs 6−15. Another group of mice was exposed to 1,000 mg/m^3 of 1,2-DCA for 4 hours/day on GDs 9 and 10. Maternal toxicity evaluations were not reported. Upon sacrifice on GD 18, the numbers of implantations, resorptions, and live and dead fetuses were recorded. Fetuses were examined for external, skeletal, and visceral anomalies; however, the preparation and examination techniques were not reported. Although the details of the study design are poorly reported in this paper, it appears that additional groups of mice received the same treatments and were allowed to give birth. Offspring survival was recorded on PND 4 and 21, and body weight was measured periodically for 2 months after birth. Developmental milestones (appearance of hair and teeth, eye and ear opening, as well as some poorly described

neurobehavioral milestones[5]) were noted. After 2 months, some of the offspring (numbers not reported) were sacrificed and necropsied, and the heart, spleen, kidneys, and brains were weighed. Other groups of treated and control offspring (F1) were mated to evaluate effects in the second generation. Pregnancy rates, and body weight and survival of offspring (F2) were recorded.

In the first group of mice sacrificed on GD 18, there were no deaths, and body weight was not affected by treatment (Zhao et al., 1984). The data showed no significant treatment-related effects on number of implantations, resorptions, or live or dead fetuses, nor on fetal weight, length, or incidence of external, visceral, or skeletal malformations. Similarly, there were no exposure-related effects on offspring survival, body weight, and growth, or developmental milestones in the F1 offspring reared for 2 months. Necropsy results and organ weight data showed no effects of 1,2-DCA treatment on the F1 offspring. Finally, neither survival nor body weight of F2 offspring showed any relationship to treatment (body weight data not shown). Based on the lack of developmental or reproductive effects, the high concentration (250 mg/m^3) may represent a NOAEL; however, poor reporting limits the reliability of this study.

In the fifth study, published in Russian with a brief English abstract, Vozovaya (1974) assessed the reproductive and developmental toxicity of inhaled 1,2-DCA in rats. This study was reviewed by Barlow and Sullivan (1982); the study summary herein is based on information provided in the review. According to the review, 28 female rats were exposed to 14 ppm (57 mg/m^3) of 1,2-DCA for 4 hours/day, 6 days/week for 6 months prior to mating with untreated males, and during pregnancy and rearing of the young. A group of 26 control rats were exposed to air on the same schedule. Toxicological evaluations were not described in the English abstract or the review. During the premating exposure period, the average length of the estrous cycle was increased (prolonged diestrus), but females did not become infertile. Treated females took more days with males before becoming pregnant, compared with controls. According to Barlow and Sullivan (1982), maternal toxicity was not evident. The average litter size of treated dams was significantly reduced (n = 6.5± 1.1) compared with controls (n = 9.7± 0.6), but it could not be determined if reduced litter sizes were due to reproductive effects in females or increased embryo and/or fetal death. An increased incidence of stillbirths (23.1% in treated dams versus 5.1% in controls) suggests a fetotoxic effect. Birth weight of treated pups was also reduced by 20% compared to controls. Mortality during the first month after birth (exposure was continued) was 20% in treated pups and only 3% in controls. The postweaning growth rate of treated female offspring was decreased compared with controls, while males were unaffected (no details provided). Maturation and development (assessed by noting timing of incisor eruption, hair growth, eye and ear opening) of offspring exposed in utero were otherwise normal. According to Barlow and Sullivan (1982), Vozovaya (1974) assessed central nervous system and liver function, muscular endurance, and limited hematology (leukocytes counts and neutrophil phagocytic activity) in the offspring at 2, 4, and 6 months of age, but no treatment-related changes were observed. Prolonged estrous was also noted in female offspring exposed to 1,2-DCA (1.32 ± 0.07 days in treated offspring versus 1.02 ± 0.01 days in controls). At 3 months of age, the female offspring exposed in utero and continuously after birth were mated with untreated males. Fertility of the F1 females was not

[5]Reported in the translation as "the initial establishing times for the baby mice to flip over on a flat surface or in the air and the times for cross-section avoidance reflection and moving straight forward."

affected, but neonatal mortality was 18% in treated litters compared with 7% in controls. Barlow and Sullivan (1982) reported that microscopic examination of the ovaries, uterus, and fallopian tubes of treated female offspring sacrificed at 6 months of age did not reveal evidence of histopathology. These data suggest a LOAEL of 57 mg/m^3 for increased estrous cycle and prolonged time-to-pregnancy in maternal animals and for reduced litter size, increased number of stillbirths, decreased birth weight, and decreased neonatal survival in offspring. However, because the available information on this study is derived from a review of the original study, and the original data were not examined, the reliability of this LOAEL is uncertain. In addition, later, well-described developmental and reproductive toxicity studies in rats observed no effects on litter size, pre and postnatal survival, or birth weight at higher exposure concentrations (Rao et al., 1980; Payan et al., 1995), calling into question the findings of Vozovaya (1974).

The sixth study (Vozovaya, 1977), reviewed by WHO, (1995) was published in Russian without an English summary. According to WHO (1995), exposure of rats (number and strain not specified) to 15 mg/m^3, 4 hours/day, 6 days/week for 4 months prior to and after the mating period produced an increased estrous cycle and an increase in embryo mortality (27% in exposed animals versus 11% in controls) (Vozovaya, 1977, as cited in WHO, 1995). The review indicated that preimplantation losses were five times greater in treated animals compared with controls. WHO (1995) reported that there were no fetal abnormalities other than hematomas of the head, neck, and anterior extremities (incidences not reported). The available information was not sufficient to determine effect levels. Further, as noted earlier, the effects observed by Vozovaya (1974,1977) could not be reproduced in later developmental and reproductive toxicity studies in rats exposed to higher concentrations of 1,2-DCA (Rao et al., 1980; Payan et al., 1995).

OTHER STUDIES

Toxicokinetics

The toxicokinetics of 1,2-DCA have been extensively studied in rodents although not in humans (ATSDR, 2001). Available information suggests that 1,2-DCA is readily absorbed after oral, inhalation, and dermal exposure and is distributed throughout the body (ATSDR, 2001). This compound is metabolized via mixed-function oxidases and glutathione conjugation; products of mixed-function oxidases include chloroacetaldehyde, 2-chloroethanol, and 2-chloroacetic acid (ATSDR, 2001). ATSDR (2001) reported that metabolism of 1,2-DCA appears to be saturable at gavage doses ≥25 mg/kg and after inhalation of concentrations of ≥150 ppm. The saturation of metabolic pathways may be responsible for the greater toxicity observed with bolus doses of 1,2-DCA compared with drinking water exposures (NTP, 1991). The toxicokinetics of other halocarbons have been widely assessed, and it is recognized that rodents have a greater capacity than humans to metabolically activate 1,2,3-trichloropropane, trichloroethylene, perchloroethylene, and 1,2-dibromo-3-chloropropane (U.S. EPA, 1985b). However, no such information is available for 1,2-DCA.

Sweeney et al. (2008) published an updated PBPK model for 1,2-DCA in rats. The model provided good fit to pharmacokinetic data obtained after inhalation, gavage, and intravenous exposure in Osborne-Mendel, Sprague-Dawley, Wistar, and F344/N rats. Sweeney et al. (2008) determined that their model is most appropriately used for conducting route-to-route extrapolations for acute and repeated-exposure toxicity studies in rats. Currently, the limited human metabolism and kinetic data for 1,2-DCE preclude the development of a human model.

Immunotoxicity

There were two immunotoxicity studies: one oral mouse study and one inhalation study in rats and mice. In the oral study evaluating the immunotoxicity of 1,2-DCA, male CD-1 mice (32/group) were treated with drinking water containing 0, 20, 200, or 2,000 mg/L of 1,2-DCA (purity not specified) (0, 3, 24, or 189 mg/kg-day, as calculated by the authors using measured fluid consumption) for 90 days (Munson et al., 1982). Body weight and fluid consumption were measured at unspecified intervals. Immunotoxicology analyses included antibody response to sheep erythrocytes (antibody forming plaques in the spleen and antibody titers in blood), delayed hypersensitivity response to sheep erythrocytes, and lymphocyte response to the mitogens LPS (lipopolysaccharide from *S. typhosa* 0901) and concanavalin A. Blood was collected (presumably at sacrifice, although the report is not clear) for hematology analysis (RBC, WBC and platelet counts; Hgb, Hct, prothrombin time, and fibrinogen). The function of the reticuloendothelial system was assessed in separate groups of mice by measuring the vascular clearance and tissue uptake of radiolabeled sheep erythrocytes injected into exposed mice prior to sacrifice. Necropsies were performed on all animals at sacrifice at the end of exposure; brain, liver, spleen, lungs, thymus, kidneys, and testes were weighed. Reduced water consumption, probably indicating an organoleptic effect of 1,2-DCA, was seen at 24 and 189 mg/kg-day (5.0, 5.5, 4.2, and 2.8 mL/mouse/day in control through high-dose groups). In addition, an appreciable decrease in growth was seen in the high-dose group (about 10% lower terminal body weight, based on data presented graphically and without statistical analysis). The reduction in body weight at the high dose was most likely a result of dehydration from markedly lower water intake. No significant treatment-related effects were seen on absolute or relative organ weights, hematological parameters, or immunological function. A dose-dependent decrease in hemagglutination titers was observed, but the change from control was not statistically significant at any dose. Histological examination of organs and tissues was not conducted. The NOAEL for this study would be the highest dose tested, 198 mg/kg-day.

In the second study, the immunotoxic effects of inhaled 1,2-DCA in young male Sprague-Dawley rats and young female CD-1 mice were examined by Sherwood et al. (1987). Rats were exposed for 3 or 5 hours nominally to 0, 100, or 200 ppm (0, 405, or 810 mg/m^3) of 1,2-DCA or, in multiple exposure experiments, to 0, 10, 20, 50, or 100 ppm (0, 41, 81, 202, or 405 mg/m^3) of 1,2-DCA (purity not reported) 5 hours/day, 5 days/week for 12 exposures. Mice were exposed to 0 or 2.3 ppm (0 or 9.3 mg/m^3) of 1,2-DCA 3 hours/day for 5 days. Additional mice were exposed to 0, 2.3, 5.4, 10.8, or 100 ppm (0, 9.3, 21.9, 43.7, or 405 mg/m^3) of 1,2-DCA for a single 3-hour period. Testing was conducted after the conclusion of the single exposure or repeated exposure periods. The number of animals/species/exposure level varied with the test, ranging from 5 for alveolar macrophage cytostasis in rats to 140 for mortality from streptococcal pneumonia in mice. In rats, no effects were observed on pulmonary bactericidal activity to inhaled *Klebsiella pneumonia*, in vitro phagocytotic activity of alveolar macrophages, cytostatic and cytolytic capacity of alveolar macrophages, alveolar macrophage ectoenzymes activity, or mitogenic stimulation of lymphocytes from lung-associated, mesenteric, or popliteal lymph nodes. In mice, a single 3-hour exposure to 21.9 or 43.7 mg/m^3 of 1,2-DCA significantly increased mortality (monitored over a 14-day postexposure period) in a dose-related manner, relative to controls, due to exposure to an aerosol of viable *Streptococcus zooepidemicus* [$\sim 2 \times 10^4$ streptococci]). However, a single exposure or repeated exposures to 9.3 mg/m^3 had no significant effects. An exposure level of 43.7 mg/m^3 of 1,2-DCA significantly decreased bactericidal activity towards inhaled *K. pneumonia* ($p < 0.01$); lower exposure levels were without effect. Single exposure to 43.7 or 405 mg/m^3 of 1,2-DCA did not affect the total

numbers or differential counts of cells recovered by pulmonary lavage or the phagocytic or cytostatic ability of the alveolar macrophages in vitro. Sherwood et al. (1987) suggested that the evident interspecies differences in immunotoxic susceptibility argue against extrapolating from animals to humans; given that mice and rats responded differentially, it is difficult to extrapolate the response to humans. In addition, the massive streptococcal challenge to mice, consisting of whole-body, 30-minute exposures to aerosols of bacteria for an estimated challenge exposure of 2×10^4 inhaled viable streptococci, is unlikely to be relevant to normal human immunological challenge.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 1,2-DICHLOROETHANE

Table 8 summarizes the studies available for use in deriving provisional oral toxicity values for 1,2-DCA; these studies include subchronic gavage studies in rats (Van Esch et al., 1977; NTP, 1991; Daniel et al., 1994); subchronic drinking water studies in rats and mice (NTP, 1991); a subchronic immunotoxicity study in mice (Munson et al., 1982); chronic gavage studies in rats and mice (NCI, 1978); a developmental toxicity study in rats (Payan et al., 1995); and a multigeneration reproductive toxicity study in mice (Lane et al., 1982). An additional chronic rat study examining a small number of hepatotoxicity and reproductive toxicity endpoints (Alumot et al., 1976) was also located. However, poor reporting, substantial limitations in the toxicological evaluations, and great uncertainty in the dose estimates precluded both determination of reliable effect levels from this study and the use of this study for POD determination. Table 8 shows oral exposures and effect levels associated with the remaining studies. The available information suggests that rats are more sensitive than mice to the effects of 1,2-DCA exposure, and that gavage administration results in effects at lower doses than that observed following drinking water administration in rats. Gavage doses of 240 mg/kg-day, 5 days/week (equivalent to 171 mg/kg-day continuously) for up to 13 weeks were lethal in rats (NTP, 1991); in a chronic study, doses of 95 mg/kg-day, 5 days/week (equivalent to 68 mg/kg-day) increased mortality. In contrast, rats survived 13 weeks of exposure to higher doses (~500 mg/kg-day) administered in drinking water (NTP, 1991). No rats consuming any dose of 1,2-DCA in their water died, while all or most all male and female rats succumbed to the higher bolus doses with noted pathological changes, serum clinical chemistry, and hematological alterations often seen. These changes were not observed in any animal receiving 1,2-DCA via drinking water.

Table 8. Summary of Oral Noncancer Dose-Response Information

Species and Study Type	Exposure	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Duration-Adjusted[a] NOAEL (mg/kg-day)	Duration-Adjusted[a] LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
Subchronic								
Wistar Rat 10/sex/dose Gavage	0, 10, 30, or 90 mg/kg-day, 5 d/wk for 90 days	30	90	21	64	Increased relative kidney and liver weights		Van Esch et al., 1977
Sprague-Dawley Rat 10/sex/dose Gavage	0, 37.5, 75, or 150 mg/kg-day for 90 consecutive days	37.5	75	37.5	75	Increased relative liver weight and increased serum ALP		Daniel et al., 1994
F344/N Rat 10/sex/dose Gavage	0, 30, 60, 120, 240, or 480 mg/kg-day (M); 0, 18, 37, 75, 150, 300 mg/kg-day (F), 5 d/wk for 13 wks	37	75	26	54	Increased absolute kidney weight in females		NTP, 1991
F344/N Rat 10/sex/dose Drinking water	0, 49, 86, 147, 259, or 515 mg/kg-day (M); 0, 58, 102, 182, 320, or 601 mg/kg-day (F) for 13 wks	NA	58	NA	58	Increased absolute kidney weight in females	Dose-related increases in renal regeneration in females at higher doses	NTP, 1991
Sprague-Dawley Rat 10/sex/dose Drinking water	0, 60, 99, 165, 276, or 518 mg/kg-day (M); 0, 76, 106, 172, 311, or 531 mg/kg-day (F) for 13 wks	NA	76	NA	76	Increased absolute and relative kidney weight in females		NTP, 1991
Osborne-Mendel Rat 10/sex/dose Drinking water	0, 54, 88, 146, 266, or 492 mg/kg-day (M); 0, 82, 126, 213, 428, or 727 mg/kg-day (F) for 13 wks	NA	82	NA	82	Increased absolute and relative kidney weight in females		NTP, 1991

Table 8. Summary of Oral Noncancer Dose-Response Information

Species and Study Type	Exposure	NOAEL (mg/kg-day)	LOAEL (mg/kg-day)	Duration-Adjusted[a] NOAEL (mg/kg-day)	Duration-Adjusted[a] LOAEL (mg/kg-day)	Responses at the LOAEL	Comments	Reference
B6C3F1 Mouse 10/sex/dose Drinking water	0, 249, 448, 781, or 2,710 mg/kg-day (M); 0, 244, 647, 1,182, or 2,478 mg/kg-day (F) for 13 wks	249	448	249	448	Increased kidney weight in males	Dose-related increases in renal histopathology in males at higher doses	NTP, 1991
CD-1 Mouse Immunotoxicity Drinking water	0, 3, 24, or 189 mg/kg-day for 90 days	189	NA	189	NA	None	Limited evaluations	Munson et al., 1982
Chronic								
Osborne-Mendel Rat Gavage	TWA doses of 0, 47, or 95 mg/kg-day, 5 d/wk for 78 weeks	NA	47	NA	34	Clinical signs	Study limited by dose adjustments and poor survival	NCI, 1978
B6C3F1 Mouse Gavage	TWA doses of 0, 97, or 195 mg/kg-day (M); 0, 149, or 299 mg/kg-day (F), via gavage in corn oil 5d/wk for 78 weeks	97	195	69	139	Increased incidence of chronic murine pneumonia in males	Study limited by dose adjustments	NCI, 1978
Reproductive/Developmental								
Sprague-Dawley Rat Developmental 25−26 F/dose	0, 119, 158, 198, or 238 mg/kg-day via gavage on GDs 6−20	158 (maternal and develop-mental)	198 (maternal and develop-mental)	158 (maternal and develop-mental)	198 (maternal and develop-mental)	Decreased body-weight gain in dams; increased resorptions		Payan et al., 1995
ICR Swiss Mouse Multigeneration reproduction 10 M and 30 F/dose	0, 5, 15, or 50 mg/kg-day in drinking water for two generations	50 (parental and offspring)	NA	50 (parental and offspring)	NA	None		Lane et al., 1982

[a]Adjusted to continuous exposure based on exposure regimen shown in table

The available studies as a whole suggest the liver and kidney as target organs for 1,2-DCA toxicity via oral exposure. Evidence of toxicity to these organs includes increases in liver and kidney weights in all of the subchronic animal oral studies (Daniel et al., 1994; NTP, 1991; Van Esch et al., 1977), clinical chemistry changes indicative of potential liver toxicity in an oral study (Daniel et al., 1994), and dose-related kidney histopathology in both female rats and male mice in subchronic drinking water studies (NTP, 1991). At lethal doses in rats, fatty degeneration of the liver has been reported (Van Esch et al., 1977). Liver and kidney effects of 1,2-DCA have also been shown in at least one human exposed to 1,2-DCA; autopsy on a man acutely poisoned with 1,2-DCA via inhalation exposure revealed hepatocellular and renal tubular necrosis (Nouchi et al., 1984).

SUBCHRONIC p-RfD

Among the subchronic and reproductive or developmental toxicity studies of oral exposure to 1,2-DCA, the lowest duration-adjusted LOAEL values (54 and 58 mg/kg-day) were based on increased absolute kidney weights in female F344/N rats exposed via drinking water or gavage (both reported by NTP, 1991). In order to select a point of departure (POD) for the derivation of the subchronic p-RfD, data on both absolute and relative kidney weights in the drinking water study were considered for benchmark dose (BMD) modeling; these data are shown in Table 3. Although the gavage study resulted in a similar LOAEL, the drinking water study was selected as the basis for the subchronic p-RfD because this exposure is more relevant to likely human exposures.

The data on absolute and relative kidney weights in female F344/N rats exposed via drinking water (NTP, 1991) were modeled using the continuous data models in the EPA Benchmark Dose Software (BMDS) (v. 2.0). Appendix A describes the modeling approach and results. In the absence of a biologically relevant benchmark response level (BMR), a default BMR of 1 standard deviation (SD) from the control mean was used. No model fit was achieved with any continuous data model, even when the high-dose groups were sequentially dropped from the analysis. As a result, the LOAEL from the NTP (1991) study (>10% increase in absolute kidney weights in female F344/N rats) was selected as the POD for the subchronic p-RfD (a NOAEL was not identified).

A provisional **subchronic RfD of 2×10^{-2} mg/kg-day** for 1,2-DCA was derived by applying an UF of 3,000 to the rat LOAEL of 58 mg/kg-day as follows:

Subchronic p-RfD	=	LOAEL ÷ UF
	=	58 mg/kg-day ÷ 3,000
	=	**0.02 or 2×10^{-2} mg/kg-day**

The composite UF of 3,000 was composed of the following UFs:

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human responses are insufficient.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are insufficient.
- UF_D: The database for oral 1,2-DCA includes subchronic gavage studies in rats (Van Esch et al., 1977; Daniel et al., 1994; NTP, 1991); subchronic drinking water studies in rats and mice (NTP, 1991); a subchronic immunotoxicity study in

mice (Munson et al., 1982); chronic gavage studies in rats and mice (NCI, 1978); a developmental toxicity study in rats (Payan et al., 1995), and a multigeneration reproductive toxicity study in mice (Lane et al., 1982). Despite the relatively complete database, a factor of 3 (i.e., $10^{0.5}$) is applied for database inadequacies. Human case reports and limited epidemiology (reviewed by ATSDR, 2001 and WHO, 1995) have suggested that 1,2-DCA may result in neurotoxicity, but data for evaluating potential neurotoxicity are inadequate.

- UF$_L$: A factor of 10 is applied for using a LOAEL as the POD.

Confidence in the key study (NTP, 1991) is medium. Adequate numbers of animals were used, and a range of toxicological endpoints were evaluated; in addition, three different strains of rats were tested along with two methods of administration (gavage and drinking water) with generally consistent findings; however, a NOAEL was not identified for F344/N rats. Confidence in the database for oral 1,2-DCA, which includes subchronic gavage studies in rats (Van Esch et al., 1977; Daniel et al., 1994; NTP, 1991), subchronic drinking water studies in rats and mice (NTP, 1991), a subchronic immunotoxicity study in mice (Munson et al., 1982), chronic gavage studies in rats and mice (NCI, 1978), a developmental toxicity study in rats (Payan et al., 1995), and a multigeneration reproductive toxicity study in mice (Lane et al., 1982) is also medium. The database lacks an assessment of potential neurotoxicity. Potential neurotoxic effects of 1,2-DCA have been suggested by human case reports and limited epidemiology (reviewed by ATSDR, 2001 and WHO, 1995). Medium confidence in the provisional subchronic RfD follows.

CHRONIC p-RfD

Two chronic oral studies of 1,2-DCA were located in the literature searches: Alumot et al. (1976) and NCI (1978). Poor reporting, considerable limitations in the toxicological evaluations, and highly uncertain dose estimates precluded determination of reliable effect levels for Alumot et al. (1976). In the gavage study conducted by NCI (1978), LOAELs of 34 and 139 mg/kg-day were identified in rats and mice for clinical signs and an increased incidence of chronic murine pneumonia (respectively). The quality of the rat study was limited by poor survival at the high dose and the use of a variable dosing regimen. Further, the clinical signs observed in rats were not seen in any of the subchronic studies of various rat strains exposed via gavage or drinking water to much higher doses.

In the absence of suitable chronic data, the POD from the subchronic p-RfD could be used to derive the chronic p-RfD; however, the composite UF would include the additional UFs of 10 for applying data from a subchronic study to assess potential effects from chronic exposure. This would result in the large composite UF of greater than 3,000, thereby relegating this derivation of the chronic p-RfD to an appendix screening value (see Appendix B).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 1,2-DICHLOROETHANE

Table 9 summarizes the available studies of inhaled 1,2-DCA. The inhalation toxicology database for 1,2-DCA, while it contains several high-quality chronic toxicity studies, lacks clear information on the critical effects of inhalation exposure. Of the few human inhalation studies,

one occupational study (Kozik, 1957) provided adequate exposure information to identify a tentative LOAEL of 61 mg/m^3 based on neurobehavioral effects; although useful, this study was limited by poor reporting, lack of information on exposure duration, small numbers of subjects, and failure to control for potential confounding factors. However, animal data are also limited. Developmental toxicity studies by Vozovaya (1974, 1977) and Zhao et al. (1984, 1989, 1997) are not useful for toxicity value derivation due to limitations in the reporting and/or translation. Further, the findings in these studies could not be reproduced in later developmental and reproductive toxicity studies (Rao et al., 1980; Payan et al., 1995). Among a number of chronic toxicity studies in several species, subchronic range-finding studies in two species, developmental toxicity studies in two species, and a multigeneration reproductive toxicity study, only two studies (Spreafico et al., 1980; Spencer et al., 1951) contained data to define LOAELs for nonlethal effects (increased liver enzymes in aged rats, and liver lesions and reduced body weight in guinea pigs, respectively). However, these studies suffered from a number of limitations; Spreafico et al., 1980 provided only limited toxicological evaluation and mostly qualitative reporting; Spencer et al., 1951 reported FELs for significant mortality at the high-dose in some species (e.g., rats, guinea pigs, monkeys); however, no effects of any kind at the same dose in other species (i.e., rabbits), and no observable effects in any species at the mid-dose. The available information does suggest a steep dose-response curve for the effects of inhaled 1,2-DCA; several studies (e.g., Spencer et al. [1951] study of rats; Nagano et al. [2006] range-finding studies of rats and mice; Payan et al. [1995]; Rao et al. [1980]) identified FELs based on lethality at concentrations approximately 2- to 3-fold higher than no-effect levels. The database also suggests some degree of species differences in sensitivity, at least with respect to mortality. Studies in mice (Nagano et al., 2006, subchronic range-finding study) and rabbits (Rao et al., 1980) suggest that these species are more susceptible to the lethal effects of 1,2-DCA (mortality FELs of 648 and 405 mg/m^3) than rats, guinea pigs, or cats (FELs ≥1,214 mg/m^3; Nagano et al., 2006; Spencer et al., 1951; Payan et al., 1995; Rao et al., 1980; Hofmann et al., 1971).

Table 9. Summary of Inhalation Noncancer Dose-Response Information

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Responses at the LOAEL	Comments	Reference
Human studies						
Human Occupational	TWA concentration of ~61 mg/m^3	NA	61 HEC[a]: 22	Impaired neurobehavioral function	Limited by poor reporting, small numbers of subjects, failure to control for potential confounders; exposure duration unknown	Kozik, 1957; NIOSH, 1976
Subchronic studies						
F344/N Rat Number not specified/sex/group	648 or 1,295 mg/m^3 for 13 wks	NA	1,295 (FEL)	100% mortality	Briefly described study; insufficient information to define NOAEL or calculate HEC	Nagano et al., 2006
BDF1 Mouse Number not specified/sex/group	324 or 648 mg/m^3 for 104 wks	NA	648 (FEL)	50% mortality	Briefly described study; insufficient information to define NOAEL or calculate HEC	Nagano et al., 2006
Chronic studies						
F344/N Rat 50/sex/group	0, 40, 162, or 648 mg/m^3, 6 hr/d, 5 d/wk for 104 wks	648 HEC[b]: 116	NA	None		Nagano et al., 2006
BDF1 Mouse 50/sex/group	0, 40, 121, or 364 mg/m^3, 6 hr/d, 5 d/wk for 104 wks	40 HEC: 7	NA	Tumor-related mortality at ≥121 mg/m^3		Nagano et al., 2006
Sprague-Dawley Rat 50/sex/group	0 or 202 mg/m^3, 7 hr/d, 5 d/wk for 2 yrs	202 HEC: 42	NA	Marginal increase in gross testicular lesions (not further described) at NOAEL, with no corresponding histological findings	Limited endpoints evaluated.	Cheever et al., 1990
Sprague-Dawley Rat 90/sex/group	0, 20, 40, 202, 607−1,012 mg/m^3, 7 hr/d, 5 d/wk, up to 78 wks	40 HEC: 8	202 HEC: 42	Serum chemistry changes indicative of liver and possibly kidney toxicity in rats treated from 14 months to 26 months of age	High concentration reduced to from 1,012 to 607 mg/m^3 after several days due to high toxicity	Maltoni et al., 1980; Spreafico et al., 1980
Rats, Rabbits, Guinea pigs, 2−5/sex/group	0, 405, 2,024 mg/m^3, 6 hr/d, 5 d/wk for up to 17 wks	405 HEC: 72	2,024 (FEL) HEC: 361	Mortality	Small numbers of animals	Hofmann et al., 1971

Table 9. Summary of Inhalation Noncancer Dose-Response Information

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Responses at the LOAEL	Comments	Reference
Cats 2/sex/group	0, 405, 2,024 mg/m^3, 6 hr/d, 5 d/wk for 6 (low conc.) and 17 (high conc.) wks	2,024 HEC: 361	NA	Slight increase in BUN at NOAEL.	Small numbers of animals	Hofmann et al., 1971
Rats 15/sex/group	0, 405, 810, 1,620 mg/m^3, 7 hr/d, 5 d/wk, up to 30 wks	810 HEC: 169	1,620 (FEL) HEC: 338	Mortality		Spencer et al., 1951
Guinea Pigs 8/sex/group	0, 405, 810, 1,620 mg/m^3, 7 hr/d, 5 d/wk, up to 35 wks	405 HEC: 84	810 HEC: 169	Liver lesions and reduced body weight	Small numbers of animals	Spencer et al., 1951
Rabbits 2M, 1F/group	0, 405, 1,620 mg/m^3, 7 hr/d, 5 d/wk, 33−35 wks	1,620 HEC: 338	NA		Small numbers of animals	Spencer et al., 1951
Monkeys 2M/group	0, 405, 1,620 mg/m^3, 7 hr/d, 5 d/wk, up to 30 wks	405 HEC: 84	1,620 (FEL) HEC: 338	Mortality	Small numbers of animals	Spencer et al., 1951
Reproductive/Developmental Studies						
Sprague-Dawley Rat One-generation reproduction 20/sex/group	0, 101, 304, 607 mg/m^3, 6 hr/d, 5 d/wk for 60 d prior to breeding, then 6 hr/d, 7 d/wk thereafter	607 HEC: 108	NA	None		Rao et al., 1980
Sprague-Dawley Rat Developmental 26F/group	0, 607, 1,028, or 1,332 mg/m^3, 6 hr/d, GDs 6−20	1,028 HEC: 257 (maternal) 1,332 HEC: 333 (develop-mental)	1,332 (FEL) HEC: 333 (maternal) NA (develop-mental)	Low maternal mortality; decreased body weight		Payan et al., 1995

Table 9. Summary of Inhalation Noncancer Dose-Response Information

Species and Study Type (*n*/sex/group)	Exposure	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Responses at the LOAEL	Comments	Reference
Sprague-Dawley Rat Developmental 16−30F/group	0, 405, or 1,214 mg/m^3, 7 hr/d, GDs 6−15	405 HEC: 118 (maternal and develop-mental)	1,214 (FEL) HEC: 354 (maternal and develop-mental)	Maternal mortality; there was only 1 litter at the high exposure level and it was totally resorbed	High maternal mortality at high exposure level only	Rao et al., 1980
Rabbit Developmental 19−21F/group	0, 405, or 1,214 mg/m^3, 7 hr/d, GDs 6−18	NA (maternal) 1,214 HEC: 354 (develop-mental)	405 (FEL) HEC: 118 (maternal) NA (develop-mental)	Maternal mortality	Low maternal mortality in both dose groups did not increase with dose, but was considered treatment-related by the researchers	Rao et al., 1980

[a]Calculated assuming inhalation of 10/20 m^3 (10 m^3 in 8-hour work day and 20 m^3 in 24 hours), 5/7 days/week

[b]HEC calculated as follows: $NOAEL_{HEC}$ = NOAEL × exposure hours/24 hours × exposure days/7 days × dosimetric adjustment

For systemic effects, the dosimetric adjustment is the ratio of the animal:human blood:gas partition coefficients for 1,2-dichloroethane (because the coefficient in animals was greater than that in humans, a default value of 1 was used)

The NOAELs and LOAELs from the available studies were converted to continuous exposure human equivalent concentrations ($NOAEL_{HEC}$ and $LOAEL_{HEC}$) based on the guidance provided in *Methods for Derivation of Inhalation Reference Concentrations (RfCs) and Application of Inhalation Dosimetry* (U.S. EPA, 1994b). Each effect level was first adjusted to an equivalent continuous exposure concentration based on the exposure regimen reported in the study. The human equivalent concentration was then calculated using the appropriate dosimetric adjustment (U.S. EPA, 1994b). As all of the observed effects were extrarespiratory (systemic) effects, 1,2-DCA was treated as a Category 3 gas, and the ratio of blood:gas partition coefficients was used to make the dosimetric adjustment. Abraham et al. (2005) reported human and rat blood:gas partition coefficients of 20 and 30, respectively, for 1,2-DCA. Because $(H_{b/g})_A > (H_{b/g})_H$, a default value of 1 was used for the rat-to-human blood:gas ratio in accordance with EPA (1994b) guidance. In the absence of blood:gas partition coefficients for other species, the default ratio of 1.0 was used. Table 9 includes the $NOAEL_{HEC}$ and $LOAEL_{HEC}$ values calculated for each of the studies.

SUBCHRONIC p-RfC

The studies available for defining a subchronic p-RfC for 1,2-DCA include the occupational health study (Kozik, 1957)[6], subchronic range-finding studies in rats and mice (Nagano et al., 2006), a multigeneration reproductive toxicity study in rats (Rao et al., 1980), and developmental toxicity studies in rats and rabbits (Payan et al., 1995; Rao et al., 1980). The lowest $LOAEL_{HEC}$ in the animal studies was a FEL for maternal mortality in rabbits (118 mg/m^3, the lowest concentration tested) in the developmental toxicity study by Rao et al. (1980). The LOAEL identified by Kozik (1957) for neurobehavioral impairment in humans was considerably lower ($LOAEL_{HEC}$ = 22 mg/m^3). Although Kozik (1957) suffered from a number of limitations (i.e., lack of description of the analytical methodology used, limited quantitative data and statistical analyses, unstated criteria for diagnosis of disease, and lack of matched control subjects), it was selected as the only feasible basis for the subchronic p-RfC derivation. The $LOAEL_{HEC}$ of 22 mg/m^3 was chosen as the POD; Kozik (1957) did not report any data that could be used for BMD modeling.

For the subchronic p-RfC derivation, the $LOAEL_{HEC}$ of 22 mg/m^3 was divided by a UF of 300, as shown below:

$$\begin{aligned} \textbf{Subchronic p-RfC} &= LOAEL_{HEC} \div UF \\ &= 22\ mg/m^3 \div 300 \\ &= \textbf{0.07 mg/m}^3 \text{ or } \textbf{7} \times \textbf{10}^{-2}\ \textbf{mg/m}^3 \end{aligned}$$

The composite UF of 300 was composed of the following UFs:

- UF_A: A factor of 1 is applied for animal-to-human extrapolation because a human study served as the basis for the p-RfC.
- UF_D: The toxicological database for inhaled 1,2-DCA includes a number of chronic toxicity studies in several species, developmental toxicity studies in two species, and a reproductive toxicity study; however, no high quality studies identified LOAELs based on nonlethal effects. A factor of 3 ($10^{0.5}$) is applied for database inadequacies, specifically, the lack of a comprehensive animal bioassay

[6] Kozik (1957) did not explicitly report the length of time that subjects in the study were exposed; it was assumed for the purpose of this review that the exposure was subchronic (<7 years for humans).

of potential neurotoxicity in light of neurobehavioral effects identified in Kozik (1957) and other human studies, and the acute neurotoxic effects reported in Dilks et al. (2005) as well as the lack of a high quality key study (Dilks et al., 2007).

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human responses are insufficient.
- UF_L: A factor of 10 is applied for using a LOAEL POD because data for establishing a NOAEL are insufficient.

Confidence in the key study (Kozik, 1957) is very low. Although the study assessed sensitive toxicological endpoints (neurobehavioral changes) and saw morbidity for liver disease (comparable to this endpoint seen in animal bioassays), it suffered from a number of limitations, including poor reporting, small number of subjects, lack of control for confounding, and uncertain exposure assessment. Confidence in the database is medium; it includes chronic toxicity studies in several species, developmental toxicity studies in two species, and a reproductive toxicity study; however, no high quality studies identified clear LOAELs. In addition, the database lacks a high quality assessment of neurotoxicity. Low confidence in the provisional subchronic RfC follows.

CHRONIC p-RfC

Studies available for use in defining a chronic p-RfC for 1,2-DCA include the occupational health study used to derive the subchronic p-RfC (Kozik, 1957) and chronic toxicity studies in several species (Nagano et al., 2006; Cheever et al., 1990; Spreafico et al., 1980; Maltoni et al., 1980; Hofmann et al., 1971; Spencer et al., 1951). Only two chronic studies identified nonlethal LOAELs (Spreafico et al., 1980 and Spencer et al., 1951). The $LOAEL_{HEC}$ of 169 mg/m^3 (for liver lesions and reduced body weight in guinea pigs) identified by Spencer et al. (1951) exceeds the FEL for mortality in rabbits (Rao et al., 1980), so this study is not useful for p-RfC derivation. Spreafico et al. (1980) identified a $LOAEL_{HEC}$ of 42 mg/m^3 for increases in ALT (4- to 9-fold higher than controls) and GGT (~2-fold higher) in rats exposed to 1,2-DCA from 14 months to 26 months of age. Changes in serum liver enzymes were not observed in rats exposed to HEC concentrations up to 116 mg/m^3 for 2 years in the only other rat study that examined clinical chemistry (Nagano et al., 2006). However, the liver has been identified as a critical target organ for oral exposure to 1,2-DCA as well as for exposure to related chlorinated solvents such as 1,1-dichloroethylene (U.S. EPA, 2008). BMD modeling of the ALT and GGT data reported by Spreafico et al. (1980) was conducted in order to determine whether these data would result in a lower POD than the LOAEL identified by Kozik (1957) and used to derive the subchronic p-RfC.

BMD modeling was performed on the changes in serum ALT in male rats and GGT in female rats exposed for 12 months (see Table 7) using the nominal exposure concentrations. While both enzymes were increased in both sexes, only the ALT in males and GGT in females exhibited monotonic increases with exposure concentration, so these were selected for modeling. Appendix C provides details of the modeling and results. The recommended Benchmark Response (BMR) of 1 SD from the control mean (U.S. EPA, 2000) was used in the absence of a biologically-based benchmark response level. No model fit was achieved with the male ALT data (even when the high exposure group was dropped from the analysis) or with the full data set for GGT in females. After dropping the high exposure group, adequate fit was achieved with the

female GGT data. For this data set, the test for homogenous variance indicated adequate fit to the variance data, and the 2-degree polynomial, 3-degree polynomial, and power models provided adequate fit to the means. The BMCL values from the models that fit were within a factor of 3, so the model with the lowest Akaike Information Criterion (AIC) (3-degree polynomial) was chosen. The BMC_{1SD} and $BMCL_{1SD}$ associated with this model are 142 and 130 mg/m^3, respectively. After adjustment for continuous exposure and calculation of the human equivalent concentration, the $BMCL_{1SDHEC}$ is 27 mg/m^3. This value is comparable to the $LOAEL_{HEC}$ (22 mg/m^3) identified by Kozik (1957). The $LOAEL_{HEC}$ of 22 mg/m^3 (Kozik, 1957) was used as the POD because it is lower and is based on human data. Furthermore, given that Kozik (1957) also assessed liver disease in the occupationally exposed individuals and found the neurobehavioral effects more sensitive, the choice of this POD would be protective against liver effects in humans.

For the chronic p-RfC derivation, the $LOAEL_{HEC}$ of 22 mg/m^3 was divided by a UF of 3,000, as shown below:

$$\begin{aligned} \textbf{Chronic p-RfC} &= LOAEL_{HEC} \div UF \\ &= 22\ mg/m^3 \div 3{,}000 \\ &= \textbf{0.007 mg/m}^{\mathbf{3}}\ \text{or}\ \mathbf{7 \times 10^{-3}\ mg/m^3} \end{aligned}$$

The composite UF of 3,000 was composed of the following UFs:

- UF_A: A factor of 1 is applied for animal-to-human extrapolation because a human study served as the basis for the p-RfC.
- UF_D: The toxicological database for inhaled 1,2-DCA includes a number of chronic toxicity studies in several species, developmental toxicity studies in two species, and a reproductive toxicity study; however, no high quality studies identified LOAELs based on nonlethal effects. A factor of 3 ($10^{0.5}$) is applied for database inadequacies, reflecting the absence of clear LOAELs and the lack of a comprehensive study of potential neurotoxicity in light of neurobehavioral effects identified in Kozik (1957) and other human studies.
- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human responses are insufficient.
- UF_L: A factor of 10 is applied for using a LOAEL POD because data for establishing a NOAEL are insufficient.
- UF_S: A factor of 10 is applied for using data from a subchronic study to assess potential effects from chronic exposure because data for evaluating response after chronic exposure are insufficient.

As noted earlier, confidence in the key study (Kozik, 1957) is very low, and confidence in the cocritical study (Spreafico et al., 1980) is also low because the results were not confirmed in the chronic study conducted by Nagano et al. (2006). Confidence in the database is medium; it includes chronic toxicity studies in several species, developmental toxicity studies in two species, and a reproductive toxicity study; however, no high quality studies identified clear LOAELs. In addition, the database lacks a high quality assessment of neurotoxicity. Low confidence in the provisional chronic RfC follows.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 1,2-DICHLOROETHANE

A provisional carcinogenicity assessment was not prepared for 1,2-DCA because IRIS (U.S. EPA, 2008) includes a cancer assessment for this compound.

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APPENDIX A. DETAILS OF BENCHMARK DOSE MODELING FOR SUBCHRONIC RfD

MODEL FITTING PROCEDURE FOR CONTINUOUS DATA

The model fitting procedure for continuous data is as follows. The simplest model (linear) is first applied to the data while assuming constant variance. If the data are consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means is evaluated, and the polynomial, power, and Hill models are fit to the data while assuming constant variance. Adequate model fit is judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all the models providing adequate fit to the data, the lowest BMDL is selected as the point of departure (POD) when the difference between the BMDLs estimated from these models are more than 3-fold; otherwise, the BMDL from the model with the lowest Akaike Information Criterion (AIC) is chosen. If the test for constant variance is negative, the linear model is run again while applying the power model integrated into the Benchmark Dose Software (BMDS) to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, then the polynomial, power, and Hill models are fit to the data and evaluated while the variance model is applied. Model fit and POD selection proceed as described earlier. If the test for constant variance is negative and the nonhomogenous variance model does not provide an adequate fit to the variance data, then the data set is considered unsuitable for modeling.

MODEL FITTING RESULTS FOR ABSOLUTE AND RELATIVE KIDNEY WEIGHT IN FEMALE F344/N RATS EXPOSED VIA DRINKING WATER (NTP, 1991)

Data on female rat absolute and relative kidney weights were modeled according to the procedure outlined above using BMDS version 2.0 with default parameter restrictions. In the absence of data regarding a biologically meaningful change in kidney weight, the BMR was chosen to be 1 standard deviation (SD) from the control mean, as recommended by EPA (2000). Tables A-1 and A-2 show the modeling results for absolute and relative kidney weights (respectively). The constant variance model provided adequate fit to the variance data for absolute kidney weight. However, none of the available models provided adequate fit to the means for this endpoint, even when higher dose groups were sequentially dropped from the analysis. For the relative kidney weight data, neither the constant nor nonconstant variance models provided adequate fit to the variance data, even when higher dose groups were sequentially dropped from the analysis. As a result, the data sets for absolute and relative kidney weights are considered unsuitable for modeling.

Table A-1. Model Predictions for Absolute Kidney Weight in Female F344/N Rats[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
All dose groups					
Linear (constant variance)[c]	0.3842	<0.0001	572.805	266.40	202.02
Polynomial, 5-degree (constant variance)[c]	0.3842	<0.0001	572.805	266.40	202.02
Polynomial, 4-degree (constant variance)[c]	0.3842	<0.0001	572.805	266.40	202.02
Polynomial, 3-degree (constant variance)[c]	0.3842	<0.0001	572.805	266.40	202.02
Polynomial, 2-degree (constant variance)[c]	0.3842	<0.0001	572.805	266.40	202.02
Power (constant variance)[d]	0.3842	<0.0001	572.805	266.40	202.02
Hill (constant variance)[d]	Failed				
Without high-dose group					
Linear (constant variance)[c]	0.3291	0.00014	477.788	296.36	217.62
Polynomial, 4-degree (constant variance)[c]	0.3291	0.00014	477.788	296.36	217.62
Polynomial, 3-degree (constant variance)[c]	0.3291	0.00014	477.788	296.36	217.62
Polynomial, 2-degree (constant variance)[c]	0.3291	0.00014	477.788	296.36	217.62
Power (constant variance)[d]	0.3291	0.00014	477.788	296.36	217.62
Hill (constant variance)[d]	Failed				
Without 2 high-dose groups					
Linear (constant variance)[c]	0.2923	0.0015	383.358	113.21	76.46
Polynomial, 3-degree (constant variance)[c]	0.2923	0.0015	383.358	113.21	76.46
Polynomial, 2-degree (constant variance)[c]	0.2923	0.0015	383.358	113.21	76.46
Power (constant variance)[d]	0.2923	0.0015	383.358	0.2923	0.0015
Hill (constant variance)[d]	Failed				
Without 3 high-dose groups					
Linear (constant variance)[c]	0.2247	0.000817	293.385	117.55	77.30

[a]NTP (1991)
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria
[c]Coefficients restricted to be positive
[d]Power restricted to ≥1

Table A-2. Model Predictions for Relative Kidney Weight in Female F344/N Rats[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	AIC	BMD_{1SD} (mg/kg-day)	$BMDL_{1SD}$ (mg/kg-day)
All dose groups					
Linear (constant variance)[c]	0.0002374	0.06744	-64.750	173.34	140.05
Linear (nonconstant variance)[c]	0.007694	0.02877	-70.617	272.28	193.84
Without high-dose group					
Linear (constant variance)[c]	0.01131	0.6615	-50.864	119.00	91.54
Linear (nonconstant variance)[c]	0.01146	0.6494	-50.754	139.93	100.38
Without 2 high-dose groups					
Linear (constant variance)[c]	0.008005	0.5135	-35.777	136.28	87.08
Linear (nonconstant variance)[c]	0.04308	0.04865	-34.600	172.27	91.72
Without 3 high-dose groups					
Linear (constant variance)[c]	0.02777	0.6331	-20.204	98.32	56.55
Linear (nonconstant variance)[c]	0.00995	0.8735	-18.929	83.97	46.00

[a]NTP (1991)
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria
[c]Coefficients restricted to be positive

APPENDIX B. DERIVATION OF CHRONIC RfD SCREENING VALUE

CHRONIC p-RfD

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for 1,2-dicholoroethane (1,2-DCA). However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

Two chronic oral studies of 1,2-DCA were located in the literature searches: Alumot et al. (1976) and National Cancer Institute [NCI] (1978). Poor reporting, limitations in the toxicological evaluations, and uncertainty in the dose estimates precluded determination of reliable effect levels for Alumot et al. (1976). In the gavage study conducted by NCI (1978), lowest-observed-adverse-effect levels (LOAELs) of 34 and 139 mg/kg-day were identified in rats and mice for clinical signs and an increased incidence of chronic murine pneumonia (respectively). The quality of the rat study was limited by poor survival at the high dose and the use of a variable dosing regimen. Further, the clinical signs observed in rats were not seen in any of the subchronic studies of various rat strains exposed via gavage or drinking water to much higher doses.

To derive the chronic p-RfD in the absence of suitable chronic data, the point of departure (POD) from the subchronic p-RfD is used. Thus, the LOAEL of 58 mg/kg-day for a >10% increase in absolute kidney weights in female F344/N rats that was used as the POD for the subchronic p-RfD was also used as the POD for the screening-level chronic p-RfD.

A provisional **screening chronic RfD** for 1,2-DCA was derived by applying an uncertainty factor (UF) of 10,000 to the subchronic rat LOAEL of 58 mg/kg-day as follows:

Screening Chronic p-RfD	=	LOAEL ÷ UF
	=	58 mg/kg-day ÷ 10,000
	=	**0.006 or 6×10^{-3} mg/kg-day**

A calculated composite UF of 30,000 is composed of the UFs shown below. Assigning this screening chronic p-RfD to an appendix emphasizes the high uncertainty associated with this p-RfD derivation. Further, a composite UF of 30,000 is unrealistic given that there is evidence that responses to chronic exposure are of similar magnitude to subchronic responses (see discussion of UFs below). Therefore, a maximum UF of 10,000 is used to derive the screening chronic p-RfD.

- UF_H: A factor of 10 is applied for extrapolation to a potentially susceptible human subpopulation because data for evaluating susceptible human responses are insufficient.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation because data for evaluating relative interspecies sensitivity are insufficient.
- UF_D: The database for oral 1,2-DCA includes subchronic gavage studies in rats (Van Esch et al., 1977; Daniel et al., 1994; National Toxicology Program [NTP], 1991), subchronic drinking water studies in rats and mice (NTP, 1991), a subchronic immunotoxicity study in mice (Munson et al., 1982), chronic gavage studies in rats and mice (NCI, 1978), a developmental toxicity study in rats (Payan et al., 1995), and a multigeneration reproductive toxicity study in mice (Lane et al., 1982). Despite the relatively complete database, a factor of 3 (i.e., $10^{0.5}$) is applied for database inadequacies. Human case reports and limited epidemiology (reviewed by Agency for Toxic Substances and Disease Registry [ATSDR], 2001 and World Health Organization [WHO], 1995) have suggested that 1,2-DCA may result in neurotoxicity, but data for evaluating potential neurotoxicity are inadequate.
- UF_L: A factor of 10 is applied for using a LOAEL as the POD.
- UF_S: A factor of 10 is applied for using data from a subchronic study to assess potential effects from chronic exposure. Data for evaluating response after chronic exposure are available, though limited. The chronic rat study identified a LOAEL of 34 mg/kg-day (NCI, 1978) for clinical signs of toxicity. This LOAEL is of similar magnitude to that of the subchronic study used to derive the p-RfD, however, the available chronic data were limited and of poor quality.

APPENDIX C. DETAILS OF BENCHMARK DOSE MODELING FOR CHRONIC RfC

MODEL FITTING PROCEDURE FOR CONTINUOUS DATA

The model fitting procedure for continuous data is as follows. The simplest model (linear) is first applied to the data while assuming constant variance. If the data are consistent with the assumption of constant variance ($p \geq 0.1$), then the polynomial, power, and Hill models are fit to the data while assuming constant variance. Adequate model fit is judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all the models providing adequate fit to the data, the lowest BMDL is selected as the point of departure (POD) when the difference between the BMDLs estimated from these models are more than 3-fold; otherwise, the BMDL from the model with the lowest Akaike Information Criterion (AIC) is chosen. If the test for constant variance is negative, the linear model is run again while applying the power model integrated into the Benchmark Dose Software (BMDS) to account for nonhomogenous variance. If the nonhomogenous variance model provides an adequate fit ($p \geq 0.1$) to the variance data, the polynomial, power, and Hill models are fit to the data and evaluated while the variance model is applied. Model fit and POD selection proceed as described earlier. If the test for constant variance is negative and the nonhomogenous variance model does not provide an adequate fit to the variance data, then the data set is considered unsuitable for modeling.

MODEL FITTING RESULTS FOR SERUM ALT IN MALE RATS (Spreafico et al., 1980)

Data on serum ALT levels in male rats exposed for 1 year beginning at 14 months of age (see Table 7) were modeled according to the procedure outlined above using BMDS version 2.0 with default parameter restrictions. Nominal exposure concentrations were used in the modeling. In the absence of data regarding a biologically meaningful change in ALT, the BMR was chosen to be 1 standard deviation (SD) from the control mean, as recommended by EPA (2000). Table C-1 shows the modeling results. While the nonconstant variance model in the software provided adequate fit to the variance data, none of the available models provided adequate fit to the means for this endpoint, even when higher dose groups were sequentially dropped from the analysis.

MODEL FITTING RESULTS FOR SERUM GGT IN FEMALE RATS (Spreafico et al., 1980)

Data on serum GGT levels in female rats exposed for 1 year beginning at 14 months of age (see Table 7) were modeled according to the procedure outlined above using BMDS version 2.0 with default parameter restrictions. Nominal exposure concentrations were used in the modeling. In the absence of data regarding a biologically meaningful change in GGT, the BMR was chosen to be 1 SD from the control mean, as recommended by EPA (2000). Table C-2 shows the modeling results. Using the full data set, neither the constant nor nonconstant variance models in the software provided adequate fit to the variance data. When the high-dose group was dropped, the constant variance model provided adequate fit to the variance data, and the polynomial (2- and 3-degree models) and power models provided adequate fit to the means data. The BMC values from the models that fit were within a factor of

3, so the model with the lowest AIC (3-degree polynomial) was chosen. Figure C-1 shows the fit of the 3-degree polynomial to the data on serum GGT in female rats. The BMC_{1SD} and $BMCL_{1SD}$ associated with this model are 142 and 130 mg/m^3, respectively.

Table C-1. Model Predictions for Serum ALT in Male Sprague-Dawley Rats[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	AIC	BMC_{1SD} (mg/m^3)	$BMCL_{1SD}$ (mg/m^3)
All dose groups					
Linear (constant variance)[c]	<0.0001	<0.0001	306.902	114.26	93.99
Linear (nonconstant variance)[c]	0.6935	<0.0001	322.201	163.18	4.80
Polynomial, 2-degree (nonconstant variance)[c]	0.6935	<0.0001	379.201	Failed	Failed
Polynomial, 3-degree (nonconstant variance)[c]	0.6935	<0.0001	346.199	387.55	4.01
Polynomial, 4-degree (nonconstant variance)[c]	0.6935	<0.0001	346.283	386.90	4.08
Power (nonconstant variance)[d]	0.6935	<0.0001	267.87	16.68	12.18
Hill (constant variance)[d]	Failed				
Without high-dose group					
Linear (constant variance)[c]	0.000116	<0.0001	186.408	21.45	17.69
Linear (nonconstant variance)[c]	0.4871	<0.0001	186.203	30.23	8.79
Polynomial, 2-degree (nonconstant variance)[c]	0.4871	<0.0001	162.298	51.19	33.65
Polynomial, 3-degree (nonconstant variance)[c]	0.4871	<0.0001	161.394	78.52	37.53
Power (constant variance)[d]	0.4871	<0.0001	160.606	168.79	57.11
Hill (constant variance)[d]	Failed				
Without 2 high-dose groups					
Linear (constant variance)[c]	0.3647	<0.0001	108.50	539.70	47.08

[a]Spreafico et al. (1980)
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria
[c]Coefficients restricted to be positive
[d]Power restricted to ≥1

Table C-2. Model Predictions for Serum GGT in Female Sprague-Dawley Rats[a]

Model	Variance *p*-Value[b]	Means *p*-Value[b]	AIC	BMC_{1SD} (mg/m^3)	$BMCL_{1SD}$ (mg/m^3)
All dose groups					
Linear (constant variance)[c]	0.08897	<0.0001	-33.496	213.82	165.79
Linear (nonconstant variance)[c]	0.04454	<0.0001	-31.502	219.18	124.02
Without high-dose group					
Linear (constant variance)[c]	0.1736	0.03846	-34.377	72.24	54.87
Polynomial, 2-degree (constant variance)[c]	0.1736	0.2688	-38.266	119.50	104.82
Polynomial, 3-degree (constant variance)[c]	**0.1736**	**0.333**	**-38.694**	**142.50**	**130.63**
Power (constant variance)[d]	0.1736	0.1454	-36.773	187.03	81.52
Hill (constant variance)[d]	Failed				

[a]Spreafico et al. (1980)
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria
[c]Coefficients restricted to be positive
[d]Power restricted to ≥1

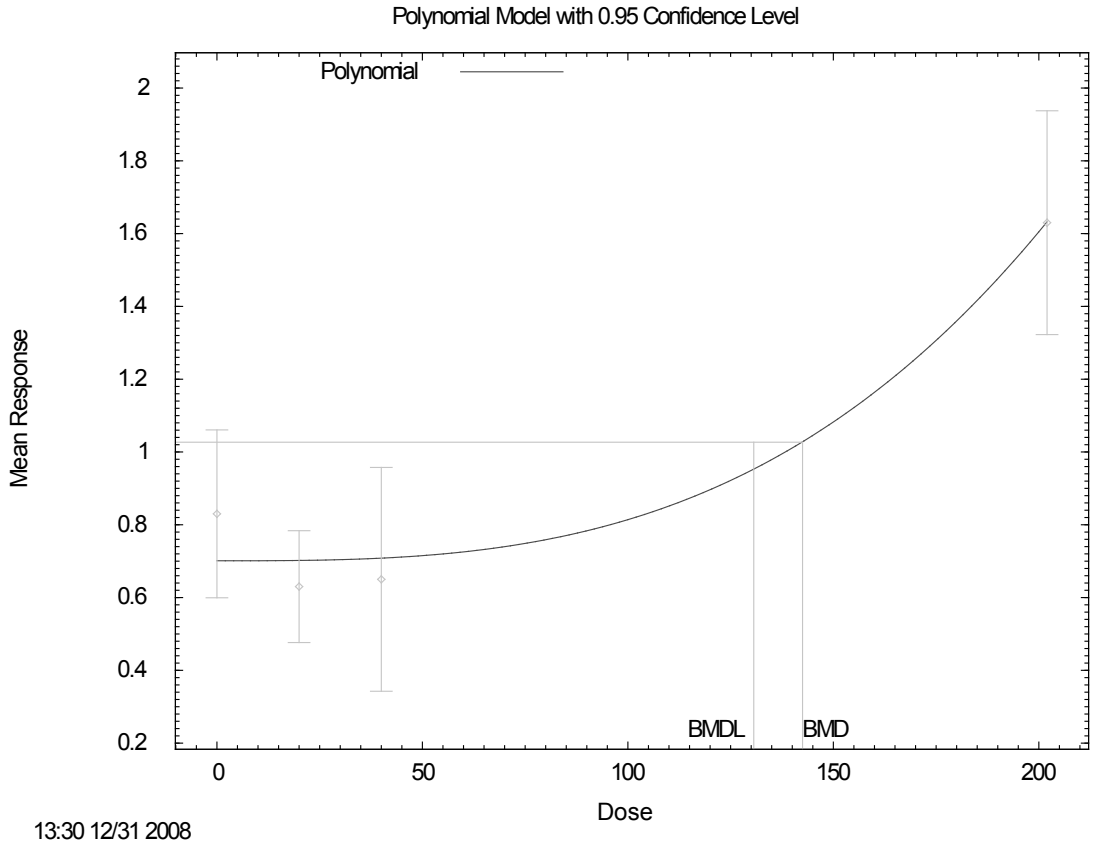

Figure C-1. Fit of Polynomial Model (3-degree) to Data on Serum GGT in Female Rats Exposed to 1,2-DCA for 1 year (Spreafico et al., 1980)

BMC and BMCL indicated are associated with a change of 1 SD from the control and are in units of mg/m^3.