NTP REPORT ON THE

TOXICITY STUDIES OF

1,2-DICHLOROETHANE

(ETHYLENE BICHLORIDE)

IN F344/N RATS, SPRAGUE DAWLEY RATS, OSBORNE-MENDEL RATS, AND B6C3F$_1$ MICE

(DRINKING WATER AND GAVAGE STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233 Research Triangle
Park, NC 27709

January 1991

NTP TOX 4
NIH Publication No. 91-3123

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for lexicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. The NTP coordinates the relevant programs, staff and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals.

These studies are designed and conducted to characterize and evaluate the toxicologic potential of selected chemicals in laboratory animals. Chemicals selected for NTP toxicology studies are chosen primarily on the bases of human exposure, level of production, and chemical structure.

Anyone who is aware of related ongoing or published studies not mentioned in this report, or of any errors in this report, is encouraged to make this information known to the NTP. Comments and questions should be directed to Dr. J.R. Bucher, NIEHS, P.O. Box 12333, Research Triangle Park, NC 27709 (919-541-4532).

These NTP Toxicity Study Reports are available for sale from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161 (703-487-4650). Single copies of this Toxicity Study Report are available without charge while supplies last from the NTP Public Information Office, NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3991).

TOXICITY STUDIES OF

1,2-DICHLOROETHANE

(ETHYLENE BICHLORIDE)

(CAS NO. 107-06-2)

IN F344/N RATS, SPRAGUE DAWLEY RATS, OSBORNE-MENDEL RATS, AND B6C3F$_1$ MICE

(DRINKING WATER AND GAVAGE STUDIES)

D. Morgan, Ph.D., Study Scientist

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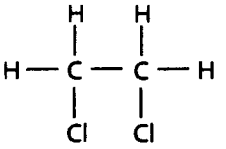

1,2-DICHLOROETHANE

CAS No. 107-06-2

$C_2H_4Cl_2$ Molecular weight 98.97

Synonyms: Ethylene dichloride; 1,2-bichloroethane; α,β-dichloroethane; *sym*-dichloroethane; ethylene chloride; glycol dichloride

Trade Names: Freon 150®; Brocide®; Dutch liquid; Dutch oil

ABSTRACT

Thirteen-week studies were conducted to investigate potential differences in rat strain susceptibility to 1,2-dichloroethane toxicity. F344/N rats, Sprague Dawley rats, Osborne-Mendel rats, and B6C3F$_1$ mice (10 animals of each sex) were exposed to 1,2-dichloroethane in drinking water at 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm for 13 weeks. In addition, groups of 10 F344/N rats of each sex were administered 1,2-dichloroethane in corn oil by gavage to compare toxicity resulting from bolus administration with that of continuous exposure in drinking water. Gavage doses of 1,2-dichloroethane were within the range of daily doses resulting from exposure in drinking water.

No compound-related deaths occurred in any of the rat strains exposed to 1,2-dichloroethane in drinking water. Weight gain depression was common in each sex of all three rat strains in the 4,000- and 8,000-ppm groups throughout the studies. Water consumption was decreased by 50%-60% with increasing dose for all exposed male and female rats regardless of strain. Kidney and liver weights were increased in dosed rats of all three strains. No chemical-related lesions were observed except for a dose-related incidence of renal tubular regeneration in female F344/N rats.

Nine of 10 female mice exposed to 8,000 ppm 1,2-dichloroethane in drinking water died before the end of the study. Mean body weights of males at 500 ppm or more and females at 1,000 ppm or more were lower than those of controls throughout most of the studies. Kidney weights were significantly increased for dosed males and females. Renal tubular cell regeneration was seen in males at 8,000 ppm; at 4,000 ppm, minimal regeneration was present in 8/10 male mice.

All male F344/N rats that received 240 or 480 mg/kg and 9/10 females that received 300 mg/kg 1,2-dichloroethane by gavage died before the end of the studies. Mean body weights of the highest dose males and females were lower than those of vehicle controls throughout the studies. Liver and kidney weights were increased for dosed males and females; however, no compound-related lesions were observed. Necrosis of the cerebellum, hyperplasia, inflammation, and mineralization of the forestomach, and necrosis of the thymus were seen in animals that died or were killed in moribund condition.

Rat strain differences in susceptibility to 1,2-dichloroethane toxicity were not apparent at the drinking water concentrations used in these studies; only female F344/N rats exhibited mild chemical-related renal lesions. Male B6C3F$_1$ mice appeared to be more susceptible than rats to toxicity of 1,2-dichloroethane administered in drinking water; renal tubule regeneration was observed in male mice in the 4,000- and 8,000-ppm groups. The higher toxicity in mice was likely due to higher water consumption, resulting in up to tenfold higher doses to mice than to rats. 1,2-Dichloroethane administered in drinking water resulted in less toxicity to F344/N rats than administration of similar doses by gavage.

CONTRIBUTORS

The NTP Report on the Toxicity Studies of 1,2-Dichloroethane is based on the various 13-week studies of 1,2-dichloroethane that began in November 1985 and ended in November 1986 at EG&G Mason Research Institute (Worcester, MA).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft report on the Toxicity Studies on 1,2-dichloroethane on June 27, 1989, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have four major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, and (d) to judge the significance of the experimental results by scientific criteria.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICITY STUDIES OF 1,2-DICHLOROETHANE

On June 27, 1989, the draft Technical Report on the toxicity studies of 1,2-dichloroethane received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

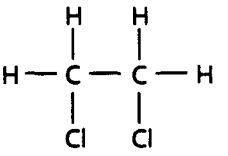
Dr. D.L. Morgan, NIEHS, introduced the short-term toxicity studies of 1,2-dichloroethane by reviewing the rationale, experimental design, and results.

Dr. Klaassen, a principal reviewer, commented that stating the rationale for the studies earlier in the Report, especially in the Abstract, would be helpful. Dr. Morgan agreed.

Dr. Popp, a second principal reviewer, said that the Report was clearly written and adequately presents the background and current studies. He inquired as to the rationale for a separate group of animals for evaluation of clinical pathology parameters. Dr. Morgan replied that this was done because of uncertainty about the effects of bleeding on animal response to the chemical.

Dr. Mirer observed that if the comparative route studies were aimed at determining if there was saturation of metabolic mechanisms, the question was not answered. He said that this could be more directly addressed by an absorption and distribution study. Dr. Gold said that newer human exposure data should be available. Dr. J. Haartz, National Institute for Occupational Safety and Health, said that newer exposure data were available. Dr. L. Zeise, California Department of Health Services, suggested that it would be helpful to include discussion of how the delivered dose was calculated in the drinking water studies. Dr. Bucher said that this information would be included in the Report and in future reports of drinking water studies (see Table 15, page 31).

Dr. Scala said that seeing no objections, the Panel would accept the Technical Report with the modifications as discussed.



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I. INTRODUCTION

Physical and Chemical Properties

1,2-Dichloroethane (ethylene dichloride) is a low molecular weight, chlorinated, aliphatic hydrocarbon. It is a clear, colorless, oily liquid with a chloroform-like odor (Patterson et al., 1976). Other physical and chemical properties are shown in Table 1.

Production and Use

1,2-Dichloroethane is produced commercially either by the vapor- or liquid-phase reaction of chlorine with ethylene in the presence of 1,2-dibromoethane or a metal chloride catalyst or by reaction of ethylene with oxygen and hydrogen chloride in the presence of a copper(II) chloride catalyst (Drury and Hammons, 1979). The annual production of 13 billion pounds (6 billion kg) in 1986 (USITC, 1987) makes 1,2-dichloroethane one of the largest volume synthetic chemicals produced in the United States. World capacity production of 1,2-dichloroethane was estimated to be 51 billion pounds (23 billion kg) in 1980 (Gold, 1980).

About 85% of the 1,2-dichloroethane produced in the United States is used in the synthesis of vinyl chloride, and 2%-4% is used in the production of other chemicals, such as 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene, vinylidine chloride, and ethyleneamines (IARC, 1979). 1,2-Dichloroethane is used as a lead scavenger in gasoline (IARC, 1979); in 1976, about

TABLE 1. SOME CHEMICAL AND PHYSICAL PROPERTIES OF 1,2-DICHLOROETHANE (a)

Melting point	−35° C
Boiling point	83° C
Water solubility	8.69 g/liter at 20° C
Log *n*-octanol/water partition coefficient	1.48
Relative density	1.23 at 20° C
Vapor pressure	8.53 kPa (64 mm mercury) at 20° C
Flash point	13° C (closed cup)
Flammability limits	0.25-0.64 g/liter, 6%-16% by volume
Conversion factor	1 ppm in air ≡ 4.05 mg/m^3 (at 25° C and 760 mm mercury)

(a) IPCS (1987)

92 million kg of 1,2-dichloroethane was used in the United States for this purpose. About 0.1% of 1,2-dichloroethane produced in the United States in 1977 was used in fumigants for grain, upholstery, and carpets and as a solvent for metal degreasing (Gold, 1980).

Exposure

The greatest potential for human exposure to 1,2-dichloroethane occurs in the industrial setting, where an estimated 80,000 workers could be at risk (NIOSH, 1989 unpublished data). The primary contact with 1,2-dichloroethane in the workplace results from its use as a solvent. 1,2-Dichloroethane concentrations ranging from 40 to 800 mg/m^3 (Cetnarowicz, 1959) have been detected in industrial settings (IPCS, 1987). In a U.S. antiknock-agent blending plant, the maximum exposure concentration measured was 8.9 mg/m^3 (Jacobs, 1980).

Nonoccupational exposure to 1,2-dichloroethane can occur by inhalation of contaminated air. Singh et al. (1983) estimated the exposure to 1,2-dichloroethane from urban air in the United States to be between 8 and 140 µg/day. Near production sites in the United States, an estimated 12.5 million people were exposed to 1,2-dichloroethane at an average annual concentration of up to 40 µg/m^3 (Elfers, 1979; Kellam and Dusetzina, 1980).

Nonoccupational exposure to 1,2-dichloroethane can also occur by consumption of contaminated water. The National Organics Reconnaissance Survey (Symons et al., 1975) measured 1,2-dichloroethane concentrations of 0-6 µg/liter in finished drinking water in 26 of 80 U.S. cities sampled. Ewing et al. (1977) detected levels of 1,2-dichloroethane greater than 1 µg/liter in surface water from 53 of 204 heavily industrialized U.S. sites. Letkiewicz et al. (1982) estimated that 1,2-dichloroethane levels in all groundwater and surface water systems in the United States are below 10 µg/liter and that most are below 1.0 µg/liter. Daily intake of 1,2-dichloroethane from drinking water containing 10 µg/liter was estimated to be 0.29 µg/kg for a 70-kg adult.

Symons et al. (1975) observed 1,2-dichloroethane more frequently in finished water than in untreated water, suggesting that contamination may occur during water chlorination (IPCS, 1987). Production of 1,2-dichloroethane by water chlorination has been suggested by others (Versar, 1975; Seufert et al., 1980); however, industrial discharges to surface water and leaching of solid wastes are considered the primary causes of 1,2-dichloroethane contamination in drinking water (Letkiewicz et al., 1982).

Absorption and Distribution

1,2-Dichloroethane is rapidly absorbed into the blood of rodents after dermal (Tsuruta, 1975; Jakobson et al., 1982), oral (Sopikov and Gorshunova, 1979; Reitz et al., 1982), or inhalation (Spreafico et al., 1980; Reitz et al., 1982) exposure. Spreafico et al. (1980) observed that 1,2-dichloroethane administered to rats by gavage at doses of 25, 50, or 150 mg/kg was rapidly absorbed, with peak levels in the blood occurring within 20 minutes. Similarly, Reitz et al. (1980, 1982) found that [^{14}C]1,2-dichloroethane administered to rats by gavage (150 mg/kg) was completely absorbed.

After administration by gavage, 1,2-dichloroethane was found to accumulate most rapidly in the liver, with peak levels attained within 10 minutes of administration (Spreafico et al., 1980). Levels of 1,2-dichloroethane in the lung appeared to be in equilibration with levels in blood. Accumulation in epididymal adipose tissue was slower, with peak levels occurring 45-60 minutes after administration; however, these levels were significantly higher than those in blood.

In the same study, Spreafico et al. (1980) compared 1,2-dichloroethane distribution in rats exposed by inhalation (250 ppm for 6 hours) or gavage (50 mg/kg). These doses resulted in comparable peak concentrations of 1,2-dichloroethane in blood. After inhalation exposure, peak 1,2-dichloroethane concentrations were higher than after oral exposure in the lung and adipose tissues and lower in the liver. 1,2-Dichloroethane concentrations in the spleen, kidney, and brain were similar to concentrations in blood after administration by either route. During inhalation exposure of rats, equilibrium between blood and tissues (adipose, liver, and lung) was

established after 2 hours of exposure to 50 ppm 1,2-dichloroethane and after 3 hours at 250 ppm.

In similar studies, Reitz et al. (1980, 1982) investigated the distribution of radioactivity in tissues after oral (150 mg/kg by gavage) and inhalation (150 ppm for 6 hours) exposure to [^{14}C]1,2-dichloroethane. During inhalation exposure, equilibration of 1,2-dichloroethane between blood and tissues required 2-3 hours. Target tissues (forestomach, liver, spleen) that developed neoplasms in rats exposed to 1,2-dichloroethane by gavage (NCI, 1978), as well as nontarget tissues (kidney, lung, stomach, and remaining carcass homogenate), were surveyed. No striking differences were seen in the distribution of radioactivity in target and nontarget tissues when evaluated 48 hours after oral or inhalation exposure. Levels of radioactivity were consistently about two times higher in tissues from animals exposed by gavage than in tissues from animals exposed by inhalation.

1,2-Dichloroethane crosses the placental barrier and has been detected in the fetus. After inhalation exposure of pregnant rats at 1,000 mg/m^3 for 4 hours per day, 1,2-dichloroethane was found to accumulate in the placental and fetal tissues over a period of 7 days (Vosovaya, 1977). Withey and Karpinski (1985) also demonstrated that inhalation exposure of pregnant rats resulted in dose-dependent accumulation of 1,2-dichloroethane in the fetus. Urusova (1953) reported that 1,2-dichloroethane accumulated in human breast milk (5.4-6.4 mg/liter) during occupational exposure.

Metabolism

1,2-Dichloroethane has been shown to be metabolized extensively via two principal pathways involving microsomal cytochrome P450 and cytosolic glutathione-*S*-transferase (GST) with reduced glutathione (GSH) (Figure 1). The cytochrome P450-catalyzed metabolism of 1,2-dichloroethane results in an unstable *gem*-chlorohydrin intermediate that rapidly eliminates hydrochloric acid to form 2-chloroacetaldehyde, followed by oxidation to chloroacetic acid or reduction to 2-chloroethanol (Guengerich et al., 1980; IPCS, 1987). These intermediates may undergo further reaction with GSH and appear as nontoxic urinary metabolites.

The GST-dependent metabolic pathways of 1,2-dichloroethane do not occur to any extent with the other chlorinated ethanes (Anders and Jakobson, 1985). This pathway involves the direct reaction of 1,2-dichloroethane with GSH to form *S*-(2-chloroethyl)glutathione, which is nonenzymatically converted to a glutathione episulfonium ion that can undergo several fates (IPCS, 1987). Reaction with water results in the formation of *S*-(hydroxyethyl)glutathione, and reaction with GSH produces ethene bisglutathione. These reaction products undergo further metabolism to nontoxic urinary metabolites. However, the episulfonium ion is a putative alkylating agent that can also form adducts with protein, RNA, and DNA (Inskeep et al., 1986). This pathway is considered to be the major in vivo route for DNA damage by 1,2-dichloroethane (Guengerich et al., 1980; Rannug, 1980; Sundheimer et al., 1982; Inskeep et al., 1986; IPCS, 1987).

Excretion

1,2-Dichloroethane is excreted rapidly by rats and mice, regardless of the route of exposure. Approximately 89% or more of 1,2-dichloroethane administered to mice by intraperitoneal injection was excreted within 24 hours (Yllner, 1971) or within 48 hours by mice receiving the chemical orally (Mitoma et al., 1985) and by rats exposed by gavage or inhalation (Reitz et al., 1982; Mitoma et al., 1985). Excretion of 1,2-dichloroethane or its metabolites occurs primarily in exhaled air and in urine in rats and mice exposed by various routes (Davidson et al., 1982; IPCS, 1987). Yllner (1971) found that up to 42% of the 1,2-dichloroethane given to mice by intraperitoneal injection was recovered unchanged in the exhaled air. The percentage of unmetabolized 1,2-dichloroethane exhaled was greater at higher doses than at lower doses, indicating a limited capacity for metabolism. Similarly, in rats, 29% of an oral dose of 1,2-dichloroethane (150 mg/kg) and 1.8% of a lower dose administered by inhalation (150 ppm for 6 hours) were recovered unchanged in the breath (Reitz et al., 1982).

Toxicity in Humans

Data on the effects of 1,2-dichloroethane in humans are limited to reports of accidental

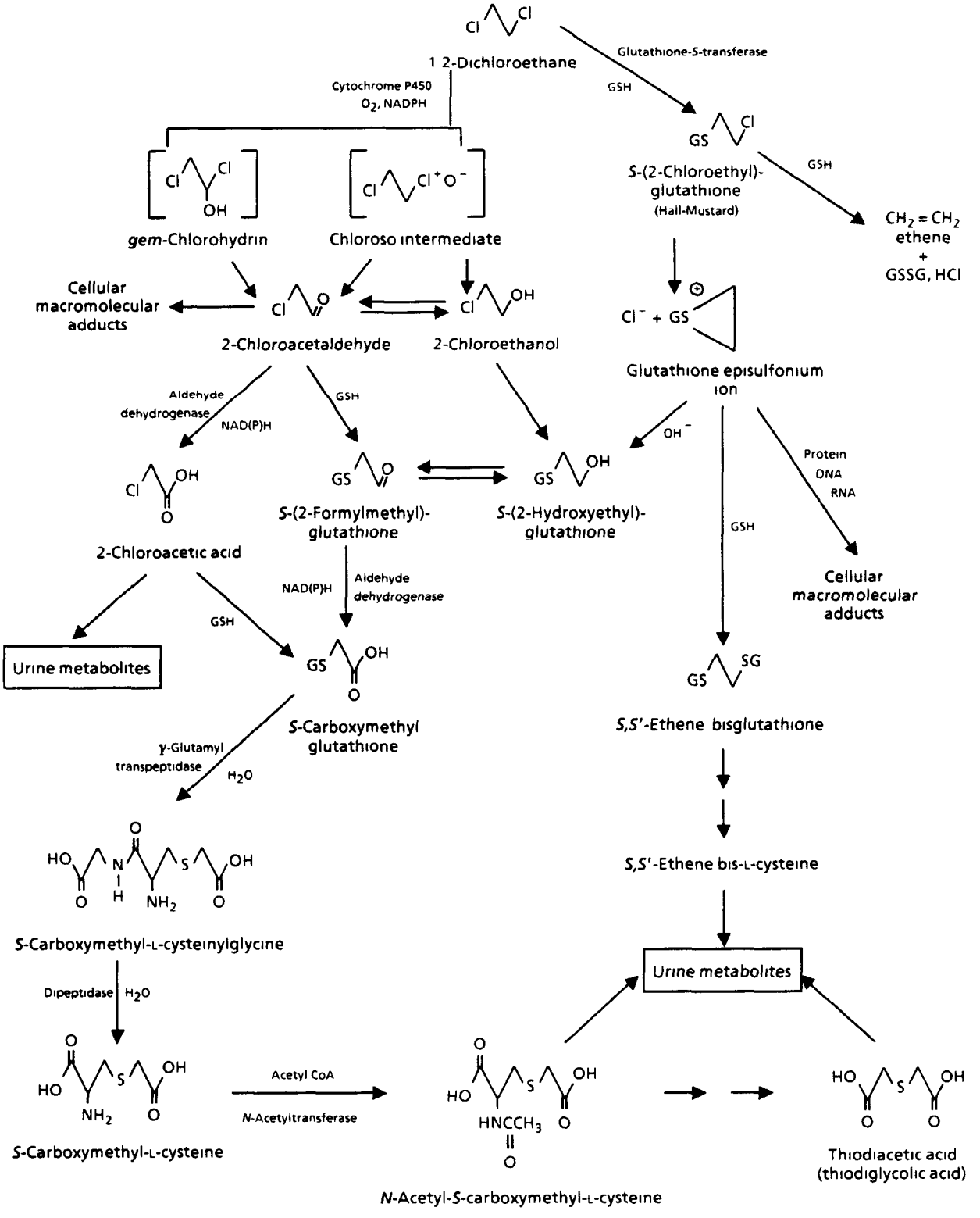


FIGURE 1. PROPOSED PATHWAYS FOR 1,2-DICHLOROETHANE METABOLISM
(from IPCS, 1987)

exposures, and many of these are concerned with mixed chemical exposures. Short-term inhalation exposure to 1,2-dichloroethane at high concentrations initially affects the central nervous system. Signs and symptoms include headache, dizziness, weakness, muscle spasms, cyanosis, hypotonia, vomiting, epigastric pain, and diarrhea. Unconsciousness and death may follow. Irritation and inflammation of the respiratory tract result in symptoms of cough and rales. Bronchial inflammation and respiratory insufficiency due to central nervous system depression may result in cyanosis (Kozik, 1957; Cetnarowicz, 1959; USEPA, 1985; IPCS, 1987). Changes in heart rhythm, probably secondary to cardiac sensitization to catecholamines, were reported (Suveev and Babichenko, 1969).

Short-term oral exposure of humans to 1,2-dichloroethane produces effects similar to, but more pronounced than, those after short-term inhalation exposure. In addition, ocular effects such as dilation or constriction of the pupils, impairment of eye reflexes (Weiss, 1957; Troisi and Cavallazzi, 1961), conjunctivitis (Menschick, 1957), and corneal opacity (Weiss, 1957) have been reported after oral exposure to 1,2-dichloroethane.

Toxicity in Animals

The effects of short-term (4-9 months) inhalation exposure to 1,2-dichloroethane were investigated in several studies in a number of laboratory animal species (Heppel et al., 1946; Spencer et al., 1951; Hofmann et al., 1971). Of the species studied, rats and mice appear to be the most sensitive to the toxic effects of 1,2-dichloroethane. The no-observed-adverse-effect level for short-term exposure (4-9 months) of rats in three investigations is about 100 ppm (IPCS, 1987). The oral LD_{50} for 1,2-dichloroethane was 413 (female) or 489 (male) mg/kg body weight in CD®-1 mice (Munson et al., 1982), 680-850 mg/kg in rats (McCollister et al., 1956; Larionov and Kokarovtseva, 1976), and 2,500 mg/kg in dogs (Barsoum and Saad, 1934).

Spreafico et al. (1980) investigated the effects of long-term 1,2-dichloroethane inhalation exposure on clinical chemistry indices of Sprague Dawley rats. Three-month-old rats of each sex were exposed to 0, 5, 10, 50, or 250 ppm for 7 hours per day, 5 days per week for 3, 6, or 18 months. The highest exposure concentration was reduced to 150 ppm after several weeks because of high mortality. An additional group of 14-month-old rats was exposed for 12 months at the same 1,2-dichloroethane concentrations. In the older rats, changes were detected in serum aspartate aminotransferase, serum alanine aminotransferase, and γ-glutamyl transpeptidase activity and in serum uric acid, blood urea nitrogen, and serum cholesterol concentrations after exposure for 12 months. These effects were not observed after the 3-month-old animals were exposed for 3, 6, or 18 months.

Administration of 1,2-dichloroethane to rats by gavage, five times per week for 2 weeks at doses of 150 mg/kg or less, had no effect on organ or body weights, histology, clinical chemistry, or hematology (Van Esch et al., 1977; Reitz et al., 1982). When rats were administered 30 or 90 mg/kg 1,2-dichloroethane by gavage, 5 days per week for 13 weeks, decreased weight gain was observed (Van Esch et al., 1977). Relative kidney weights of rats of each sex and relative brain and liver weights of females receiving 90 mg/kg 1,2-dichloroethane by gavage were increased. Histology and clinical chemistry were normal. Six of six rats died after receiving 300 mg/kg 1,2-dichloroethane by gavage for 5 days; fatty degeneration of liver and an increase in liver triglycerides were observed (Van Esch et al., 1977).

Alumot et al. (1976) observed increased total liver fat and triglycerides in rats after ingestion of approximately 100 mg/kg 1,2-dichloroethane per day in feed for 7 weeks. In a long-term study, rats were administered feed that had been fumigated with 1,2-dichloroethane, resulting in doses of 0, 11-17, or 23-25 mg/kg per day. After exposure for 2 years, no adverse effects were observed on growth, survival, or serum composition.

Immunotoxicity

Immunosuppression was observed in rabbits exposed to 1,2-dichloroethane at 100 mg/m^3 for 3 hours per day, 6 days per week for 7.5-8 months (Shmuter, 1977). Production of antibodies against typhoid vaccine was reduced by 80% in exposed animals, and a concomitant twofold

increase in Forsman sheep erythrocyte antibodies was observed.

Munson et al. (1982) reported a 30% reduction in leukocyte counts in CD®-1 mice administered 49 mg/kg 1,2-dichloroethane by gavage for 14 days. The number of antibody-forming cells in the spleen was decreased by 25% and 40% in mice receiving 4.9 and 49 mg/kg by gavage, respectively. No effects were observed on cell-mediated immunity in a second group of mice receiving 3, 24, or 189 mg/kg 1,2-dichloroethane in drinking water for 13 weeks.

Teratology and Reproductive Toxicology

Administration of 1,2-dichloroethane either by inhalation (Rao et al., 1980), in drinking water (Lane et al., 1982), or in formulated diets (Alumot et al., 1976) did not affect fertility, nor did it induce embryotoxic, fetotoxic, or teratogenic effects in several species. Vosovaya (1977) observed a possible adverse effect of 1,2-dichloroethane on reproduction after female rats were exposed to 1,2-dichloroethane by inhalation at 15 mg/m^3 for 4 hours per day, 6 days per week for 4 months before mating. During this period, the length of the estrous cycle increased. The rats were then mated and the exposure continued. Total embryonal mortality was increased, and preimplantation losses were about five times greater in exposed rats than in controls. In another study (Vosovaya, 1974), female rats were exposed to 57 $\pm$ 10 mg/m^3 for 4 hours per day, 6 days per week for 6 or 9 months. The fertility of mated females and the weight of newborn rats were reduced, and perinatal mortality was increased.

Genetic Toxicology

1,2-Dichloroethane has been shown to be mutagenic in a variety of in vitro tests. It induced DNA damage in *Escherichia coli* (Brem et al., 1974; Rosenkranz, 1977) and gene mutations in Salmonella (McCann et al., 1975; Bignami et al., 1977; Rosenkranz, 1977; Simmon et al., 1977; NTP unpublished data). 1,2-Dichloroethane has also been shown to induce sex-linked recessive lethal mutations in Drosophila (Shakarnis, 1969; King et al., 1979; Kramers and Bissumbhar, 1983) and gene mutations in mammalian lymphoblastoid cells (Crespi et al., 1985). Additional effects observed in mammalian cells in vitro include induction of sister chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells (NTP unpublished data).

Although mutagenic in vitro, 1,2-dichloroethane has demonstrated no genotoxic activity in mammalian cells in vivo, as shown by results from a limited number of studies. Analysis of peripheral blood smears obtained from the 13-week study animals showed no increase in micronucleated erythrocytes (NTP unpublished data), and bone marrow micronucleus studies in mice that received one or two intraperitoneal injections of 1,2-dichloroethane were also negative (King et al., 1979; Jenssen and Ramel, 1980).

Carcinogenicity

The potential carcinogenicity of 1,2-dichloroethane was investigated in a number of studies in which 1,2-dichloroethane was administered to rats and mice by various routes. The results of studies evaluating the carcinogenicity of 1,2-dichloroethane are conflicting.

The National Cancer Institute carcinogenesis studies of 1,2-dichloroethane conducted in Osborne-Mendel rats and B6C3F$_1$ mice via gavage in corn oil indicated that 1,2-dichloroethane caused squamous cell carcinomas of the forestomach, hemangiosarcomas, and subcutaneous tissue fibromas in male rats and mammary gland adenocarcinomas in female rats. Alveolar/bronchiolar adenomas were observed in exposed male and female B6C3F$_1$ mice, and mammary adenocarcinomas and endometrial tumors were observed in female mice (NCI, 1978). However, results of inhalation studies in Sprague Dawley rats and Swiss mice were negative (Maltoni et al., 1980). Attempts to reconcile the results of these two conflicting reports have centered around the purity of the study chemical, strain and route differences, contamination of the animal room with known carcinogens, and other technical considerations (Maltoni et al., 1980). Although most confounding factors can be excluded, species and route differences remain the most likely reasons for the contradictory findings.

Pharmacokinetic data showing more rapidly attained and sustained levels of 1,2-dichloroethane in blood of Osborne-Mendel rats after oral exposure, as opposed to inhalation of 1,2-dichloroethane at comparable doses, correlated with greater DNA alkylation after oral exposure (Reitz et al., 1982). A comparable route-specific genotoxic effect was reported by Storer et al. (1984), who showed significant hepatic DNA damage in mice after short-term oral or intraperitoneal administration but not with comparable inhalation exposure to 1,2-dichloroethane.

Van Duuren et al. (1979) gave female Swiss mice dermal applications of 42 or 126 mg 1,2-dichloroethane in acetone, three times per week for 440-594 days; an increased incidence of lung papillomas was detected in mice given 126 mg. Another group of female mice received one application of 1,2-dichloroethane, followed 2 weeks later by application of phorbol myristate acetate in acetone three times per week for 428-576 days. Although 1,2-dichloroethane was found to induce a significant increase in the incidences of benign lung papillomas, it did not initiate skin neoplasms.

Klaunig et al. (1986) investigated the effect of 1,2-dichloroethane on the incidences of liver and lung neoplasms in male $B6C3F_1$ mice according to a two-stage initiation/promotion protocol. Mice received 10 mg/liter diethylnitrosamine in drinking water for 4 weeks and then 835 or 2,500 mg/liter 1,2-dichloroethane in drinking water for 52 weeks. Neither the incidences of lung or liver neoplasms nor the number of neoplasms per mouse were affected in mice receiving 1,2-dichloroethane alone or after initiation with diethylnitrosamine.

Theiss et al. (1977) conducted a pulmonary tumor bioassay with 1,2-dichloroethane administered to A/St mice by intraperitoneal injection. Doses were 20, 40, or 100 mg/kg, three times per week for 24 weeks. The number of lung adenomas per mouse increased with dose; however, the number of adenomas was not significantly greater than that in controls.

Study Rationale

1,2-Dichloroethane was included in the first group of 24 priority chemicals for toxicologic evaluation by the National Toxicology Program (NTP) as part of an interagency agreement between the NTP and the Agency for Toxic Substances and Disease Registry. Drinking water may be an important source of human exposure to 1,2-dichloroethane because of contamination from industrial discharge and because of leaching from dump sites into surface water and groundwater. An adequate study of 1,2-dichloroethane toxicity and carcinogenicity using oral, nonbolus (i.e., formulated drinking water mixtures or feed) administration has not been conducted.

Conflicting results in earlier studies of 1,2-dichloroethane may have been due to differences in routes of administration and/or rat strains (Hooper et al., 1980). Potential differences in toxicity resulting from bolus or continuous administration were investigated by administering 1,2-dichloroethane to F344/N rats by gavage or in drinking water; potential differences in rat strain susceptibility to 1,2-dichloroethane toxicity were investigated in F344/N, Osborne-Mendel, and Sprague Dawley rats administered 1,2-dichloroethane in drinking water.

II. MATERIALS AND METHODS

Procurement and Characterization of 1,2-Dichloroethane

1,2-Dichloroethane was obtained in one lot from B.F. Goodrich Chemicals Group (Cleveland, OH). Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the 1,2-dichloroethane studies are on file at the National Institute of Environmental Health Sciences.

The study material was identified as 1,2-dichloroethane by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy, the purity was determined to be greater than 99% by elemental analysis, Karl Fischer water analysis, potentiometric titration in methanol with 0.01 N aqueous sodium hydroxide to determine free acid content, and gas chromatography

The stability of the chemical during the toxicology studies was monitored by gas chromatography. No deterioration of the 1,2-dichloroethane was seen over the course of the studies.

Preparation and Characterization of Dose Formulations in Corn Oil and in Drinking Water

The appropriate amounts of 1,2-dichloroethane and corn oil were mixed (w/v) to give the desired concentrations for the gavage studies. Stability studies of 1,2-dichloroethane in corn oil (approximately 10 mg/ml), using gas chromatography, established that the solutions were stable for at least 3 weeks when stored in the dark at room temperature. Solutions maintained under simulated animal-room conditions (open to air and light for 3 hours) had a chemical loss of approximately 4%. During the studies, dose formulations were stored for no longer than 3 weeks at approximately 4° C in serum vials.

Three complete sets of corn oil formulations were analyzed over the course of the 13-week studies, and all were within specifications (±10% of the target concentration) (Table 2). The analysis of the formulations remaining after dosing was completed gave results that were in reasonable agreement with those from samples taken immediately after mixing, indicating no loss of chemical during dose administration. Two referee analyses confirmed the results obtained by the study laboratory.

For the drinking water formulations, the appropriate amounts of 1,2-dichloroethane and deionized water were mixed (v/v) to give the desired concentrations. Stability studies of 1,2-dichloroethane in water (approximately 5 mg/ml), using gas chromatographic analysis of methylene chloride extracts of the water

TABLE 2. RESULTS OF ANALYSIS OF CORN OIL FORMULATIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 1,2-DICHLOROETHANE

Target Concentration (mg/g)	Determined Concentration (a) (mg/g)
3.9	3.8 ± 0.05
6.5	6.5 ± 0.23
8.1	7.8 ± 0.19
13.3	12.9 ± 0.31
16.1	15.6 ± 0.55
26.5	25.2 ± 0.43
32.0	31.1 ± 1.14
52.3	(b) 51.3 ± 0.49
63.5	62.3 ± 0.59
103.4	(c) 103.2

(a) Mean ± standard deviation for three determinations unless otherwise specified; for each determination, all samples analyzed in duplicate.
(b) Results for two determinations
(c) Results for a single determination

solutions, established that the solutions were stable for at least 3 weeks in the dark at 5° C in sealed bottles. 1,2-Dichloroethane solutions maintained under simulated animal-room conditions (clear glass drinking water bottles under normal room light) had losses of 1,2-dichloroethane of 13%, 22%, and 27% after 1, 2, and 3 days, respectively. Because of concerns about the stability of dose formulations during the toxicology studies, drinking water formulations were stored in sealed bottles for no longer than 3 weeks and drinking water bottles were changed at the end of each day.

Three complete sets of drinking water formulations were analyzed over the course of the 13-week studies. Four of the 16 formulations were out of specifications (varied by more than ±10% from the target concentration), with values ranging from −12% to −33% of target (Table 3). Samples that were out of specifications were restirred and reanalyzed and were then found to be within specifications. Two referee analyses confirmed the results obtained by the study laboratory. The analysis of formulations remaining in the drinking water bottles after 24 hours in the animal cages showed that the concentrations of the formulations had decreased an average of 29% (with values ranging from −13% to −53%) of target concentrations. Fresh drinking water mixtures were placed in the cages at the end of each day; thus, animals were exposed at concentrations ranging between the initial concentration and the concentration found at the end of 24 hours.

Thirteen-Week Study Design

Groups of 20 male rats and 10 female rats of each strain and 10 mice of each sex were exposed to drinking water containing 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm 1,2-dichloroethane for 13 weeks. Groups of 10 or 20 male F344/N rats were administered 0, 30, 60, 120, 240, or 480 mg/kg 1,2-dichloroethane in corn oil by gavage 5 days per week. Groups of 10 female F344/N rats were administered 0, 18, 37, 75, 150, or 300 mg/kg in corn oil by gavage on the same schedule.

The male and female F344/N rats, Sprague Dawley rats, Osborne-Mendel rats, and B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced under barrier conditions at Taconic Farms (Sprague Dawley rats), Frederick Cancer Research Facility (B6C3F$_1$ mice and F344/N rats), or CAMM Research Institute (Osborne-Mendel rats). Animals were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Animals were shipped to the study laboratory at 4 weeks of age. The rats were quarantined at the study laboratory for 11-14 days and mice for 12-14 days. All animals were placed on study at approximately 6 weeks of age.

Hematologic and serum chemical analyses were performed on days 3, 7, 14, and 45 and at the terminal kill on groups of 10 male rats of each strain that received 0, 2,000, 4,000, or 8,000 ppm

TABLE 3. RESULTS OF ANALYSIS OF DRINKING WATER FORMULATIONS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE

Target Concentration (ppm)	Determined Concentration (a) (ppm)
500	(b) 462 ± 10
1,000	897 ± 153
2,000	1,767 ± 338
4,000	3,640 ± 546
8,000	7,190 ± 148

(a) Mean ± standard deviation for the determination of three formulations unless otherwise specified; for each determination, all analyses performed in triplicate.
(b) Four formulations were analyzed.

1,2-dichloroethane in drinking water and on groups of 10 male F344/N rats that were administered 0, 120, 240, or 480 mg/kg 1,2-dichloroethane in corn oil by gavage. A separate group of animals was used for evaluation of hematologic and serum chemical parameters at 3, 7, 14, and 45 days because the effects of bleeding on the animals' response to 1,2-dichloroethane exposure is not known. The core group animals were bled at the terminal kill for clinical pathology evaluation at 90 days. Blood ($\leq$1.2 ml) was drawn from the tail of each animal and analyzed for erythrocyte and leukocyte counts, hemoglobin, hematocrit, mean cell volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration; a qualitative evaluation of number and morphology of platelets, leukocytes, number of reticulocytes, and erythrocyte morphology was performed. Serum samples were analyzed for sorbitol dehydrogenase, creatine kinase, alanine aminotransferase, alkaline phosphatase, and blood urea nitrogen. Rats used for clinical pathology evaluations were killed without necropsy, and their tissues were not saved.

Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals not used in hematologic and serum chemical studies. In some instances, a particular organ was autolyzed or lost; thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study. Tissues examined are listed in Table 4.

Organs and tissues were examined for gross lesions. Tissues were preserved in 10% neutral buffered formalin and routinely processed for preparation of histologic sections for microscopic examination. Tissues and groups examined are listed in Table 4. The liver, right kidney, brain, heart, thymus, lung, and right testis were weighed.

Upon completion of the histologic evaluation by the laboratory pathologist, slides, paraffin blocks, and residual wet tissues were sent to the National Toxicology Program Archives for inventory, slide/block match, and wet tissue audit. The slides, individual animal data records, and pathology tables were sent to an independent pathology laboratory where quality assessment was performed, and the results were reviewed and evaluated by the NTP Pathology Working Group (PWG). The target organs reviewed by the PWG were the forestomach, brain, kidney, and thymus for F344/N rats dosed by gavage and the kidney for all rat strains and $B6C3F_1$ mice receiving formulated drinking water. The final diagnoses represent a consensus of contractor pathologists and the PWG. Details of these review procedures have been described by Maronpot and Boorman (1982) and Boorman et al. (1985).

Statistical Methods

The analysis of organ weight, hematologic, and serum chemistry data was carried out by using the nonparametric multiple comparison procedures of Dunn (1964) or Shirley (1977). Jonckheere's test (Jonckheere, 1954) was used to evaluate the significance of dose-response trends and to determine whether Dunn's or Shirley's test was more appropriate for pairwise comparisons. The incidences of nonneoplastic lesions were assessed by the Fisher exact test.

Dose Selection

The solubility of 1,2-dichloroethane in water was the limiting factor in setting the high concentration for drinking water studies. The maximum solubility of 1,2-dichloroethane in water is about 9,000 ppm. Gavage doses were selected to be within the range of doses (in milligrams per kilogram per day) ingested by rats exposed to formulated drinking water.

Quality Assurance

The studies of 1,2-dichloroethane were performed in compliance with Good Laboratory Practices and regulations (21 CFR 58). The Quality Assurance Unit of EG&G Mason Research Institute performed audits and inspections of protocols, procedures, data, and reports throughout the conduct of the studies. The operations of the Quality Assurance Unit were monitored by the NTP, including a site visit during the period of study performance.

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE THIRTEEN-WEEK STUDIES OF 1,2-DICHLOROETHANE

Drinking Water Studies	Gavage Studies
Strain and Species F344/N rats, Osborne-Mendel rats, Sprague Dawley rats, and B6C3F$_1$ mice	F344/N rats
Study Laboratory EG&G Mason Research Institute	EG&G Mason Research Institute
Size of Study Groups 10 or 20 males and 10 females of each strain and species	10 or 20 males and 10 females
Doses 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm 1,2-dichloroethane in drinking water	Male--0, 30, 60, 120, 240, or 480 mg/kg 1,2-dichloroethane in corn oil by gavage; female--0, 18, 37, 75, 150, or 300 mg/kg; dose vol--5 ml/kg
Method of Animal Distribution Animals distributed to weight classes and then assigned to cages by one table of random numbers and to groups by another table of random numbers	Same as drinking water studies
Diet NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as drinking water studies
Animal Room Environment F344/N rats--temp: 68°-72° F; hum: 38%-56%; Sprague Dawley rats--temp: 66°-73° F, hum: 37%-53%, Osborne-Mendel rats--temp: 68°-73° F; hum: 35%-53%; B6C3F$_1$ mice--temp: 68°-77° F; hum: 38%-56%; fluorescent light 12 h/d for all animals	Temp--70°-74° F; hum--24%-64%; fluorescent light 12 h/d
Age When Placed on Study 6 wk	6 wk
Duration of Dosing 13 wk, dosed until necropsy	5 d/wk for 13 wk, dosed at least 2 consecutive days before necropsy
Type and Frequency of Observation Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially and 1 × wk thereafter
Necropsy, Histologic Examinations, and Supplemental Studies Necropsy performed on all mice and on all rats not used in the serial hematologic and serum chemical studies, the following tissues examined histologically for all control and high dose animals and for female mice receiving 4,000 ppm: adrenal glands, brain, esophagus, eyes (if grossly abnormal), gallbladder (mice), gross lesions and tissue masses and regional lymph nodes, heart, kidneys, large intestine, liver, lungs and mainstem bronchi, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity and turbinates, ovaries, pancreas, parathyroids, pharynx (if grossly abnormal), pituitary gland, preputial or clitoral glands (rats), prostate, salivary glands, skin, small intestine, spinal cord and sciatic nerve (if neurologic signs present), spleen, sternebrae or femur or vertebrae including marrow, stomach, testes/epididymis/seminal vesicles, thymus, thyroid gland, trachea, urinary bladder, and uterus. Hematologic and serum chemical analyses performed on groups of 10 male rats of each strain at d 3, 7, 14, and 45 and at terminal kill Organ weights obtained at necropsy	Necropsy performed on all rats not used in the serial hematologic and serum chemical studies; the following tissues examined histologically for all vehicle control and high dose animals, males receiving 120 or 240 mg/kg, and females receiving 150 mg/kg adrenal glands, brain, esophagus, eyes (if grossly abnormal), gross lesions and tissue masses and regional lymph nodes, heart, kidneys, large intestine, liver, lungs and mainstem bronchi, mammary gland, mandibular and mesenteric lymph nodes, nasal cavity and turbinates, ovaries, pancreas, parathyroids, pharynx (if grossly abnormal), pituitary gland, preputial or clitoral glands (rats), prostate, salivary glands, skin, small intestine, spinal cord and sciatic nerve (if neurologic signs present), spleen, sternebrae or femur or vertebrae including marrow, stomach, testes/epididymis/seminal vesicles, thymus, thyroid gland, trachea, urinary bladder, and uterus. Hematologic and serum chemical analyses performed on groups of 10 male rats at d 3, 7, 14, and 45 and at terminal kill. Organ weights obtained at necropsy

III. RESULTS

THIRTEEN-WEEK STUDIES IN RATS

Drinking Water Studies

F344/N Rats: No deaths of F344/N rats occurred during the studies (Table 5). Mean body weights of males exposed to 4,000 ppm or more and of females exposed to 8,000 ppm were lower than those of controls throughout the studies (Figure 2). Water consumption at the higher concentrations was about 60% that by controls. The increase in erythrocyte counts, mild decreases in mean cell volume, and the mild increases in blood urea nitrogen in the high dose male rats are all indicative of animal dehydration (Table A3). The decrease in mean cell volume (hematocrit/erythrocytes) may be related to dehydration resulting in an increase in serum osmolarity, with a subsequent loss of water from and shrinkage of the erythrocytes. The absolute and relative kidney weights and relative liver weights were increased for dosed males and females (Tables 6 and 7). No compound-related clinical signs were observed. Renal tubular regeneration was observed in all dosed and control male rats and consisted of one or more foci of basophilic-staining tubules lined by closely packed tubular epithelium in the cortex or outer medulla of the kidney. The lesion was minimal to mild and occurred in 9/10 rats in each group. No difference in severity was seen between groups. The incidence of renal tubular regeneration in females, however, was dose related and was observed in 9/10 at 8,000 ppm, 3/10 at 4,000 ppm, 2/10 at 2,000 ppm, 1/10 at 1,000 ppm, 0/10 at 500 ppm, and in 0/10 controls. This lesion was of minimal severity in all affected rats. No lesions attributable to 1,2-dichloroethane were observed in the liver.

TABLE 5. SURVIVAL, MEAN BODY WEIGHTS, AND WATER CONSUMPTION OF F344/N RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Water Consumption (d)
MALE						
0	10/10	134 ± 2	358 ± 4	+223 ± 3		25
500	10/10	133 ± 2	359 ± 7	+226 ± 6	100	24
1,000	10/10	133 ± 2	358 ± 5	+225 ± 5	100	21
2,000	10/10	132 ± 2	358 ± 3	+226 ± 3	100	18
4,000	10/10	134 ± 1	329 ± 3	+195 ± 3	92	15
8,000	10/10	133 ± 2	302 ± 4	+168 ± 4	84	14
FEMALE						
0	10/10	109 ± 2	202 ± 2	+93 ± 2		19
500	10/10	108 ± 1	204 ± 3	+96 ± 2	101	18
1,000	10/10	108 ± 1	207 ± 2	+99 ± 1	102	16
2,000	10/10	108 ± 2	199 ± 3	+92 ± 1	99	14
4,000	10/10	105 ± 3	195 ± 1	+90 ± 3	97	12
8,000	10/10	106 ± 1	187 ± 2	+81 ± 2	93	11

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean.
(c) Mean body weight change of the group ± standard error of the mean
(d) Grams per animal per day; not corrected for spillage.

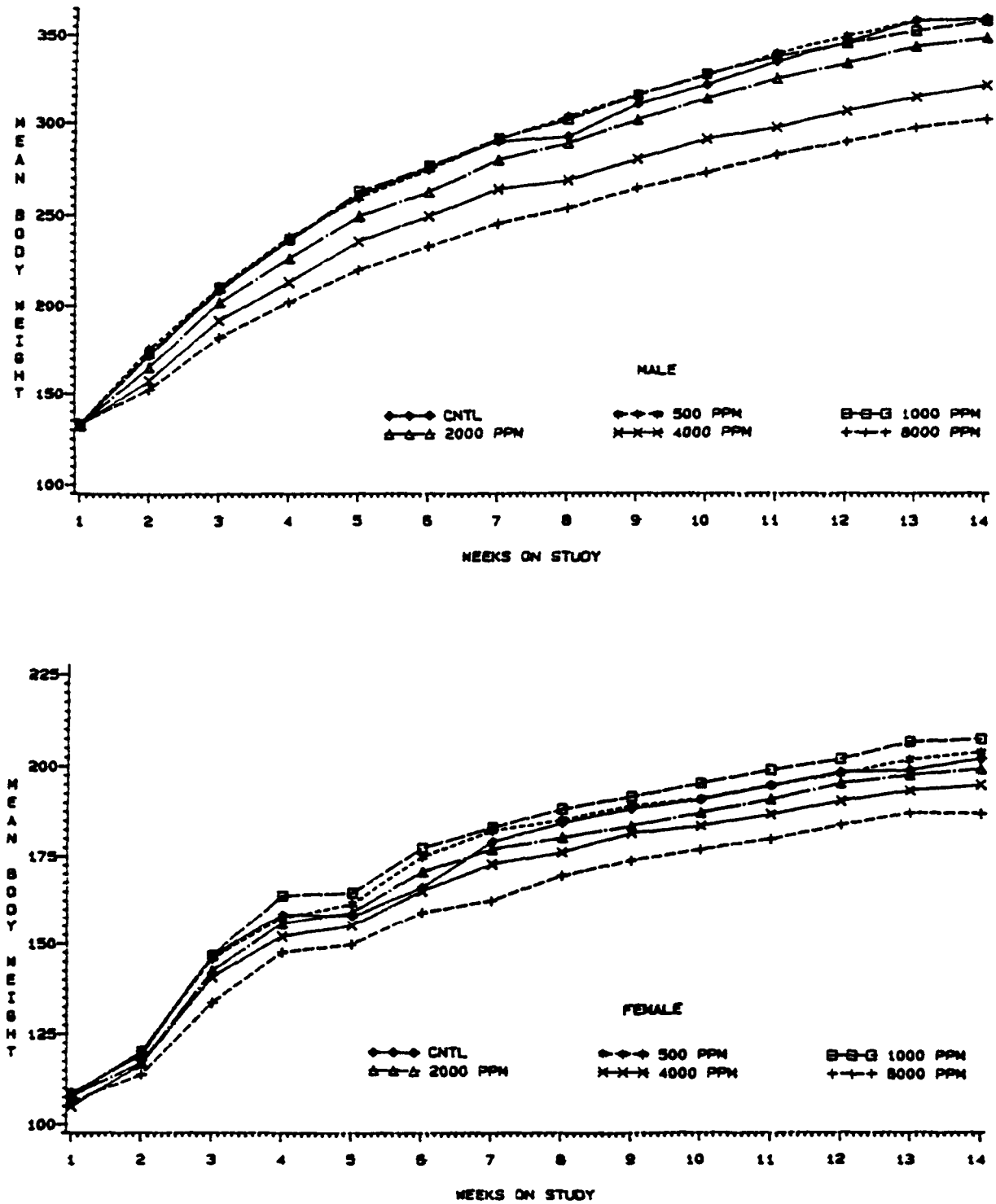


FIGURE 2. GROWTH CURVES FOR F344/N RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE

TABLE 6. ORGAN WEIGHT DATA FOR MALE RATS IN THE THIRTEEN-WEEK STUDIES OF 1,2-DICHLOROETHANE (a)

Study/Strain/Organ	Dose or Concentration					
Drinking water studies						
F344/N	**Control**	**500 ppm**	**1,000 ppm**	**2,000 ppm**	**4,000 ppm**	**8,000 ppm**
Body weight (grams)	363 ± 12 0	354 ± 6 9	355 ± 4 5	355 ± 2 8	**327 ± 2 8	**300 ± 4 3
Kidney						
Absolute	1,232 ± 48	1,345 ± 38	**1 433 ± 28	**1,523 ± 15	**1,451 ± 18	**1,377 ± 22
Relative	3 4 ± 0 16	3 8 ± 0 08	**4 0 ± 0 09	**4 3 ± 0 04	**4 4 ± 0 06	**4 6 ± 0 07
Liver						
Absolute	15 450 ± 660	16 500 ± 540	16,960 ± 570	*17,840 ± 250	16,050 ± 330	14,760 ± 340
Relative	42 9 ± 2 17	46 5 ± 0 95	47 7 ± 1 37	**50 2 ± 0 49	*49 1 ± 0 79	*49 2 ± 0 85
Sprague Dawley						
Body weight (grams)	449 ± 11 0	446 ± 7 9	431 ± 7 0	432 ± 11 3	436 ± 7 9	*414 ± 9 2
Kidney						
Absolute	1,871 ± 74	1,943 ± 59	1,954 ± 58	1,856 ± 74	2,000 ± 52	2,008 ± 55
Relative	4 2 ± 0 14	4 4 ± 0 11	*4 5 ± 0 08	4 3 ± 0 11	*4 6 ± 0 11	**4 9 ± 0 11
Liver						
Absolute	18,480 ± 790	20,080 ± 590	18,810 ± 570	20,100 ± 790	19,970 ± 490	19,230 ± 560
Relative	41 1 ± 1 03	*45 0 ± 1 15	*43 6 ± 0 75	**46 5 ± 1 11	**45 9 ± 0 82	**46 5 ± 1 20
Osborne-Mendel						
Body weight (grams)	421 ± 25 3	477 ± 13 1	465 ± 17 2	433 ± 14 0	393 ± 11 8	*380 ± 11 3
Kidney						
Absolute	(b) 1,506 ± 36	1,600 ± 41	**1,751 ± 40	1,656 ± 59	1,613 ± 44	1,507 ± 68
Relative	(b) 3 7 ± 0 28	3 4 ± 0 09	3 8 ± 0 14	3 8 ± 0 09	**4 1 ± 0 13	*4 0 ± 0 18
Liver						
Absolute	(b) 16,230 ± 810	17 830 ± 610	**21 080 ± 840	19,310 ± 800	15,190 ± 510	15,900 ± 800
Relative	(b) 39 2 ± 2 01	37 4 ± 0 85	*45 4 ± 0 90	*44 6 ± 1 24	38 8 ± 1 45	41 9 ± 1 59
Gavage study						
F344/N	**Vehicle Control**	**30 mg/kg**	**60 mg/kg**	**120 mg/kg**		
Body weight (grams)	339 ± 4 8	353 ± 6 7	354 ± 9 0	341 ± 8 1		
Kidney						
Absolute	1,324 ± 29	*1,441 ± 26	**1,600 ± 54	**1,653 ± 47		
Relative	3 9 ± 0 06	4 1 ± 0 10	**4 5 ± 0 08	**4 9 ± 0 07		
Liver						
Absolute	17,000 ± 440	(b) 17,960 ± 510	18,270 ± 540	*(b) 19 400 ± 660		
Relative	50 2 ± 0 87	(b) 50 9 ± 0 97	51 7 ± 0 92	**(b) 57 4 ± 0 83		

(a) Mean ± standard error in milligrams (absolute) or milligrams per gram (relative) for groups of 10 animals unless otherwise specified, P values vs the controls by Dunn s test (Dunn, 1964) or Shirley s test (Shirley, 1977)
(b) Nine animals were weighed
*P<0 05
**P<0 01

TABLE 7. ORGAN WEIGHT DATA FOR FEMALE RATS IN THE THIRTEEN-WEEK STUDIES OF 1,2-DICHLOROETHANE (a)

Study/Strain/Organ	Dose or Concentration					
Drinking water studies						
F344/N	**Control**	**500 ppm**	**1,000 ppm**	**2,000 ppm**	**4,000 ppm**	**8,000 ppm**
Body weight (grams)	194 ± 2 4	199 ± 2 9	213 ± 10 1	196 ± 2 4	193 ± 1 3	185 ± 2 3
Kidney						
Absolute	739 ± 26	*814 ± 16	**885 ± 16	**845 ± 17	**932 ± 15	**923 ± 15
Relative	3 8 ± 0 13	4 1 ± 0 07	*4 2 ± 0 17	**4 3 ± 0 07	**4 8 ± 0 09	**5 0 ± 0 04
Liver						
Absolute	6,829 ± 154	7,268 ± 179	**7,627 ± 177	7,278 ± 165	*7,551 ± 171	7,134 ± 147
Relative	35 3 ± 0 85	36 6 ± 0 60	36 3 ± 1 57	37 2 ± 0 75	**39 2 ± 0 94	**38 5 ± 0 61
Sprague Dawley						
Body weight (grams)	271 ± 5 5	283 ± 7 8	287 ± 6 4	271 ± 4 5	265 ± 6 6	256 ± 4 8
Kidney						
Absolute	1,030 ± 36	*1,160 ± 27	**1,221 ± 28	**1,211 ± 33	**1,208 ± 50	**1,342 ± 16
Relative	3 8 ± 0 11	*4 1 ± 0 09	*4 3 ± 0 13	**4 5 ± 0 11	**4 6 ± 0 16	**5 2 ± 0 10
Liver						
Absolute	11,140 ± 350	11,890 ± 530	12,200 ± 680	10,990 ± 310	11,500 ± 370	(b) 11,950 ± 450
Relative	41 2 ± 1 07	42 0 ± 1 49	42 7 ± 2 60	40 6 ± 1 32	43 5 ± 1 37	*(b) 46 6 ± 1 41
Osborne-Mendel						
Body weight (grams)	274 ± 9 9	279 ± 5 6	271 ± 4 7	256 ± 6 5	270 ± 6 6	266 ± 11 2
Kidney						
Absolute	894 ± 28	**1,017 ± 15	**1,041 ± 22	**1,020 ± 24	**1,096 ± 37	**1,094 ± 33
Relative	3 3 ± 0 11	*3 7 ± 0 06	**3 9 ± 0 06	**4 0 ± 0 16	**4 1 ± 0 14	**4 2 ± 0 26
Liver						
Absolute	10,390 ± 450	11,580 ± 360	10,810 ± 230	10,390 ± 430	10,750 ± 300	10,100 ± 410
Relative	37 9 ± 1 04	41 5 ± 0 96	40 0 ± 0 81	41 0 ± 2 39	39 8 ± 0 73	38 6 ± 2 49
Gavage study						
F344/N	**Vehicle Control**	**18 mg/kg**	**37 mg/kg**	**75 mg/kg**	**150 mg/kg**	
Body weight (grams)	190 ± 1 9	190 ± 2 5	194 ± 3 3	197 ± 2 7	192 ± 1 9	
Kidney						
Absolute	800 ± 16	717 ± 70	798 ± 20	**898 ± 23	**984 ± 9	
Relative	4 2 ± 0 08	3 8 ± 0 37	4 1 ± 0 09	*4 6 ± 0 08	**5 1 ± 0 08	
Liver						
Absolute	7,345 ± 120	*8,000 ± 201	*7 920 ± 191	**8,577 ± 197	**9,775 ± 151	
Relative	38 7 ± 0 54	**42 1 ± 0 87	*40 8 ± 0 61	**43 6 ± 0 69	**51 0 ± 1 08	

(a) Mean ± standard error in milligrams (absolute) or milligrams per gram (relative) for groups of 10 animals unless otherwise specified, P values vs the controls by Dunn's test (Dunn, 1964) or Shirley s test (Shirley, 1977)
(b) Nine animals were weighed
*P<0 05
**P<0 01

Sprague Dawley Rats: All Sprague Dawley rats lived to the end of the studies (Table 8). Mean body weights of males and females exposed to 4,000 ppm or more were lower than those of controls throughout the studies (Figure 3). Water consumption by the three highest dose groups was about half that by controls for males and was less than half that by controls for females. Mild increases in erythrocyte counts, hemoglobin, hematocrit, and blood urea nitrogen at days 3 and 7 in dosed male rats are evidence of mild animal dehydration (Table A6). The absolute and relative kidney weights for dosed females, relative kidney weights for dosed males, and the relative liver weights for dosed males and females were significantly increased (see Tables 6 and 7). No compound-related clinical signs were observed. Tubular regeneration occurred in the kidney of males and females in all dosed and control groups; the severity and incidence did not differ between groups. No lesions in the liver were attributed to 1,2-dichloroethane administration.

TABLE 8. SURVIVAL, MEAN BODY WEIGHTS, AND WATER CONSUMPTION OF SPRAGUE DAWLEY RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Water Consumption (d)
MALE						
0	10/10	170 ± 2	457 ± 11	+288 ± 10		43
500	10/10	169 ± 2	452 ± 7	+283 ± 7	99	37
1,000	10/10	169 ± 2	439 ± 6	+270 ± 6	96	30
2,000	10/10	169 ± 2	436 ± 12	+267 ± 12	95	25
4,000	10/10	168 ± 2	440 ± 8	+272 ± 7	96	21
8,000	10/10	169 ± 3	418 ± 9	+248 ± 7	91	19
FEMALE						
0	10/10	139 ± 2	281 ± 6	+141 ± 5		44
500	10/10	144 ± 2	291 ± 8	+147 ± 8	104	33
1,000	10/10	143 ± 2	290 ± 5	+147 ± 4	103	23
2,000	10/10	143 ± 2	276 ± 5	+133 ± 4	98	18
4,000	10/10	141 ± 2	270 ± 7	+128 ± 6	96	16
8,000	10/10	135 ± 2	257 ± 5	+123 ± 4	91	13

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean
(d) Grams per animal per day; not corrected for spillage.

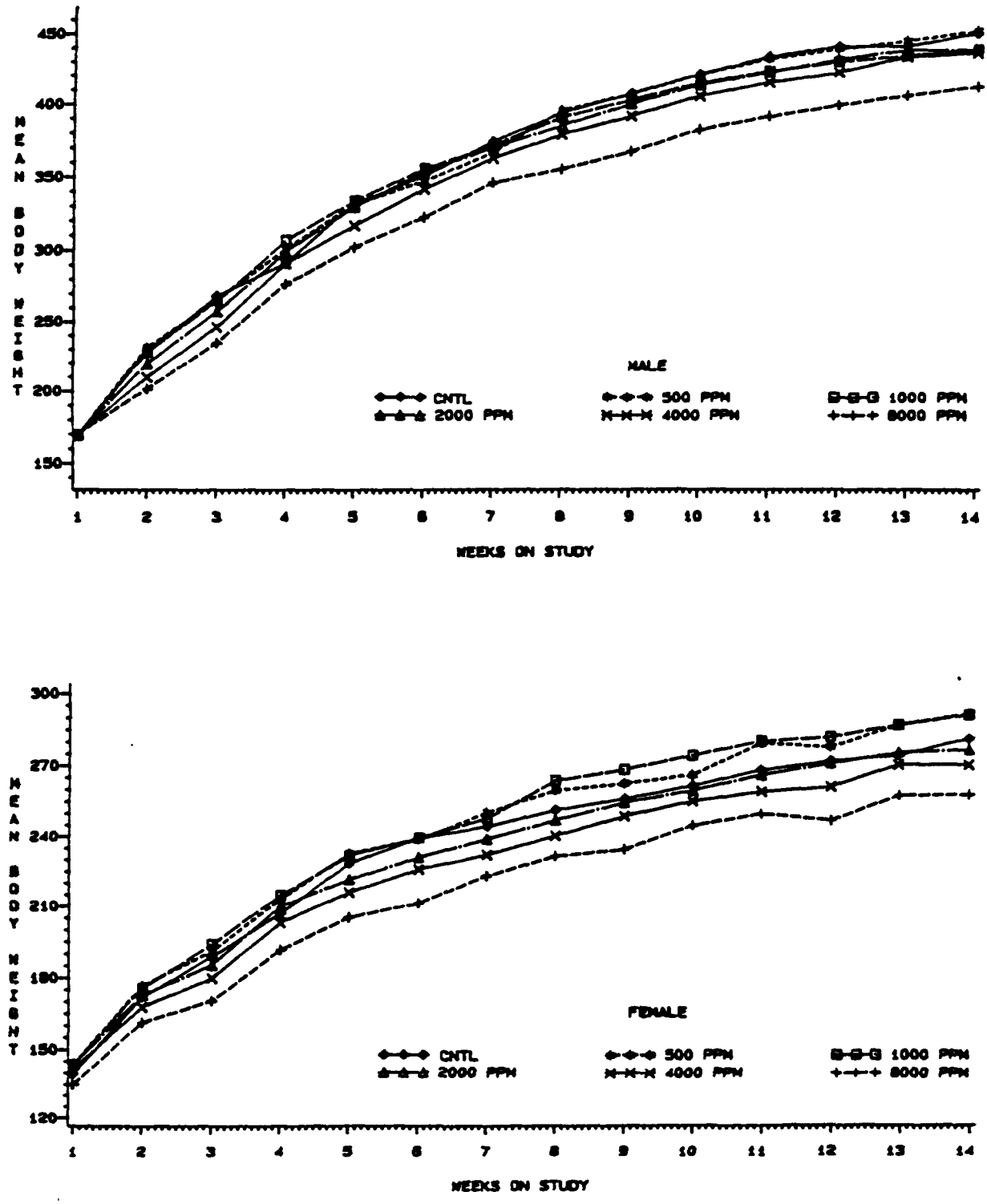


FIGURE 3. GROWTH CURVES FOR SPRAGUE DAWLEY RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE

Osborne-Mendel Rats: No compound-related deaths occurred in Osborne-Mendel rats (Table 9). Mean body weights of males exposed to 2,000 ppm or more and of females exposed to 1,000 ppm or more were lower than those of controls throughout the studies (Figure 4). Water consumption by the three highest dose groups was half or less than half that by controls. The increases in erythrocyte counts, hematocrit, and hemoglobin (day 3) and the decrease in mean cell volume in dosed male rats are evidence of animal dehydration (Table A9). The absolute and relative kidney weights were increased for dosed females, and the relative liver weights were increased for males receiving 1,000 or 2,000 ppm (see Tables 6 and 7). No compound-related clinical signs were observed. Renal tubular regeneration was seen in all dosed and control groups of each sex; although the incidences were increased in rats administered the higher doses of 1,2-dichloroethane, the increases were not clearly dose related and the severity was not different between groups.

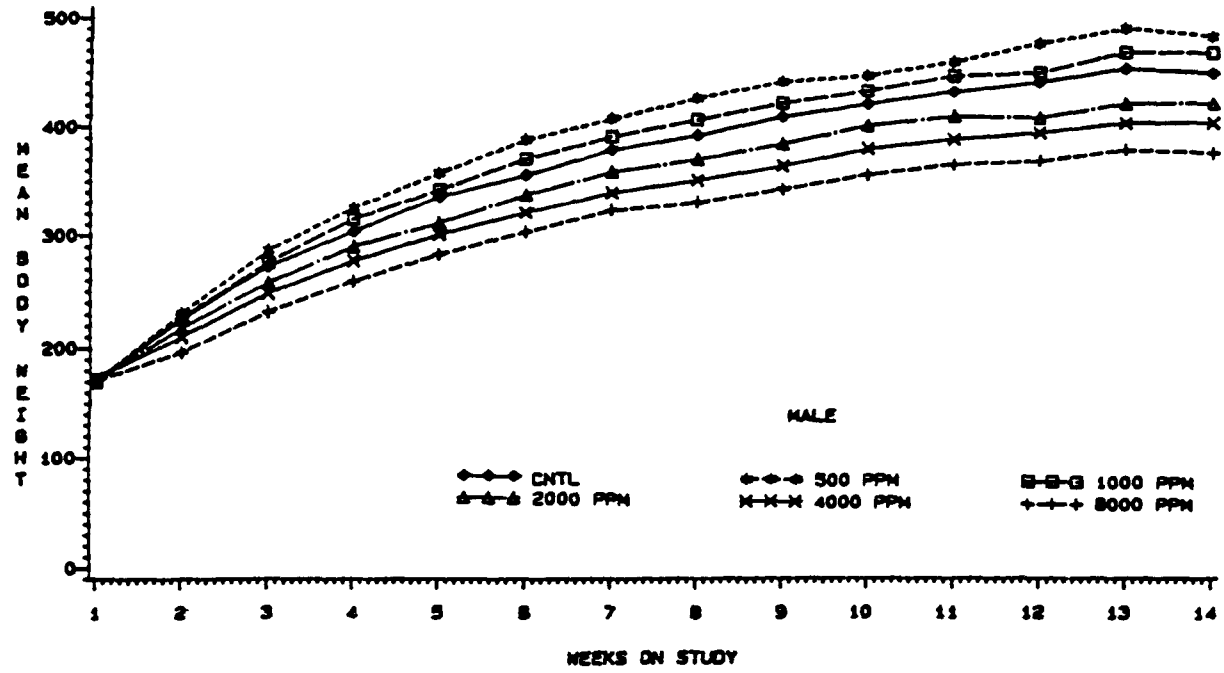
Gavage Studies

All male F344/N rats that received 240 or 480 mg/kg and 9/10 females that received 300 mg/kg died before the end of the studies (Table 10). Mean body weights of males at 480 mg/kg and of females at 300 mg/kg were lower than those of vehicle controls throughout the studies (Figure 5). The mean body weight for one cage of female vehicle controls was decreased at week 9, possibly due to not receiving water. Compound-related clinical signs included tremors, salivation, emaciation, abnormal postures, ruffled fur, and dyspnea in males at 240 mg/kg and in females at 300 mg/kg. The absolute and relative kidney and liver weights were increased for dosed males and females (see Tables 6 and 7). Hyperplasia, inflammation, and mineralization were seen in the mucosa of the forestomach in animals that died or were killed in a moribund condition (Table 11). Foci of epithelial necrosis were sometimes seen with hyperplasia and inflammation. Necrosis of the cerebellum and of the thymus

TABLE 9. SURVIVAL, MEAN BODY WEIGHTS, AND WATER CONSUMPTION OF OSBORNE-MENDEL RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Water Consumption (d)
MALE						
0	(e) 9/10	172 ± 3	452 ± 15	+281 ± 16		42
500	10/10	171 ± 4	482 ± 13	+311 ± 14	107	35
1,000	10/10	170 ± 3	468 ± 17	+298 ± 18	104	28
2,000	10/10	169 ± 3	435 ± 14	+266 ± 14	96	22
4,000	10/10	172 ± 3	399 ± 12	+227 ± 14	88	19
8,000	10/10	171 ± 3	382 ± 11	+211 ± 12	85	17
FEMALE						
0	10/10	138 ± 3	278 ± 12	+140 ± 12		43
500	10/10	139 ± 3	277 ± 6	+137 ± 5	100	34
1,000	10/10	138 ± 3	275 ± 5	+138 ± 3	99	26
2,000	10/10	137 ± 3	261 ± 4	+124 ± 3	94	23
4,000	10/10	136 ± 2	275 ± 7	+139 ± 5	99	22
8,000	10/10	138 ± 2	258 ± 5	+121 ± 4	93	18

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day; not corrected for spillage.
(e) Week of death: 7



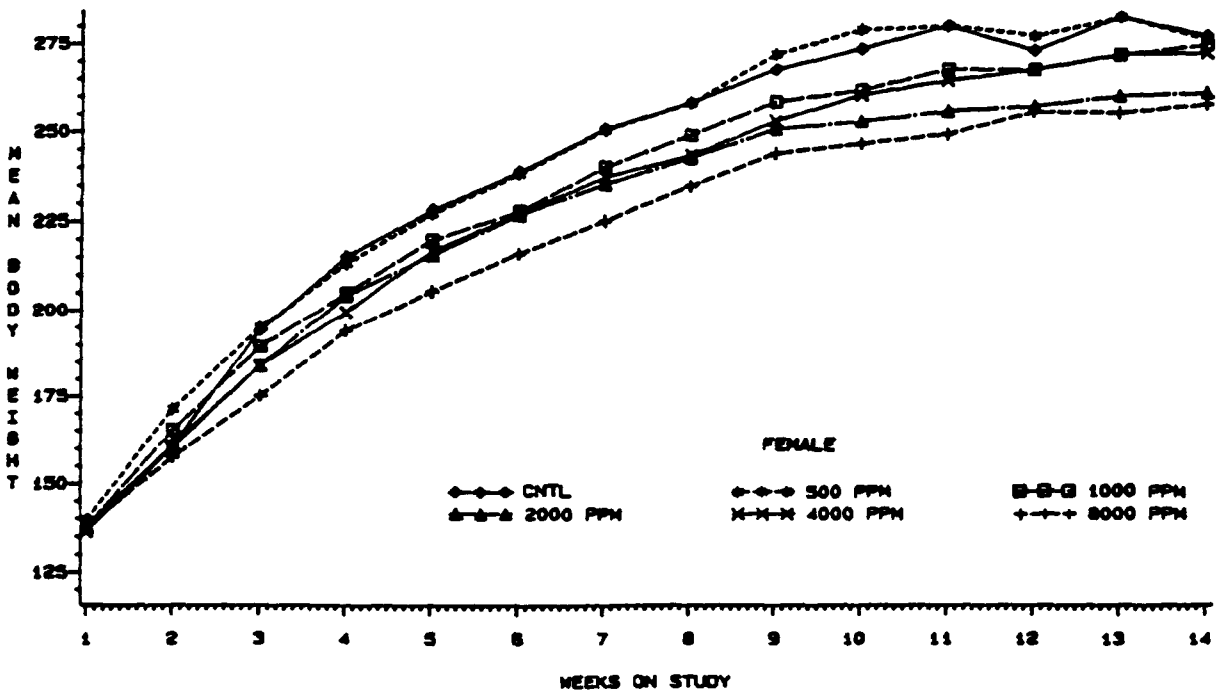


FIGURE 4. GROWTH CURVES FOR OSBORNE-MENDEL RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE

TABLE 10. SURVIVAL AND MEAN BODY WEIGHTS OF F344/N RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 1,2-DICHLOROETHANE

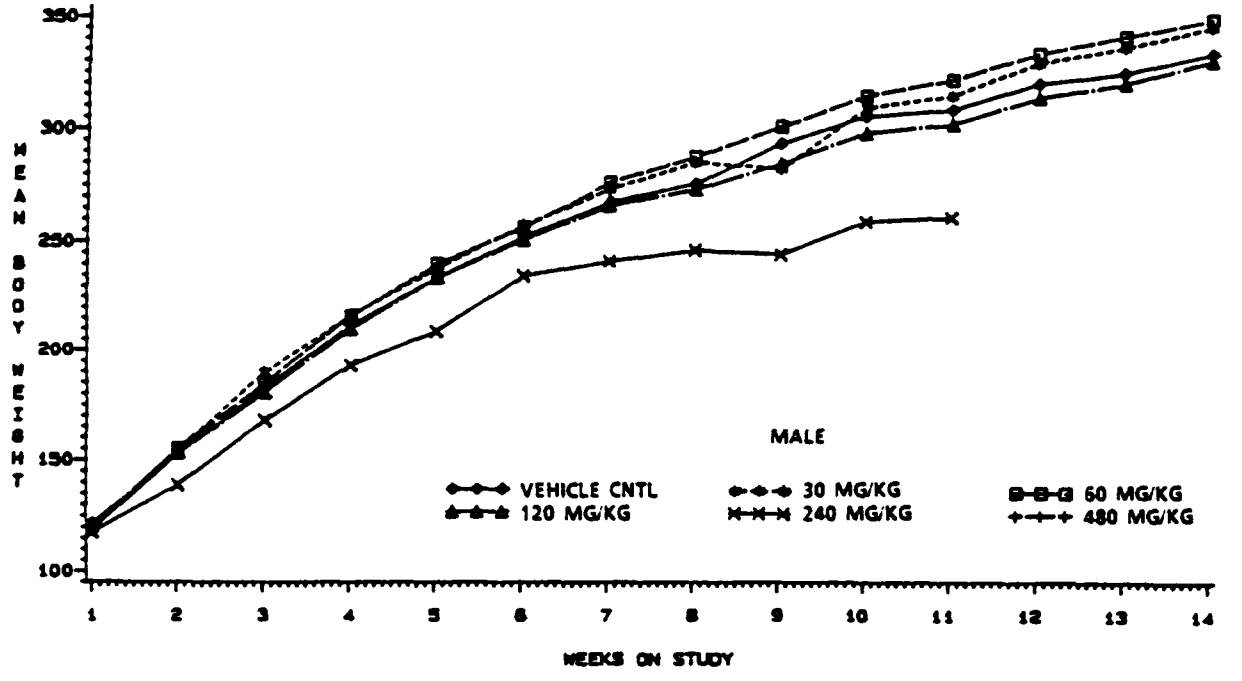
Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	118 ± 4	333 ± 4	+215 ± 6	
30	10/10	119 ± 5	346 ± 5	+226 ± 4	104
60	10/10	120 ± 4	349 ± 9	+229 ± 9	105
120	10/10	120 ± 4	338 ± 9	+218 ± 7	102
240	(d) 0/10	118 ± 4	(e)	(e)	(e)
480	(f) 0/10	117 ± 4	(e)	(e)	(e)
FEMALE					
0	10/10	104 ± 2	193 ± 2	+89 ± 3	
18	10/10	102 ± 2	193 ± 2	+91 ± 2	100
37	10/10	102 ± 2	197 ± 3	+95 ± 3	102
75	10/10	104 ± 2	199 ± 3	+95 ± 2	103
150	10/10	104 ± 2	194 ± 3	+90 ± 3	101
300	(g) 1/10	101 ± 2	177	+76	92

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 1,1,5,5,6,7,8,8,9,11
(e) No data are reported due to 100% mortality in this group.
(f) Week of death: all 1
(g) Week of death: 1,1,2,2,2,3,5,11,13

TABLE 11. NUMBERS OF F344/N RATS WITH SELECTED LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 1,2-DICHLOROETHANE (a)

Site/Lesion	Group			
MALE	**Vehicle Control**	**120 mg/kg**	**240 mg/kg**	**480 mg/kg**
Forestomach				
Hyperplasia	0	1	*5	2
Mineralization	0	0	3	2
Inflammation	0	1	*5	3
Cerebellum				
Necrosis	0	0	3	0
Thymus				
Necrosis	0	0	4	**10
FEMALE	**Vehicle Control**	**75 mg/kg**	**150 mg/kg**	**300 mg/kg**
Forestomach				
Hyperplasia	0	--	0	3
Mineralization	0	--	0	1
Inflammation	0	--	0	1
Cerebellum				
Necrosis	0	--	0	3
Thymus				
Necrosis	0	--	0	*5

(a) Ten animals were examined microscopically in each group.
*P<0.05 vs. vehicle controls
**P<0.01 vs. vehicle controls



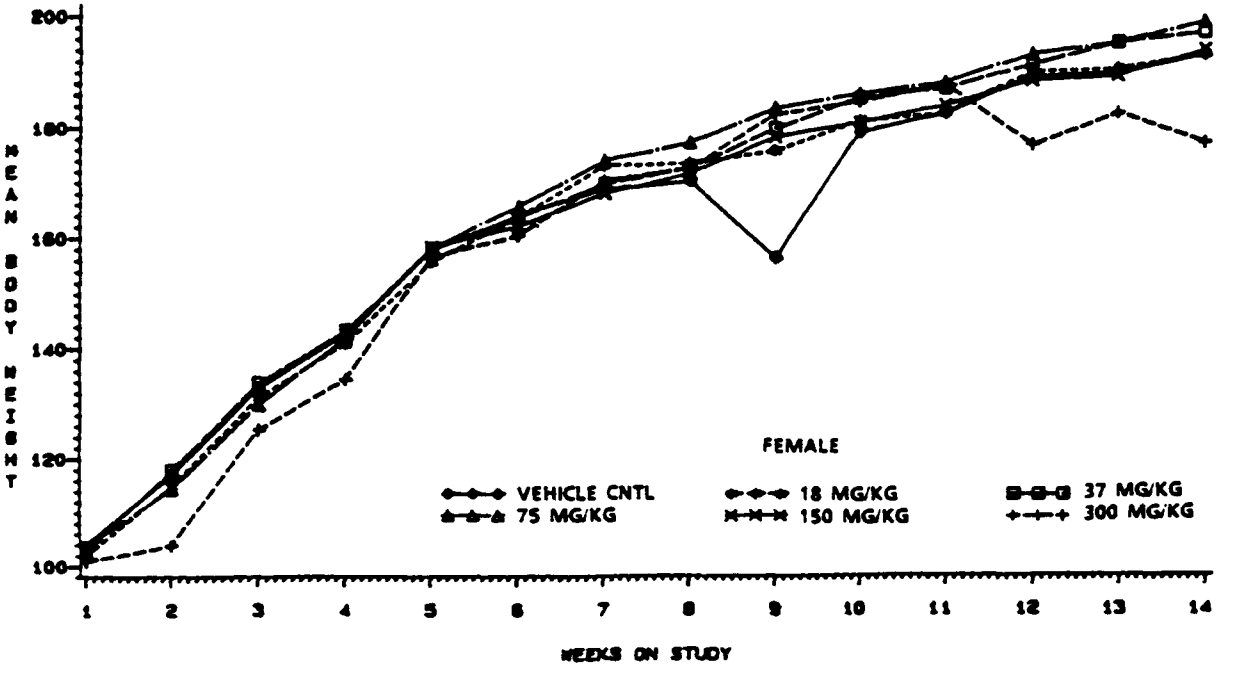


FIGURE 5. GROWTH CURVES FOR F344/N RATS ADMINISTERED 1,2-DICHLOROETHANE IN CORN OIL BY GAVAGE FOR THIRTEEN WEEKS

was also observed. Necrosis in the cerebellum was mainly in the granular layer of the lateral folia, and mineralization was also present in the areas of necrosis in a few animals. Renal tubular regeneration in vehicle control and dosed groups of males or females did not differ in incidence or severity.

THIRTEEN-WEEK STUDIES IN MICE

Drinking Water Studies: Nine of 10 female mice exposed to 8,000 ppm died before the end of the studies (Table 12). Mean body weights of males exposed to 500 ppm or more and of females exposed to 1,000 ppm or more were lower than those of controls throughout most of the studies (Figure 6).

Water consumption varied greatly from week to week, but overall water consumption by dosed and control groups appeared to be similar. The absolute and relative kidney and liver weights were significantly increased for dosed males and females (Table 13). No compound-related clinical signs were observed. Compound-related lesions were seen in the kidney of male mice and were most prominent at the highest concentration (Table 14). At 8,000 ppm, a minimal-to-moderate tubular cell regeneration consisting of foci of basophilic-staining tubular epithelium was seen in the cortex of the kidney. Karyomegaly in the tubular epithelium, particularly in areas of regeneration, was characterized by nuclei that were slightly enlarged and more variable in size than in controls. Protein casts were present in the lumen of a few tubules and were sometimes associated with tubular dilatation. In addition, foci of mineralization were present in the renal papilla at the highest dose. At 4,000 ppm, minimal tubular cell regeneration was present in 8/10 male mice; a similar change was present in only one or two mice per group at the lower doses.

TABLE 12. SURVIVAL, MEAN BODY WEIGHTS, AND WATER CONSUMPTION OF MICE IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE

Concentration (ppm)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Controls (percent)	Water Consumption (d)
MALE						
0	10/10	21.2 ± 0.2	31.4 ± 0.6	+10.2 ± 0.4		13.1
500	10/10	20.5 ± 0.4	28.9 ± 0.6	+8.4 ± 0.4	92.0	12.3
1,000	10/10	21.1 ± 0.4	29.3 ± 0.5	+8.2 ± 0.6	93.3	11.3
2,000	10/10	20.8 ± 0.4	29.4 ± 0.8	+8.6 ± 0.7	93.6	9.8
4,000	10/10	20.3 ± 0.2	28.6 ± 0.7	+8.3 ± 0.6	91.1	16.6
8,000	10/10	20.5 ± 0.3	25.9 ± 0.7	+5.4 ± 0.8	82.5	12.2
FEMALE						
0	10/10	17.1 ± 0.2	25.9 ± 0.6	+8.8 ± 0.5		8.1
500	10/10	17.8 ± 0.3	24.7 ± 0.5	+6.9 ± 0.4	95.4	10.4
1,000	10/10	16.9 ± 0.2	23.2 ± 0.6	+6.3 ± 0.5	89.6	13.0
2,000	10/10	16.9 ± 0.3	23.7 ± 0.5	+6.8 ± 0.4	91.5	12.0
4,000	10/10	17.1 ± 0.3	23.8 ± 0.6	+6.7 ± 0.5	91.9	12.7
8,000	(e) 1/10	17.2 ± 0.4	23.4	+4.7	90.3	12.5

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Grams per animal per day; average of determinations from week 2 to week 13; not corrected for spillage.
(e) Week of death: 1,1,5,5,9,10,10,11,13

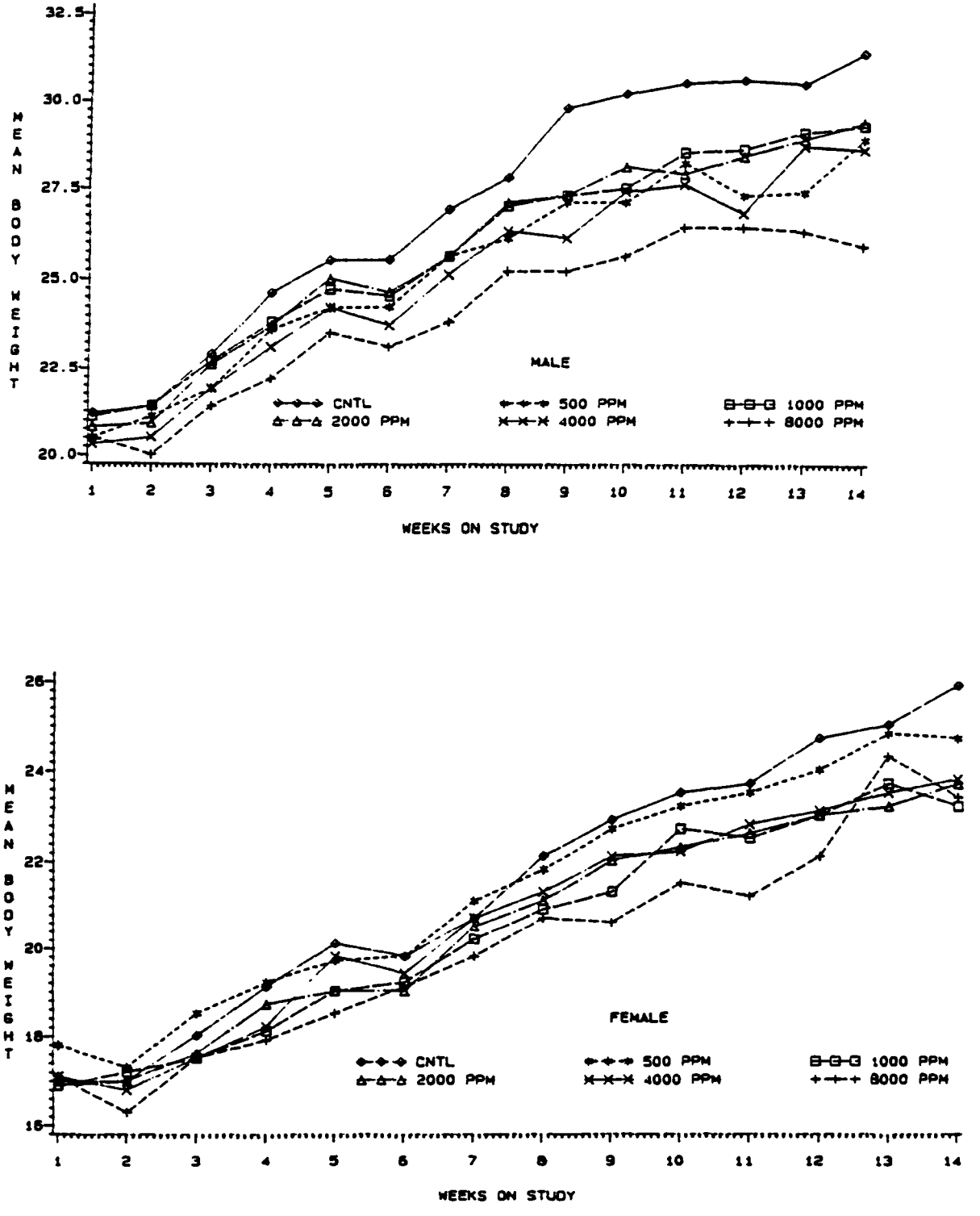


FIGURE 6. GROWTH CURVES FOR MICE IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE

TABLE 13. ORGAN WEIGHT DATA FOR MICE IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (a)

Organ	Control	500 ppm	1,000 ppm	2,000 ppm	4,000 ppm	8,000 ppm
MALE						
Number weighed	10	9	10	10	9	10
Body weight (grams)	30.0 ± 0.73	28.0 ± 0.81	28.4 ± 0.47	29.0 ± 0.79	28.3 ± 0.68	**25.4 ± 0.65
Kidney						
Absolute	305 ± 7	301 ± 8	*323 ± 7	**358 ± 8	**385 ± 9	**379 ± 12
Relative	10.2 ± 0.22	10.8 ± 0.12	**11.4 ± 0.12	**12.4 ± 0.33	**13.8 ± 0.40	**15.0 ± 0.54
Liver						
Absolute	1,455 ± 55	1,490 ± 42	1,519 ± 55	1,571 ± 56	*1,628 ± 54	*1,598 ± 78
Relative	48.5 ± 1.06	**53.6 ± 0.91	**53.4 ± 1.18	**54.3 ± 1.46	**57.6 ± 1.10	**62.8 ± 2.13
FEMALE						
Number weighed	10	8	10	9	10	(b) 1
Body weight (grams)	24.0 ± 0.59	23.7 ± 0.52	22.5 ± 0.54	22.8 ± 0.57	23.2 ± 0.57	23.0
Kidney						
Absolute	191 ± 4	**225 ± 6	**211 ± 5	**212 ± 7	**215 ± 7	217
Relative	8.0 ± 0.23	**9.4 ± 0.21	**9.4 ± 0.17	**9.3 ± 0.24	**9.3 ± 0.22	9.4
Liver						
Absolute	1,258 ± 39	1,258 ± 52	1,263 ± 34	1,314 ± 56	*1,383 ± 29	1,391
Relative	52.5 ± 0.85	51.5 ± 0.95	*56.0 ± 0.67	*56.1 ± 1.18	**59.7 ± 1.01	60.5

(a) Mean ± standard error in milligrams (absolute) or milligrams per gram (relative) unless otherwise specified; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Not included in statistical analysis
*P<0.05
**P<0.01

TABLE 14. NUMBERS OF MICE WITH RENAL LESIONS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (a)

Lesion	Control	500 ppm	1,000 ppm	2,000 ppm	4,000 ppm	8,000 ppm
MALE						
Tubular regeneration	0	1	2	2	**8	**9
Karyomegaly	0	0	0	0	0	**10
Dilatation	0	0	0	0	0	*5
Protein casts	0	0	0	0	0	**8
Mineralization	0	0	0	0	0	*5
FEMALE						
Tubular regeneration	0	0	0	0	1	0

(a) Ten mice were examined microscopically in each group.
*P<0.05 vs. controls
**P<0.01 vs. controls

Daily intake doses, on a milligram per kilogram body weight basis, were estimated for rats administered 1,2-dichloroethane in drinking water or by gavage (Table 15). For the drinking water studies, these estimates were obtained by dividing the mean water consumption over the 13-week studies by the mean of the initial and final body weights. All rat strains received approximately the same dose of 1,2-dichloroethane in drinking water; female Osborne-Mendel rats received a slightly higher dose than male Osborne-Mendel rats. Because mice typically consume more water than rats on a milligram per kilogram body weight basis, they received considerably higher doses of 1,2-dichloroethane than rats in the drinking water studies. Administration of 8,000 ppm 1,2-dichloroethane in drinking water resulted in up to eightfold higher doses in mice than in in rats.

TABLE 15. ESTIMATED DAILY DOSES OF 1,2-DICHLOROETHANE ADMINISTERED BY GAVAGE OR IN DRINKING WATER IN THE THIRTEEN-WEEK STUDIES

F344/N Gavage Dose (mg/kg/day)	Concentration in Drinking Water (ppm)	Estimated Intake Drinking Water Dose (a)			
		F344/N	Sprague Dawley	Osborne-Mendel	$B6C3F_1$ Mice
MALE					
30	500	49	60	54	249
60	1,000	86	99	88	448
120	2,000	147	165	146	781
240	4,000	259	276	266	2,710
480	8,000	515	518	492	4,207
FEMALE					
18	500	58	76	82	244
37	1,000	102	106	126	647
75	2,000	182	172	213	1,182
150	4,000	320	311	428	2,478
300	8,000	601	531	727	4,926

(a) Milligrams per kilogram per day based on the mean of the initial and final body weights for ten animals

IV. DISCUSSION AND CONCLUSIONS

1,2-Dichloroethane administered at up to 8,000 ppm in drinking water for 13 weeks caused few adverse effects in F344/N, Sprague Dawley, and Osborne-Mendel rats. No deaths occurred in exposed rats, and body weight changes were similar for all three rat strains of each sex. The high dose level of 1,2-dichloroethane (8,000 ppm) was selected based on limitations in the solubility and palatability of the chemical in drinking water. The maximum solubility of 1,2-dichloroethane in water is about 9,000 ppm (Torkelson and Rowe, 1981).

Weight gain depression was common in males and females in the two higher dose groups throughout the studies and was likely caused by dehydration due to poor palatability of the formulated drinking water. Water consumption decreased substantially with increasing dose for all exposed male and female rats, regardless of strain. The decrease in water intake, which was as much as 60% at the highest dose in male and female Osborne-Mendel rats, indicates that the dose received by all exposed animals was less than the target dose; however, because water intake was reduced at most exposure levels, equivalent exposure did not occur at different dose levels within a strain.

The estimated daily intake of 1,2-dichloroethane was similar for each rat strain at each dose level. Rats administered drinking water containing 8,000 ppm 1,2-dichloroethane received an estimated intake of about 500-725 mg/kg per day. This estimated daily intake is close to the reported oral LD_{50} for 1,2-dichloroethane administered by gavage (680-850 mg/kg) (McCollister et al., 1956); however, intake of this dose over 24 hours rather than as a bolus resulted in little toxicity.

1,2-Dichloroethane toxicity administered by gavage or in formulated drinking water was compared in F344/N rats. Gavage doses were calculated to be approximately equivalent (in milligrams per kilogram) to the range of exposures resulting from the formulated water mixtures. The F344/N rats were more sensitive to 1,2-dichloroethane administered by gavage than in drinking water, as evidenced by the fact that all males receiving 240 and 480 mg/kg and 9/10 females receiving 300 mg/kg died before the end of the studies.

Necrosis of the cerebellum, observed in the brains of three males receiving 240 mg/kg and three females receiving 300 mg/kg, appeared to be related to 1,2-dichloroethane administration. Morphologic alterations in cells of the cerebellum, parenchymous changes in the brain and spinal cord, and hyperemia and hemorrhage of the brain have been observed in humans who died of acute oral poisoning by 1,2-dichloroethane (Hueper and Smith, 1935; Lochhead and Close, 1951).

Hyperplasia, inflammation, and mineralization of the forestomach were observed in eight male and three female F344/N rats dosed by gavage which died or were killed in a moribund condition. Although forestomach lesions were chemical related, they were not considered life threatening. However, hyperplasia of the forestomach epithelium after 13 weeks of exposure may be of significance, since long-term administration of 1,2-dichloroethane by gavage has been shown to cause neoplasms of the forestomach in Osborne-Mendel rats (NCI, 1978).

Thymic necrosis in four mid dose and all high dose males and in five high dose females was attributed to stress in animals that died or were killed in a moribund condition.

Administration of bolus doses of 1,2-dichloroethane by gavage may result in saturation of 1,2-dichloroethane elimination and increased levels of 1,2-dichloroethane in the blood (Reitz et al., 1982). Exposure at lower concentrations of 1,2-dichloroethane over the course of the day (in drinking water or by inhalation) would result in lower peak blood levels and a lower area under the curve (the integral of the 1,2-dichloroethane concentration in blood as a function of time) and the chemical could be rapidly eliminated, even when the total daily dose was equal to the

amount administered by gavage (Reitz et al., 1982). This mechanism may explain the greater toxicity for F344/N rats of 1,2-dichloroethane administered by gavage compared with that after drinking water exposure.

Based on the significant organ weight changes in rats receiving the chemical by either the drinking water or gavage routes, the liver and kidney appear to be target organs for 1,2-dichloroethane. Liver weights were usually increased in rats of all strain, sex, and dose combinations. The kidney was also increased in weight and was significantly increased more frequently than the liver. Despite increases of 10%-20% in kidney and liver weights, no histologic changes could be clearly attributed to 1,2-dichloroethane, except perhaps for renal tubular epithelium regeneration in female F344/N rats. Serum chemistry data were not indicative of liver or kidney injury. Increased blood urea nitrogen was attributed to dehydration.

Regenerative lesions of the rat kidney are commonly seen and are associated with chronic progressive nephropathy, which occurs in most strains of albino rats. The incidence and severity of progressive nephropathy are sex dependent; in general, male rats are more susceptible than females, with the earliest lesions appearing at about 3 months of age (Goldstein et al., 1988).

Rats were 4.5 months old at the end of the current studies. Renal tubular epithelial regeneration was present in many dosed and control animals of all strains; however, only female F344/N rats exposed to 1,2-dichloroethane in drinking water had a higher incidence of kidney lesions than controls. The degree of severity was not increased, however, and was minimal even in the highest dose group.

Administration of up to 8,000 ppm 1,2-dichloroethane in drinking water resulted in greater toxicity to $B6C3F_1$ mice than to rats. Nine of 10 female mice exposed to 8,000 ppm 1,2-dichloroethane died before the end of the study. The estimated daily intake of 1,2-dichloroethane in mice (with no corrections made for spillage) administered 8,000 ppm 1,2-dichloroethane was approximately 4,200 mg/kg in males and 4,900 mg/kg in females. These intake levels are approximately tenfold greater than the reported LD_{50} of 1,2-dichloroethane administered by gavage (489 mg/kg for male mice and 413 mg/kg for female mice) (Munson et al., 1982). The estimated daily intake of 1,2-dichloroethane was considerably higher for mice than for rats receiving the same concentrations in drinking water. Mice typically consume more water than rats on a milligram per kilogram body weight basis, and palatability did not reduce water consumption by mice.

Based on organ weight changes, the target organs for male and female $B6C3F_1$ mice exposed to 1,2-dichloroethane in drinking water were the liver and kidney. However, histopathologic changes were limited to protein casts, mineralization, karyomegaly, and regeneration in the renal tubules of male mice. The regenerative lesions were similar to those observed in rats; however, such lesions are generally less common in mice than in rats. Although significant increases were observed in kidney weights of most exposed female mice, regeneration was detected in only one mouse.

Long-term studies have shown that 1,2-dichloroethane administered by gavage causes neoplasms in the mammary gland, endometrium, and lungs (but not in the kidney) in $B6C3F_1$ mice (NCI, 1978); inhalation exposure of Swiss mice resulted in no carcinogenic effects (Maltoni et al., 1980). The differing results of the two long-term studies have been attributed to a difference in responsiveness in the test strains and to the different routes of administration (Hooper et al., 1980).

The results from a short-term study on $B6C3F_1$ mice indicated that 1,2-dichloroethane is capable of inducing single-strand breaks and/or alkali-labile lesions in hepatic DNA when administered by intraperitoneal injection or by gavage, but not after inhalation exposure to comparable doses (Storer et al., 1984); this suggests that the liver is more likely to be a target organ when 1,2-dichloroethane is administered orally or parenterally than when administered by inhalation. The current drinking water studies in $B6C3F_1$ mice demonstrated increases in liver weights in mice receiving drinking water containing 1,2-dichloroethane, although histologic lesions were not observed. In addition, lesions

were observed in the kidney, which had not previously been identified as a target organ in mice.

1,2-Dichloroethane administered at up to 8,000 ppm in drinking water for 13 weeks was relatively nontoxic for F344/N, Sprague Dawley, and Osborne-Mendel rats. Administration of the same drinking water concentrations of 1,2-dichloroethane to $B6C3F_1$ mice resulted in greater toxicity; 9/10 female mice exposed to 8,000 ppm 1,2-dichloroethane died before the end of the study. The estimated daily intake (milligram per kilogram per day) of 1,2-dichloroethane in mice was about eightfold greater than in rats.

Based on organ weight increases, the liver and kidney appeared to be target organs in both rats and mice, although histologic evidence of toxicity was found only in the kidney of female F344/N rats (minimal) and male $B6C3F_1$ mice. Because of limitations in the solubility and palatability of 1,2-dichloroethane, it was not possible to obtain a high enough dose in drinking water to see biologically significant toxic effects in rats. Based on mortality and chemical-related lesions, the no-effect levels for 1,2-dichloroethane administered by gavage to F344/N rats were 120 mg/kg for males and 150 mg/kg for females. For $B6C3F_1$ mice, the no-effect levels for 1,2-dichloroethane in drinking water were 2,000 ppm (780 mg/kg per day) for males, based on kidney lesions, and 4,000 ppm (2,500 mg/kg per day) for females, based on mortality.

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APPENDIX

ORGAN WEIGHT, HEMATOLOGIC, AND SERUM CHEMICAL DATA IN THE THIRTEEN-WEEK STUDIES OF 1,2-DICHLOROETHANE

TABLE A1. ABSOLUTE ORGAN WEIGHTS FOR F344/N RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (a)

	Control	500 ppm	1,000 ppm	2,000 ppm	4,000 ppm	8,000 ppm
MALE						
Brain	1,959 ± 23	1,927 ± 30	1,958 ± 24	1,954 ± 21	1,930 ± 30	1,908 ± 28
Heart	1,044 ± 24	1,077 ± 23	1,062 ± 18	1,078 ± 24	*991 ± 9	**927 ± 12
Right kidney	1,232 ± 48	1,345 ± 38	**1,433 ± 28	**1,523 ± 15	**1,451 ± 18	**1,377 ± 22
Liver	15,450 ± 660	16,500 ± 540	16,960 ± 570	*17,840 ± 250	16,050 ± 330	14,760 ± 340
Lung	1,731 ± 41	1,864 ± 74	(b) 1,824 ± 97	1,770 ± 61	1,634 ± 72	1,632 ± 47
Right testis	1,462 ± 15	1,460 ± 33	1,467 ± 19	1,462 ± 24	1,476 ± 19	1,422 ± 30
Thymus	285 ± 14	304 ± 17	287 ± 8	302 ± 15	307 ± 21	258 ± 13
FEMALE						
Brain	1,795 ± 16	1,817 ± 20	1,786 ± 28	1,772 ± 17	1,801 ± 16	1,773 ± 37
Heart	633 ± 17	654 ± 12	665 ± 9	667 ± 13	648 ± 8	643 ± 12
Right kidney	739 ± 26	*814 ± 16	**885 ± 16	**845 ± 17	**932 ± 15	**923 ± 15
Liver	6,829 ± 154	7,268 ± 179	**7,627 ± 177	7,278 ± 165	*7,551 ± 171	7,134 ± 147
Lung	1,203 ± 35	1,488 ± 169	1,353 ± 126	1,175 ± 61	1,243 ± 35	1,224 ± 50
Thymus	242 ± 9	247 ± 7	242 ± 13	221 ± 16	236 ± 13	234 ± 12

(a) Mean ± standard error in milligrams for groups of 10 animals unless otherwise specified; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Lungs of nine animals were weighed.
*P<0.05
**P<0.01

TABLE A2. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR F344/N RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (a)

	Control	500 ppm	1,000 ppm	2,000 ppm	4,000 ppm	8,000 ppm
MALE						
Body weight (grams)	363 ± 12.0	354 ± 6.9	355 ± 4.5	355 ± 2.8	**327 ± 2.8	**300 ± 4.3
Brain	5.4 ± 0.15	5.5 ± 0.11	5.5 ± 0.07	5.5 ± 0.08	**5.9 ± 0.06	**6.4 ± 0.11
Heart	2.9 ± 0.08	3.0 ± 0.06	3.0 ± 0.04	3.0 ± 0.07	3.0 ± 0.03	3.1 ± 0.03
Right kidney	3.4 ± 0.16	3.8 ± 0.08	**4.0 ± 0.09	**4.3 ± 0.04	**4.4 ± 0.06	**4.6 ± 0.07
Liver	42.9 ± 2.17	46.5 ± 0.95	47.7 ± 1.37	**50.2 ± 0.49	*49.1 ± 0.79	*49.2 ± 0.85
Lung	4.8 ± 0.18	5.3 ± 0.23	(b) 5.2 ± 0.29	5.0 ± 0.17	5.0 ± 0.21	5.5 ± 0.18
Right testis	4.1 ± 0.11	4.1 ± 0.05	4.1 ± 0.07	4.1 ± 0.05	**4.5 ± 0.05	**4.7 ± 0.08
Thymus	0.8 ± 0.05	0.9 ± 0.04	0.8 ± 0.02	0.9 ± 0.05	0.9 ± 0.07	0.9 ± 0.04
FEMALE						
Body weight (grams)	194 ± 2.4	199 ± 2.9	213 ± 10.1	196 ± 2.4	193 ± 1.3	185 ± 2.3
Brain	9.3 ± 0.15	9.2 ± 0.13	8.5 ± 0.30	9.0 ± 0.07	9.4 ± 0.09	9.6 ± 0.14
Heart	3.3 ± 0.09	3.3 ± 0.05	3.2 ± 0.12	3.4 ± 0.05	3.4 ± 0.05	*3.5 ± 0.05
Right kidney	3.8 ± 0.13	4.1 ± 0.07	*4.2 ± 0.17	**4.3 ± 0.07	**4.8 ± 0.09	**5.0 ± 0.04
Liver	35.3 ± 0.85	36.6 ± 0.60	36.3 ± 1.57	37.2 ± 0.75	**39.2 ± 0.94	**38.5 ± 0.61
Lung	6.2 ± 0.15	7.5 ± 0.82	6.4 ± 0.60	6.0 ± 0.27	6.5 ± 0.17	6.6 ± 0.23
Thymus	1.3 ± 0.04	1.2 ± 0.04	1.2 ± 0.09	1.1 ± 0.08	1.2 ± 0.07	1.3 ± 0.06

(a) Mean ± standard error in milligrams per gram for groups of 10 animals unless otherwise specified; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977)
(b) Lungs of nine animals were weighed.
*P<0.05
**P<0.01

TABLE A3. HEMATOLOGIC AND SERUM CHEMICAL DATA FOR MALE F344/N RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (a)

Analysis	Day	Control	2,000 ppm	4,000 ppm	8,000 ppm
Number examined (b)		8	10	10	10
Leukocytes (1,000/µl)	3	20.7 ± 4.28	(c) 15.1 ± 5.64	(d) 24.9 ± 6.89	*6.9 ± 0.47
	7	(e) 7.4 ± 0.96	8.9 ± 1.18	(c) 7.9 ± 0.54	7.2 ± 0.39
	14	6.9 ± 0.61	6.6 ± 0.34	6.4 ± 0.30	6.9 ± 0.27
	45	7.7 ± 0.48	8.1 ± 0.21	7.6 ± 0.19	7.0 ± 0.36
	90	7.2 ± 0.35	8.8 ± 0.82	7.6 ± 0.24	6.9 ± 0.27
Hematocrit (percent)	3	40.7 ± 1.18	(c) 40.1 ± 0.56	(d) 40.5 ± 0.61	**44.7 ± 0.66
	7	(e) 41.2 ± 0.71	41.8 ± 0.52	*(c) 44.1 ± 0.87	41.5 ± 0.38
	14	43.5 ± 0.50	43.8 ± 0.38	44.3 ± 0.33	43.5 ± 0.51
	45	45.4 ± 1.03	45.5 ± 1.04	47.1 ± 0.29	46.8 ± 0.70
	90	46.5 ± 0.37	46.3 ± 0.43	46.5 ± 0.44	46.9 ± 0.51
Hemoglobin (g/dl)	3	13.7 ± 1.13	(c) 14.3 ± 0.20	(d) 14.0 ± 0.23	*15.4 ± 0.17
	7	(e) 14.8 ± 0.17	14.9 ± 0.12	(c) 15.5 ± 0.28	15.1 ± 0.19
	14	15.0 ± 0.12	15.2 ± 0.10	15.3 ± 0.14	15.2 ± 0.19
	45	17.0 ± 0.15	17.1 ± 0.13	17.4 ± 0.07	16.8 ± 0.07
	90	16.8 ± 0.07	16.7 ± 0.08	16.7 ± 0.12	16.8 ± 0.07
Mean corpuscular hemoglobin (pg)	3	21.5 ± 1.24	(c) 22.6 ± 0.68	(d) 22.4 ± 0.54	*20.7 ± 0.25
	7	(e) 22.5 ± 0.29	22.0 ± 0.45	(c) 22.0 ± 0.25	**21.2 ± 0.12
	14	22.2 ± 0.18	21.5 ± 0.35	21.5 ± 0.26	**20.7 ± 0.14
	45	20.0 ± 0.41	19.8 ± 0.58	19.6 ± 0.19	*18.8 ± 0.27
	90	18.9 ± 0.16	18.4 ± 0.24	*18.2 ± 0.10	**18.1 ± 0.12
Mean cell hemoglobin concentration (g/dl)	3	33.4 ± 2.28	(c) 35.7 ± 0.49	(d) 34.6 ± 0.43	34.5 ± 0.32
	7	(e) 36.0 ± 0.43	35.7 ± 0.27	(c) 35.1 ± 0.25	36.5 ± 0.27
	14	34.4 ± 0.24	34.7 ± 0.28	34.5 ± 0.29	35.0 ± 0.24
	45	37.6 ± 0.85	37.9 ± 0.93	36.8 ± 0.25	36.0 ± 0.46
	90	36.2 ± 0.33	36.0 ± 0.37	36.0 ± 0.27	35.8 ± 0.31
Mean cell volume (μ^3)	3	65.4 ± 2.26	(c) 63.3 ± 1.89	(d) 65.0 ± 2.06	60.0 ± 0.33
	7	(e) 62.6 ± 0.87	62.0 ± 1.00	(c) 62.7 ± 0.97	**57.9 ± 0.35
	14	64.5 ± 0.53	*62.1 ± 0.85	62.4 ± 0.92	**59.4 ± 0.31
	45	53.1 ± 0.64	52.5 ± 0.58	53.3 ± 0.30	52.3 ± 0.33
	90	52.0 ± 0.57	50.9 ± 0.23	*50.6 ± 0.34	*50.3 ± 0.37
Platelets (1,000/µl)	3	(e) 979 ± 58.3	(c) 943 ± 53.0	(e) 1,019 ± 57.2	(c) 872 ± 18.7
	7	(e) 861 ± 34.8	831 ± 27.4	(c) 821 ± 27.5	**738 ± 20.8
	14	836 ± 33.6	775 ± 25.6	738 ± 37.1	**706 ± 24.3
	45	(e) 540 ± 25.7	550 ± 17.8	543 ± 7.6	544 ± 6.6
	90	471 ± 24.9	488 ± 24.2	488 ± 17.2	508 ± 19.2
Erythrocytes (10^6/µl)	3	6.3 ± 0.36	(c) 6.4 ± 0.23	(d) 6.3 ± 0.24	**7.4 ± 0.13
	7	(e) 6.6 ± 0.11	6.8 ± 0.14	(c) 7.0 ± 0.16	**7.2 ± 0.09
	14	6.8 ± 0.08	7.1 ± 0.12	7.1 ± 0.11	**7.3 ± 0.07
	45	8.6 ± 0.17	8.7 ± 0.22	8.9 ± 0.07	*8.9 ± 0.14
	90	8.9 ± 0.10	9.1 ± 0.10	9.2 ± 0.08	**9.3 ± 0.07
Alkaline phosphatase (IU/liter)	3	638 ± 20.2	(e) 614 ± 41.7	(d) 614 ± 24.3	609 ± 19.5
	7	690 ± 44.2	*(c) 590 ± 10.7	**(c) 553 ± 21.5	**(c) 562 ± 32.1
	14	631 ± 21.5	561 ± 19.8	594 ± 30.5	(c) 557 ± 19.1
	45	330 ± 12.5	316 ± 11.9	329 ± 7.4	338 ± 17.1
	90	290 ± 5.7	263 ± 8.0	278 ± 9.0	285 ± 9.6
Alanine aminotransferase (IU/liter)	3	(f) 50.0 ± 4.40	(g) 41.6 ± 1.08	*(h) 36.8 ± 2.43	*(f) 40.0 ± 3.29
	7	(e) 38.7 ± 1.74	(e) 37.6 ± 1.29	(d) 36.9 ± 2.86	*(e) 32.0 ± 1.36
	14	(e) 37.6 ± 2.00	(g) 35.8 ± 2.31	(d) 35.5 ± 1.35	(d) 36.8 ± 1.62
	45	(e) 48.3 ± 3.24	47.8 ± 3.40	(c) 43.1 ± 2.40	48.7 ± 3.32
	90	(e) 73.1 ± 6.07	(c) 61.0 ± 3.87	**(e) 54.0 ± 3.73	**(e) 54.3 ± 2.20

TABLE A3. HEMATOLOGIC AND SERUM CHEMICAL DATA FOR MALE F344/N RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (Continued)

Analysis	Day	Control	2,000 ppm	4,000 ppm	8,000 ppm
Blood urea nitrogen (mg/dl)	3	(i) 14.0 ± 0.00	(h) 17.3 ± 2.17	*(f) 26.8 ± 2.00	(g) 19.2 ± 1.85
	7	(e) 19.4 ± 1.46	*(c) 24.7 ± 1.76	*(c) 25.1 ± 1.40	**(e) 30.9 ± 4.23
	14	(e) 16.4 ± 0.90	**(d) 23.4 ± 1.51	**(c) 24.7 ± 1.44	**(f) 21.8 ± 1.97
	45	(d) 25.1 ± 2.16	27.9 ± 1.54	(e) 25.4 ± 2.08	25.7 ± 1.37
	90	(d) 20.8 ± 0.88	20.5 ± 0.67	21.3 ± 0.60	21.3 ± 0.90
Creatine kinase (IU/liter)	3	(c) 986 ± 225	(c) 605 ± 96	695 ± 86	718 ± 129
	7	587 ± 125	(c) 598 ± 42	803 ± 118	(c) 504 ± 39
	14	381 ± 53	400 ± 28	351 ± 34	374 ± 48
	45	562 ± 49	478 ± 49	424 ± 33	441 ± 48
	90	341 ± 33	351 ± 39	315 ± 21	320 ± 12
Sorbitol dehydrogenase (IU/liter)	3	(e) 6.6 ± 0.65	(e) 7.4 ± 1.19	(f) 11.7 ± 4.94	(e) 8.7 ± 0.52
	7	(e) 8.6 ± 0.48	(c) 9.9 ± 0.77	(e) 9.1 ± 0.60	(d) 12.3 ± 2.84
	14	(g) 9.2 ± 0.97	(c) 8.7 ± 0.24	(d) 9.4 ± 0.32	*10.2 ± 0.33
	45	10.3 ± 0.82	(d) 11.9 ± 1.61	(e) 11.3 ± 0.84	*13.5 ± 1.15
	90	(e) 22.0 ± 9.75	12.0 ± 1.14	10.0 ± 0.56	10.4 ± 1.16

(a) Mean ± standard error; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Unless otherwise specified
(c) Nine animals were examined.
(d) Eight animals were examined.
(e) Seven animals were examined.
(f) Six animals were examined.
(g) Five animals were examined.
(h) Four animals were examined.
(i) Three animals were examined.
*P<0.05
**P<0.01

TABLE A4. ABSOLUTE ORGAN WEIGHTS FOR SPRAGUE DAWLEY RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (a)

	Control	500 ppm	1,000 ppm	2,000 ppm	4,000 ppm	8,000 ppm
MALE						
Brain	2,089 ± 37	2,139 ± 41	2,125 ± 23	2,117 ± 22	2,105 ± 25	2,103 ± 19
Heart	1,847 ± 85	1,729 ± 41	*1,623 ± 54	*1,597 ± 54	**1,579 ± 55	**1,566 ± 55
Right kidney	1,871 ± 74	1,943 ± 59	1,954 ± 58	1,856 ± 74	2,000 ± 52	2,008 ± 55
Liver	18,480 ± 790	20,080 ± 590	18,810 ± 570	20,100 ± 790	19,970 ± 490	19,230 ± 560
Lung	2,468 ± 83	2,728 ± 161	2,407 ± 127	2,558 ± 95	2,342 ± 68	2,220 ± 96
Right testis	1,821 ± 48	1,728 ± 53	1,843 ± 54	1,756 ± 53	1,704 ± 35	1,825 ± 34
Thymus	493 ± 32	477 ± 25	448 ± 32	474 ± 39	468 ± 33	485 ± 34
FEMALE						
Brain	1,975 ± 29	1,975 ± 36	2,005 ± 31	1,963 ± 19	1,913 ± 29	1,956 ± 34
Heart	1,069 ± 26	1,072 ± 30	1,084 ± 24	1,061 ± 32	1,041 ± 27	1,085 ± 36
Right kidney	1,030 ± 36	*1,160 ± 27	**1,221 ± 28	**1,211 ± 33	**1,208 ± 50	**1,342 ± 16
Liver	11,140 ± 350	11,890 ± 530	12,200 ± 680	10,990 ± 310	11,500 ± 370	(b) 11,950 ± 450
Lung	1,929 ± 89	1,988 ± 114	1,861 ± 65	1,993 ± 109	1,915 ± 99	1,941 ± 135
Thymus	364 ± 23	395 ± 36	337 ± 17	365 ± 23	359 ± 30	326 ± 23

(a) Mean ± standard error in milligrams for groups of 10 animals unless otherwise specified; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Nine livers were weighed.
*P<0.05
**P<0.01

TABLE A5. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR SPRAGUE DAWLEY RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (a)

	Control	500 ppm	1,000 ppm	2,000 ppm	4,000 ppm	8,000 ppm
MALE						
Body weight (grams)	449 ± 11.0	446 ± 7.9	431 ± 7.0	432 ± 11.3	436 ± 7.9	*414 ± 9.2
Brain	4.7 ± 0.16	4.8 ± 0.10	4.9 ± 0.09	4.9 ± 0.17	4.9 ± 0.12	*5.1 ± 0.10
Heart	4.1 ± 0.20	3.9 ± 0.08	3.8 ± 0.11	3.7 ± 0.09	*3.6 ± 0.13	3.8 ± 0.11
Right kidney	4.2 ± 0.14	4.4 ± 0.11	*4.5 ± 0.08	4.3 ± 0.11	*4.6 ± 0.11	**4.9 ± 0.11
Liver	41.1 ± 1.03	*45.0 ± 1.15	*43.6 ± 0.75	**46.5 ± 1.11	**45.9 ± 0.82	**46.5 ± 1.20
Lung	5.5 ± 0.18	6.1 ± 0.33	5.6 ± 0.29	5.9 ± 0.19	5.4 ± 0.18	5.4 ± 0.20
Right testis	4.1 ± 0.14	3.9 ± 0.11	4.3 ± 0.12	4.1 ± 0.17	3.9 ± 0.10	4.4 ± 0.15
Thymus	1.1 ± 0.07	1.1 ± 0.06	1.1 ± 0.08	1.1 ± 0.07	1.1 ± 0.07	1.2 ± 0.08
FEMALE						
Body weight (grams)	271 ± 5.5	283 ± 7.8	287 ± 6.4	271 ± 4.5	265 ± 6.6	256 ± 4.8
Brain	7.3 ± 0.13	7.0 ± 0.16	7.0 ± 0.16	7.3 ± 0.10	7.2 ± 0.17	7.7 ± 0.19
Heart	4.0 ± 0.08	3.8 ± 0.11	3.8 ± 0.11	3.9 ± 0.12	3.9 ± 0.09	4.2 ± 0.09
Right kidney	3.8 ± 0.11	*4.1 ± 0.09	*4.3 ± 0.13	**4.5 ± 0.11	**4.6 ± 0.16	**5.2 ± 0.10
Liver	41.2 ± 1.07	42.0 ± 1.49	42.7 ± 2.60	40.6 ± 1.32	43.5 ± 1.37	*(b) 46.6 ± 1.41
Lung	7.1 ± 0.29	7.1 ± 0.42	6.5 ± 0.24	7.3 ± 0.34	7.2 ± 0.36	7.6 ± 0.53
Thymus	1.4 ± 0.09	1.4 ± 0.13	1.2 ± 0.07	1.4 ± 0.09	1.4 ± 0.10	1.3 ± 0.08

(a) Mean ± standard error in milligrams per gram for groups of 10 animals unless otherwise specified; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Nine livers were weighed.
*P<0.05
**P<0.01

TABLE A6. HEMATOLOGIC AND SERUM CHEMICAL DATA FOR MALE SPRAGUE DAWLEY RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (a)

Analysis	Day	Control	2,000 ppm	4,000 ppm	8,000 ppm
Leukocytes (1,000/µl)	3	10.6 ± 0.71	10.8 ± 0.74	18.5 ± 4.16	(b) 10.1 ± 0.27
	7	(c) 15.0 ± 1.31	*(d) 12.2 ± 0.68	(c) 12.6 ± 0.92	*(b) 12.9 ± 1.60
	14	11.7 ± 0.86	(b) 11.3 ± 0.80	(b) 10.8 ± 0.46	(e) 12.1 ± 1.00
	45	9.8 ± 0.59	9.7 ± 0.28	10.2 ± 0.61	*8.3 ± 0.35
	90	9.1 ± 0.24	9.2 ± 0.39	9.3 ± 0.68	8.6 ± 0.51
Hematocrit (percent)	3	38.1 ± 0.76	**42.3 ± 0.74	*40.7 ± 0.80	**(b) 44.2 ± 0.70
	7	(c) 41.5 ± 0.39	(d) 43.2 ± 0.93	**(c) 43.6 ± 0.34	*(b) 43.3 ± 0.62
	14	47.0 ± 0.55	(b) 47.7 ± 1.20	(b) 46.4 ± 0.70	(e) 47.0 ± 0.80
	45	47.1 ± 0.68	47.3 ± 0.88	46.9 ± 0.37	47.5 ± 0.42
	90	48.0 ± 0.73	49.2 ± 0.29	48.8 ± 0.51	47.9 ± 0.49
Hemoglobin (g/dl)	3	13.6 ± 0.18	**14.3 ± 0.15	13.8 ± 0.17	**(b) 15.1 ± 0.21
	7	(c) 14.2 ± 0.16	(d) 14.6 ± 0.23	**(c) 14.8 ± 0.09	*(b) 14.6 ± 0.21
	14	15.3 ± 0.11	(b) 15.6 ± 0.16	(b) 15.1 ± 0.10	(e) 15.5 ± 0.24
	45	17.0 ± 0.13	17.0 ± 0.26	16.9 ± 0.14	16.8 ± 0.13
	90	17.0 ± 0.24	17.3 ± 0.12	17.0 ± 0.12	16.8 ± 0.15
Mean corpuscular hemoglobin (pg)	3	24.5 ± 0.57	*22.7 ± 0.32	23.2 ± 0.35	*(b) 22.8 ± 0.26
	7	(c) 23.3 ± 0.28	(d) 23.0 ± 0.28	(c) 23.0 ± 0.33	(b) 22.4 ± 0.42
	14	22.9 ± 0.21	(b) 22.0 ± 0.39	(b) 22.8 ± 0.18	(e) 22.7 ± 0.64
	45	20.8 ± 0.22	20.8 ± 0.23	20.8 ± 0.12	*20.2 ± 0.17
	90	19.4 ± 0.19	18.8 ± 0.23	18.9 ± 0.17	*18.7 ± 0.24
Mean corpuscular hemoglobin concentration (g/dl)	3	35.7 ± 0.63	33.9 ± 0.43	34.0 ± 0.31	(b) 34.0 ± 0.12
	7	(c) 34.1 ± 0.21	(d) 33.8 ± 0.27	(c) 34.0 ± 0.25	(b) 33.7 ± 0.20
	14	32.6 ± 0.40	(b) 32.7 ± 0.76	(b) 32.7 ± 0.39	(e) 33.0 ± 0.66
	45	36.0 ± 0.38	35.9 ± 0.23	36.1 ± 0.28	35.3 ± 0.22
	90	35.5 ± 0.32	35.1 ± 0.26	35.0 ± 0.27	35.1 ± 0.24
Mean cell volume (μ^3)	3	68.5 ± 0.65	67.0 ± 0.70	68.2 ± 0.93	(b) 66.9 ± 0.85
	7	(c) 68.4 ± 1.09	(d) 68.2 ± 0.97	(c) 68.0 ± 1.13	(b) 66.8 ± 1.29
	14	70.6 ± 1.28	(b) 67.4 ± 1.51	(b) 70.0 ± 1.22	(e) 69.3 ± 2.59
	45	57.7 ± 0.88	58.1 ± 0.59	57.8 ± 0.25	57.1 ± 0.57
	90	54.7 ± 0.62	53.6 ± 0.76	54.2 ± 0.47	53.3 ± 0.83
Platelets (1,000/µl)	3	976 ± 47.0	1,060 ± 89.0	1,080 ± 37.6	(b) 1,031 ± 47.9
	7	(b) 1,183 ± 40.1	**949 ± 49.7	**(c) 957 ± 44.3	**(d) 946 ± 65.3
	14	(d) 990 ± 46.6	838 ± 36.4	894 ± 31.7	(b) 904 ± 58.4
	45	755 ± 27.1	775 ± 28.4	(d) 751 ± 17.6	(d) 758 ± 21.3
	90	758 ± 16.7	699 ± 27.4	723 ± 21.8	742 ± 23.7
Erythrocytes (10^6/µl)	3	5.6 ± 0.13	**6.3 ± 0.12	*6.0 ± 0.16	**(b) 6.6 ± 0.15
	7	(c) 6.1 ± 0.11	(d) 6.3 ± 0.10	*(c) 6.4 ± 0.08	*(b) 6.5 ± 0.19
	14	6.7 ± 0.07	(b) 7.1 ± 0.12	(b) 6.6 ± 0.07	(e) 6.8 ± 0.25
	45	8.2 ± 0.12	8.2 ± 0.14	8.1 ± 0.06	8.3 ± 0.07
	90	8.8 ± 0.18	9.2 ± 0.13	9.0 ± 0.11	9.0 ± 0.14
Alkaline phosphatase (IU/liter)	3	477 ± 13.3	*430 ± 14.5	441 ± 19.5	*(d) 390 ± 34.7
	7	420 ± 17.9	428 ± 24.5	(d) 403 ± 35.3	(d) 439 ± 20.7
	14	406 ± 29.9	416 ± 12.1	456 ± 22.8	(d) 423 ± 20.0
	45	245 ± 13.9	228 ± 8.0	241 ± 20.5	258 ± 19.8
	90	291 ± 15.3	*235 ± 17.7	**233 ± 11.7	*253 ± 30.8
Alanine aminotransferase (IU/liter)	3	(c) 47.4 ± 4.09	(b) 49.0 ± 2.46	(c) 41.9 ± 2.01	*(c) 38.6 ± 2.03
	7	42.2 ± 3.21	(b) 42.0 ± 2.52	(d) 37.6 ± 1.84	(d) 37.2 ± 4.24
	14	(d) 39.7 ± 2.22	(d) 41.1 ± 1.59	(d) 40.3 ± 2.12	(d) 37.9 ± 2.45
	45	50.4 ± 3.50	(c) 39.0 ± 1.68	(d) 43.3 ± 1.76	51.0 ± 4.94
	90	50.7 ± 3.11	45.7 ± 2.13	(b) 47.5 ± 3.48	(d) 45.3 ± 3.63

TABLE A6. HEMATOLOGIC AND SERUM CHEMICAL DATA FOR MALE SPRAGUE DAWLEY RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (Continued)

Analysis	Day	Control	2,000 ppm	4,000 ppm	8,000 ppm
Blood urea nitrogen (mg/dl)	3	(d) 21.7 ± 0.75	(b) 25.6 ± 1.85	(d) 21.2 ± 1.74	*(d) 27.2 ± 2.18
	7	18.6 ± 1.74	*(d) 28.4 ± 3.56	*(d) 26.3 ± 2.82	*(b) 26.4 ± 3.61
	14	(b) 23.4 ± 1.07	(d) 26.3 ± 1.22	(c) 25.4 ± 3.14	(b) 28.6 ± 2.82
	45	16.6 ± 1.33	**(d) 22.3 ± 0.53	*(d) 19.3 ± 1.63	*22.1 ± 1.69
	90	22.4 ± 1.21	20.6 ± 1.06	22.4 ± 1.51	23.9 ± 1.77
Creatine kinase (IU/liter)	3	808 ± 69	1,035 ± 119	1,008 ± 82	(d) 1,186 ± 163
	7	891 ± 115	1,079 ± 101	989 ± 112	(d) 898 ± 69
	14	(d) 742 ± 80	(d) 889 ± 72	1,057 ± 127	(d) 822 ± 49
	45	829 ± 45	1,220 ± 234	1,026 ± 100	863 ± 98
	90	818 ± 73	1,098 ± 98	959 ± 98	739 ± 46
Sorbitol dehydrogenase (IU/liter)	3	9.9 ± 1.37	(d) 10.1 ± 1.09	8.7 ± 0.40	(f) 11.0 ± 1.35
	7	(b) 7.1 ± 0.44	(d) 7.6 ± 0.24	(c) 8.6 ± 0.84	(d) 8.3 ± 0.47
	14	(d) 9.8 ± 0.49	10.9 ± 1.04	10.5 ± 0.34	*(b) 11.8 ± 0.75
	45	11.5 ± 1.52	9.2 ± 0.36	10.6 ± 0.45	13.3 ± 2.16
	90	5.8 ± 1.04	7.0 ± 0.78	7.4 ± 1.27	7.9 ± 1.05

(a) Mean ± standard error for groups of 10 animals unless otherwise specified; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Eight animals were examined.
(c) Seven animals were examined.
(d) Nine animals were examined.
(e) Six animals were examined.
(f) Four animals were examined.
*P<0.05
**P<0.01

TABLE A7. ABSOLUTE ORGAN WEIGHTS FOR OSBORNE-MENDEL RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (a)

	Control	500 ppm	1,000 ppm	2,000 ppm	4,000 ppm	8,000 ppm
MALE						
Number weighed (b)	9	10	10	10	10	10
Brain	2,056 ± 33	2,106 ± 25	2,089 ± 36	1,995 ± 37	1,991 ± 57	1,982 ± 50
Heart	1,498 ± 74	1,526 ± 48	1,605 ± 70	1,386 ± 62	1,289 ± 53	1,295 ± 59
Right kidney	1,506 ± 36	1,600 ± 41	**1,751 ± 40	1,656 ± 59	1,613 ± 44	1,507 ± 68
Liver	16,230 ± 810	17,830 ± 610	**21,080 ± 840	19,310 ± 800	15,190 ± 510	15,900 ± 800
Lung	1,821 ± 80	(c) 1,946 ± 118	2,075 ± 61	2,074 ± 123	1,960 ± 83	1,717 ± 53
Right testis	1,725 ± 59	1,655 ± 64	1,747 ± 40	1,725 ± 82	1,635 ± 53	1,631 ± 38
Thymus	314 ± 19	305 ± 28	323 ± 19	314 ± 22	326 ± 22	333 ± 27
FEMALE						
Number weighed	10	10	10	10	10	10
Brain	1,936 ± 37	1,996 ± 26	1,956 ± 22	1,907 ± 23	1,965 ± 30	1,933 ± 33
Heart	1,012 ± 40	1,051 ± 28	1,022 ± 62	939 ± 22	980 ± 34	909 ± 22
Right kidney	894 ± 28	**1,017 ± 15	**1,041 ± 22	**1,020 ± 24	**1,096 ± 37	**1,094 ± 33
Liver	10,390 ± 450	11,580 ± 360	10,810 ± 230	10,390 ± 430	10,750 ± 300	10,100 ± 410
Lung	1,532 ± 68	1,612 ± 69	1,629 ± 81	1,497 ± 79	1,565 ± 57	1,571 ± 51
Thymus	304 ± 14	319 ± 25	278 ± 40	309 ± 34	341 ± 25	258 ± 16

(a) Mean ± standard error in milligrams unless otherwise specified; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Unless otherwise specified
(c) Lungs of nine animals were weighed.
**$P<0.01$

TABLE A8. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR OSBORNE-MENDEL RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (a)

	Control	500 ppm	1,000 ppm	2,000 ppm	4,000 ppm	8,000 ppm
MALE						
Number weighed (b)	9	10	10	10	10	10
Body weight (grams)	421 ± 25.3	477 ± 13.1	465 ± 17.2	433 ± 14.0	393 ± 11.8	*380 ± 11.3
Brain	5.0 ± 0.37	4.4 ± 0.10	4.5 ± 0.17	4.6 ± 0.10	5.1 ± 0.09	5.2 ± 0.14
Heart	3.7 ± 0.31	3.2 ± 0.14	3.5 ± 0.11	3.2 ± 0.08	3.3 ± 0.09	3.4 ± 0.09
Right kidney	3.7 ± 0.28	3.4 ± 0.09	3.8 ± 0.14	3.8 ± 0.09	**4.1 ± 0.13	*4.0 ± 0.18
Liver	39.2 ± 2.01	37.4 ± 0.85	*45.4 ± 0.90	*44.6 ± 1.24	38.8 ± 1.45	41.9 ± 1.59
Lung	4.5 ± 0.47	(c) 4.1 ± 0.28	4.5 ± 0.23	4.8 ± 0.30	5.0 ± 0.19	4.5 ± 0.17
Right testis	4.2 ± 0.25	3.5 ± 0.15	3.8 ± 0.19	4.0 ± 0.21	4.2 ± 0.15	4.3 ± 0.11
Thymus	0.8 ± 0.05	0.6 ± 0.06	0.7 ± 0.05	0.7 ± 0.04	0.8 ± 0.06	0.9 ± 0.06
FEMALE						
Number weighed	10	10	10	10	10	10
Body weight (grams)	274 ± 9.9	279 ± 5.6	271 ± 4.7	256 ± 6.5	270 ± 6.6	266 ± 11.2
Brain	7.1 ± 0.23	7.2 ± 0.21	7.2 ± 0.11	7.5 ± 0.21	7.3 ± 0.14	7.3 ± 0.25
Heart	3.7 ± 0.11	3.8 ± 0.11	3.8 ± 0.19	3.7 ± 0.16	3.6 ± 0.13	3.5 ± 0.12
Right kidney	3.3 ± 0.11	*3.7 ± 0.06	**3.9 ± 0.06	**4.0 ± 0.16	**4.1 ± 0.14	**4.2 ± 0.26
Liver	37.9 ± 1.04	41.5 ± 0.96	40.0 ± 0.81	41.0 ± 2.39	39.8 ± 0.73	38.6 ± 2.49
Lung	5.6 ± 0.20	5.8 ± 0.22	6.0 ± 0.32	5.9 ± 0.32	5.8 ± 0.19	6.0 ± 0.27
Thymus	1.1 ± 0.05	1.1 ± 0.08	1.0 ± 0.14	1.2 ± 0.12	1.3 ± 0.07	1.0 ± 0.06

(a) Mean ± standard error in milligrams per gram unless otherwise specified; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Unless otherwise specified
(c) Lungs of nine animals were weighed.
*$P<0.05$
**$P<0.01$

TABLE A9. HEMATOLOGIC AND SERUM CHEMICAL DATA FOR MALE OSBORNE-MENDEL RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (a)

Analysis	Day	Control	2,000 ppm	4,000 ppm	8,000 ppm
Leukocytes (1,000/μl)	3	9.7 ± 1.06	(b) 12.7 ± 3.33	11.2 ± 1.18	10.0 ± 0.94
	7	(b) 11.6 ± 1.16	(b) 9.5 ± 0.87	(b) 11.3 ± 1.01	10.1 ± 1.23
	14	9.7 ± 0.90	8.7 ± 0.42	9.4 ± 0.91	9.9 ± 1.01
	45	9.1 ± 0.93	8.3 ± 0.53	8.2 ± 0.75	8.9 ± 0.88
	90	8.7 ± 0.62	7.2 ± 0.52	(b) 7.6 ± 0.67	8.0 ± 0.50
Hematocrit (percent)	3	38.9 ± 0.65	*(b) 41.1 ± 1.03	*41.2 ± 0.79	**45.4 ± 0.68
	7	(b) 41.3 ± 0.45	(b) 43.1 ± 0.99	(b) 43.1 ± 0.74	42.5 ± 0.58
	14	42.7 ± 0.92	44.5 ± 0.88	43.3 ± 1.22	42.5 ± 0.58
	45	46.8 ± 0.76	47.4 ± 0.70	47.4 ± 0.73	47.2 ± 0.62
	90	48.0 ± 0.52	46.8 ± 0.54	(b) 47.1 ± 0.57	47.7 ± 0.64
Hemoglobin (g/dl)	3	13.5 ± 0.16	*(b) 13.9 ± 0.46	**14.4 ± 0.23	**15.2 ± 0.24
	7	(b) 13.5 ± 0.12	*(b) 14.1 ± 0.08	**(b) 14.2 ± 0.18	13.9 ± 0.13
	14	14.9 ± 0.16	15.0 ± 0.15	15.3 ± 0.14	14.9 ± 0.09
	45	16.6 ± 0.16	16.6 ± 0.14	16.7 ± 0.09	16.6 ± 0.16
	90	16.7 ± 0.14	16.4 ± 0.13	(b) 16.6 ± 0.20	16.7 ± 0.16
Mean corpuscular hemoglobin (pg)	3	23.2 ± 0.27	(b) 22.4 ± 0.20	22.7 ± 0.29	**21.9 ± 0.30
	7	(b) 22.5 ± 0.44	(b) 21.5 ± 0.27	(b) 22.0 ± 0.26	*21.3 ± 0.38
	14	23.6 ± 0.30	**21.5 ± 0.52	*23.2 ± 0.47	**22.2 ± 0.21
	45	20.8 ± 0.23	**19.8 ± 0.19	*19.9 ± 0.30	**19.5 ± 0.26
	90	19.0 ± 0.19	18.7 ± 0.31	(b) 19.0 ± 0.19	18.5 ± 0.19
Mean corpuscular hemoglobin concentration (g/dl)	3	34.7 ± 0.35	(b) 33.8 ± 0.41	35.0 ± 0.24	33.6 ± 0.45
	7	(b) 32.8 ± 0.47	(b) 32.9 ± 0.73	(b) 33.0 ± 0.50	32.7 ± 0.47
	14	34.9 ± 0.51	33.9 ± 0.68	35.4 ± 0.79	35.1 ± 0.37
	45	35.4 ± 0.28	35.0 ± 0.43	35.3 ± 0.53	35.1 ± 0.28
	90	34.8 ± 0.17	35.1 ± 0.31	(b) 35.1 ± 0.27	34.9 ± 0.26
Mean cell volume (μ^3)	3	66.9 ± 0.77	(b) 66.3 ± 1.03	64.9 ± 0.74	65.4 ± 0.40
	7	(b) 68.9 ± 1.01	*(b) 65.7 ± 1.17	(b) 66.4 ± 0.73	*65.1 ± 0.69
	14	67.9 ± 0.60	**63.4 ± 1.01	**65.6 ± 0.43	**63.3 ± 0.72
	45	58.5 ± 0.52	*56.4 ± 0.52	*56.6 ± 0.62	**55.7 ± 0.52
	90	54.6 ± 0.64	53.5 ± 0.95	(b) 54.1 ± 0.54	53.2 ± 0.55
Platelets (1,000/μl)	3	969 ± 15.5	(b) 997 ± 55.0	939 ± 29.2	*1,106 ± 30.3
	7	(b) 1,166 ± 52.7	(b) 1,089 ± 74.7	(b) 1,049 ± 65.9	1,021 ± 48.3
	14	898 ± 26.9	867 ± 33.6	863 ± 30.0	874 ± 45.8
	45	760 ± 26.2	734 ± 31.4	681 ± 26.0	726 ± 38.0
	90	702 ± 35.9	692 ± 28.2	(b) 787 ± 35.5	685 ± 38.7
Erythrocytes (10^6/μl)	3	5.8 ± 0.11	**(b) 6.2 ± 0.22	**6.4 ± 0.12	**6.9 ± 0.09
	7	(b) 6.0 ± 0.11	**(b) 6.6 ± 0.11	*(b) 6.5 ± 0.12	**6.5 ± 0.12
	14	6.3 ± 0.12	**7.0 ± 0.15	6.6 ± 0.18	6.7 ± 0.08
	45	8.0 ± 0.12	8.4 ± 0.13	*8.4 ± 0.12	**8.5 ± 0.10
	90	8.8 ± 0.10	8.8 ± 0.12	(b) 8.7 ± 0.13	9.0 ± 0.12
Alkaline phosphatase (IU/liter)	3	387 ± 34.0	(c) 350 ± 37.6	339 ± 29.0	314 ± 21.2
	7	365 ± 26.3	370 ± 34.5	337 ± 24.9	(b) 351 ± 31.9
	14	329 ± 22.9	309 ± 24.9	292 ± 26.9	312 ± 21.1
	45	229 ± 17.0	217 ± 25.9	175 ± 14.3	217 ± 21.0
	90	180 ± 15.0	183 ± 13.5	169 ± 18.2	161 ± 5.5
Alanine aminotransferase (IU/liter)	3	(b) 52.6 ± 3.06	(d) 45.1 ± 3.78	*(b) 39.6 ± 3.46	**35.9 ± 1.68
	7	49.9 ± 1.77	45.0 ± 3.69	**41.0 ± 1.83	**37.5 ± 0.95
	14	(b) 42.8 ± 2.76	(c) 39.5 ± 3.24	*(b) 34.9 ± 2.10	*33.6 ± 1.97
	45	(d) 52.6 ± 4.28	(e) 40.7 ± 2.58	*(e) 38.0 ± 3.30	(c) 45.5 ± 3.81
	90	48.0 ± 3.81	(b) 50.7 ± 6.51	**(b) 34.9 ± 2.25	*(c) 38.5 ± 2.25

TABLE A9. HEMATOLOGIC AND SERUM CHEMICAL DATA FOR MALE OSBORNE-MENDEL RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (Continued)

Analysis	Day	Control	2,000 ppm	4,000 ppm	8,000 ppm
Blood urea nitrogen (mg/dl)	3	(c) 16.0 ± 0.93	(f) 23 3 ± 3.92	*(c) 21.9 ± 1 08	*(c) 22.6 ± 2.03
	7	18.4 ± 1.59	20.4 ± 2.09	(b) 18.9 ± 1.43	(b) 21.1 ± 2 26
	14	(b) 21.7 ± 1.89	21.0 ± 2.02	(b) 20.2 ± 1.64	(c) 21.4 ± 2 61
	45	(c) 25.6 ± 2 45	(b) 28.2 ± 1.93	27.3 ± 1.51	(b) 31.1 ± 3.61
	90	20.3 ± 0.80	18 3 ± 0.96	21.2 ± 1.09	21 3 ± 1.63
Creatine kinase (IU/liter)	3	698 ± 97	(b) 648 ± 80	703 ± 150	821 ± 130
	7	1,019 ± 163	1,039 ± 190	847 ± 111	851 ± 121
	14	691 ± 115	743 ± 61	694 ± 129	679 ± 100
	45	497 ± 95	557 ± 69	334 ± 34	493 ± 81
	90	484 ± 83	419 ± 48	443 ± 65	395 ± 50
Sorbitol dehydrogenase (IU/liter)	3	(b) 8.3 ± 0.58	(c) 8 9 ± 0.77	9.8 ± 0.87	(b) 11 0 ± 1 25
	7	8.9 ± 0.31	8 9 ± 0.50	8.3 ± 0.78	8.3 ± 0.79
	14	12.4 ± 1.03	11 8 ± 0.80	10.5 ± 0.54	11 4 ± 0 67
	45	(c) 7.6 ± 0.46	(c) 8.5 ± 1.38	6.6 ± 0.22	(b) 10.0 ± 1 65
	90	9.5 ± 1.12	10.9 ± 1.66	(b) 8.0 ± 0.37	(b) 10.3 ± 0 87

(a) Mean ± standard error for groups of 10 animals unless otherwise specified; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Nine animals were examined.
(c) Eight animals were examined.
(d) Seven animals were examined
(e) Six animals were examined
(f) Four animals were examined.
*$P<0.05$
**$P<0.01$

TABLE A10. ABSOLUTE ORGAN WEIGHTS FOR F344/N RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 1,2-DICHLOROETHANE (a)

Organ	Group				
MALE	**Vehicle Control**	**30 mg/kg**	**60 mg/kg**	**120 mg/kg**	
Brain	1,997 ± 27	1,972 ± 27	1,995 ± 18	1,958 ± 23	
Heart	1,079 ± 32	1,095 ± 29	1,115 ± 48	1,126 ± 37	
Right kidney	1,324 ± 29	*1,441 ± 26	**1,600 ± 54	**1,653 ± 47	
Liver	17,000 ± 440	(b) 17,960 ± 510	18,270 ± 540	*(b) 19,400 ± 660	
Lung	1,701 ± 52	1,726 ± 34	1,760 ± 75	1,703 ± 35	
Right testis	1,467 ± 26	1,431 ± 43	1,443 ± 18	1,388 ± 33	
Thymus	305 ± 10	310 ± 22	345 ± 19	296 ± 14	
FEMALE	**Vehicle Control**	**18 mg/kg**	**37 mg/kg**	**75 mg/kg**	**150 mg/kg**
Brain	1,815 ± 16	1,830 ± 14	1,824 ± 16	1,826 ± 26	1,816 ± 17
Heart	660 ± 10	679 ± 15	663 ± 12	*727 ± 24	**737 ± 10
Right kidney	800 ± 16	717 ± 70	798 ± 20	**898 ± 23	**984 ± 9
Liver	7,345 ± 120	*8,000 ± 201	*7,920 ± 191	**8,577 ± 197	**9,775 ± 151
Lung	1,178 ± 36	1,249 ± 65	1,210 ± 32	1,263 ± 57	1,233 ± 40
Thymus	261 ± 16	238 ± 11	248 ± 11	228 ± 17	227 ± 15

(a) Mean ± standard error in milligrams for groups of 10 animals unless otherwise specified; P values vs. the vehicle controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Nine livers were weighed.
*P<0.05
**P<0.01

TABLE A11. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR F344/N RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 1,2-DICHLOROETHANE (a)

Organ	Group				
MALE	**Vehicle Control**	**30 mg/kg**	**60 mg/kg**	**120 mg/kg**	
Body weight (grams)	339 ± 4.8	353 ± 6.7	354 ± 9.0	341 ± 8.1	
Brain	5.9 ± 0.10	5.6 ± 0.12	5.7 ± 0.14	5.8 ± 0.14	
Heart	3.2 ± 0.09	3.1 ± 0.05	3.2 ± 0.08	3.3 ± 0.12	
Right kidney	3.9 ± 0.06	4.1 ± 0.10	**4.5 ± 0.08	**4.9 ± 0.07	
Liver	50.2 ± 0.87	(b) 50.9 ± 0.97	51.7 ± 0.92	**(b) 57.4 ± 0.83	
Lung	5.0 ± 0.15	4.9 ± 0.10	5.0 ± 0.18	5.0 ± 0.17	
Right testis	4.3 ± 0.08	4.1 ± 0.16	4.1 ± 0.08	4.1 ± 0.12	
Thymus	0.9 ± 0.03	0.9 ± 0.06	1.0 ± 0.06	0.9 ± 0.04	
FEMALE	**Vehicle Control**	**18 mg/kg**	**37 mg/kg**	**75 mg/kg**	**150 mg/kg**
Body weight (grams)	190 ± 1.9	190 ± 2.5	194 ± 3.3	197 ± 2.7	192 ± 1.9
Brain	9.6 ± 0.10	9.6 ± 0.10	9.4 ± 0.12	9.3 ± 0.10	9.5 ± 0.10
Heart	3.5 ± 0.04	3.6 ± 0.08	3.4 ± 0.05	3.7 ± 0.12	**3.8 ± 0.06
Right kidney	4.2 ± 0.08	3.8 ± 0.37	4.1 ± 0.09	*4.6 ± 0.08	**5.1 ± 0.08
Liver	38.7 ± 0.54	**42.1 ± 0.87	*40.8 ± 0.61	**43.6 ± 0.69	**51.0 ± 1.08
Lung	6.2 ± 0.19	6.6 ± 0.32	6.2 ± 0.15	6.4 ± 0.25	6.4 ± 0.22
Thymus	1.4 ± 0.09	1.3 ± 0.05	1.3 ± 0.05	1.2 ± 0.08	1.2 ± 0.08

(a) Mean ± standard error in milligrams per gram for groups of 10 animals unless otherwise specified; P values vs. the vehicle controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Nine livers were weighed.
*P<0.05
**P<0.01

TABLE A12. HEMATOLOGIC AND SERUM CHEMICAL DATA FOR MALE F344/N RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 1,2-DICHLOROETHANE (a)

Analysis	Day	Vehicle Control	120 mg/kg	240 mg/kg
Number examined (b)		10	10	6
Leukocytes (1,000/μl)	3	18.4 ± 7.55	9.2 ± 0.70	29.1 ± 8.98
	7	13.7 ± 2.64	17.9 ± 3.85	16.5 ± 3.53
	14	7.4 ± 0.33	7.8 ± 0.28	6.7 ± 0.45
	45	8.2 ± 0.32	8.6 ± 0.17	(c) 8.2 ± 0.45
	90	(d) 6.8 ± 0.28	7.3 ± 0.35	--
Hematocrit (percent)	3	40.7 ± 0.85	40.4 ± 0.39	39.1 ± 0.84
	7	41.0 ± 0.47	39.6 ± 0.54	41.9 ± 0.40
	14	42.9 ± 0.22	42.9 ± 0.35	42.7 ± 0.50
	45	45.6 ± 0.39	45.0 ± 0.33	(c) 44.5 ± 0.22
	90	(d) 43.1 ± 0.41	42.3 ± 0.44	--
Hemoglobin (g/dl)	3	14.5 ± 0.37	14.1 ± 0.12	13.5 ± 0.37
	7	14.1 ± 0.13	13.7 ± 0.13	14.2 ± 0.13
	14	15.1 ± 0.07	15.0 ± 0.08	*14.7 ± 0.16
	45	16.4 ± 0.09	*16.1 ± 0.06	**(c) 15.6 ± 0.07
	90	(d) 16.1 ± 0.10	15.8 ± 0.11	--
Mean corpuscular hemoglobin (pg)	3	23.5 ± 0.61	22.2 ± 0.18	23.5 ± 0.41
	7	22.7 ± 0.40	22.6 ± 0.56	23.5 ± 0.55
	14	22.6 ± 0.29	22.3 ± 0.37	22.8 ± 0.53
	45	19.5 ± 0.11	19.2 ± 0.23	(c) 19.6 ± 0.44
	90	(d) 18.2 ± 0.09	18.2 ± 0.15	--
Mean corpuscular hemoglobin concentration (g/dl)	3	35.5 ± 0.51	35.0 ± 0.34	34.3 ± 0.30
	7	34.5 ± 0.25	34.7 ± 0.30	33.8 ± 0.16
	14	35.1 ± 0.11	34.9 ± 0.21	*34.4 ± 0.27
	45	36.0 ± 0.17	35.9 ± 0.27	(c) 35.2 ± 0.17
	90	(d) 37.2 ± 0.25	37.2 ± 0.29	--
Mean cell volume (μ^3)	3	66.2 ± 1.60	63.8 ± 0.53	68.7 ± 1.65
	7	66.0 ± 1.56	65.4 ± 1.56	69.5 ± 1.82
	14	64.6 ± 0.81	63.6 ± 1.01	66.3 ± 1.99
	45	54.2 ± 0.33	53.7 ± 0.47	(c) 56.0 ± 1.00
	90	(d) 49.0 ± 0.24	48.8 ± 0.25	--
Erythrocytes (10^6/μl)	3	6.2 ± 0.18	6.3 ± 0.08	5.7 ± 0.24
	7	6.2 ± 0.13	6.1 ± 0.20	6.1 ± 0.13
	14	6.7 ± 0.11	6.7 ± 0.14	6.5 ± 0.20
	45	8.4 ± 0.09	8.4 ± 0.09	(c) 8.0 ± 0.19
	90	(d) 8.8 ± 0.07	8.7 ± 0.09	--
Alkaline phosphatase (IU/liter)	3	(e) 740 ± 16.3	(f) 835 ± 47.9	(g) 688 ± 35.9
	7	(d) 618 ± 17.8	(d) 604 ± 20.8	575 ± 31.3
	14	(e) 594 ± 6.1	(d) 660 ± 35.7	557 ± 25.0
	45	394 ± 5.0	418 ± 9.5	(c) 393 ± 8.8
	90	(f) 1,101 ± 34.0	1,166 ± 46.5	--
Alanine aminotransferase (IU/l)	3	(e) 51.0 ± 3.48	(h) 56.2 ± 2.48	(i) 52.0 ± 4.31
	7	44.3 ± 2.13	*(d) 50.6 ± 1.45	*(i) 58.0 ± 6.32
	14	(e) 40.0 ± 1.15	**51.7 ± 4.88	**(g) 49.8 ± 1.65
	45	44.2 ± 1.28	**52.9 ± 1.47	*(c) 51.3 ± 3.67
	90	(d) 53.6 ± 1.99	54.8 ± 2.47	--
Blood urea nitrogen (mg/dl)	3	(e) 14.4 ± 0.48	(e) 15.3 ± 0.42	*(c) 19.7 ± 2.03
	7	(d) 13.3 ± 0.47	12.8 ± 0.53	12.3 ± 0.71
	14	(f) 15.8 ± 0.92	(d) 15.3 ± 0.91	*13.2 ± 0.48
	45	16.9 ± 1.09	*13.6 ± 0.22	*(c) 12.3 ± 1.20
	90	13.8 ± 0.63	**16.6 ± 0.54	--

TABLE A12. HEMATOLOGIC AND SERUM CHEMICAL DATA FOR MALE F344/N RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 1,2-DICHLOROETHANE (Continued)

Analysis	Day	Vehicle Control	120 mg/kg	240 mg/kg
Creatine kinase (IU/liter)	3	(f) 775 ± 111	931 ± 79	(i) 653 ± 82
	7	572 ± 37	(d) 629 ± 52	558 ± 74
	14	(d) 373 ± 33	389 ± 25	399 ± 40
	45	446 ± 24	481 ± 30	(c) 334 ± 62
	90	(d) 545 ± 29	543 ± 40	--
Sorbitol dehydrogenase (IU/liter)	3	(e) 11 0 ± 0.72	*(f) 12.6 ± 0 56	(c) 12 3 ± 0 33
	7	13 8 ± 0.77	15.3 ± 1.69	14 7 ± 1.52
	14	(d) 24.2 ± 3 36	23.0 ± 2.98	(g) 22 3 ± 4 33
	45	8 9 ± 0.41	**11.9 ± 0.57	*(c) 10.7 ± 1 67
	90	(d) 9 4 ± 0.56	10.5 ± 0.43	--

(a) Mean ± standard error; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Unless otherwise specified
(c) Three animals were examined.
(d) Nine animals were examined
(e) Seven animals were examined
(f) Eight animals were examined.
(g) Four animals were examined
(h) Six animals were examined.
(i) Five animals were examined
*P<0.05
**P<0.01

TABLE A13. ABSOLUTE ORGAN WEIGHTS FOR B6C3F$_1$ MICE IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (a)

	Control	500 ppm	1,000 ppm	2,000 ppm	4,000 ppm	8,000 ppm
MALE						
Number weighed (b)	10	9	10	10	9	10
Brain	459 ± 4	442 ± 6	456 ± 4	461 ± 4	455 ± 5	443 ± 5
Heart	160 ± 7	163 ± 7	171 ± 7	165 ± 5	176 ± 4	173 ± 7
Right kidney	305 ± 7	301 ± 8	*323 ± 7	**358 ± 8	**385 ± 9	**379 ± 12
Liver	1,455 ± 55	1,490 ± 42	1,519 ± 55	1,571 ± 56	*1,628 ± 54	*1,598 ± 78
Lung	230 ± 10	236 ± 15	244 ± 15	224 ± 11	208 ± 8	219 ± 9
Right testis	115 ± 2	112 ± 5	113 ± 2	116 ± 2	115 ± 3	*108 ± 2
Thymus	33 ± 1	(c) 33 ± 2	33 ± 2	34 ± 1	(d) 36 ± 2	27 ± 2
FEMALE						
Number weighed (b)	10	8	10	9	10	(e) 1
Brain	460 ± 6	475 ± 4	465 ± 8	442 ± 10	456 ± 6	437
Heart	125 ± 3	125 ± 4	130 ± 3	126 ± 5	133 ± 5	121
Right kidney	191 ± 4	**225 ± 6	**211 ± 5	**212 ± 7	**215 ± 7	217
Liver	1,258 ± 39	1,258 ± 52	1,263 ± 34	1,314 ± 56	*1,383 ± 29	1,391
Lung	192 ± 8	219 ± 10	214 ± 13	212 ± 10	228 ± 23	190
Thymus	48 ± 3	(d) 44 ± 1	45 ± 3	43 ± 2	*41 ± 1	40

(a) Mean ± standard error in milligrams; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Unless otherwise specified
(c) Eight thymuses were weighed.
(d) Seven thymuses were weighed.
(e) Not included in statistical analysis
*P<0.05
**P<0.01

TABLE A14. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR B6C3F$_1$ MICE IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE (a)

	Control	500 ppm	1,000 ppm	2,000 ppm	4,000 ppm	8,000 ppm
MALE						
Number weighed (b)	10	9	10	10	9	10
Body weight (grams)	30.0 ± 0.73	28.0 ± 0.81	28.4 ± 0.47	29.0 ± 0.79	28.3 ± 0.68	**25 4 ± 0 65
Brain	15.4 ± 0.30	15.9 ± 0.39	16.1 ± 0 33	16.0 ± 0.41	16.1 ± 0.35	**17 5 ± 0.31
Heart	5.3 ± 0.25	5.9 ± 0.15	6.0 ± 0.24	5.7 ± 0.19	**6.2 ± 0.14	**6 9 ± 0 32
Right kidney	10.2 ± 0.22	10.8 ± 0.12	**11 4 ± 0 12	**12.4 ± 0.33	**13.8 ± 0.40	**15 0 ± 0 54
Liver	48.5 ± 1.06	**53.6 ± 0.91	**53 4 ± 1.18	**54.3 ± 1.46	**57.6 ± 1.10	**62 8 ± 2 13
Lung	7.7 ± 0.33	8.5 ± 0.71	8 6 ± 0 44	7.7 ± 0.31	7 4 ± 0.38	8 7 ± 0 39
Right testis	3.9 ± 0.09	4.1 ± 0.08	4 0 ± 0 10	4.0 ± 0.09	4.1 ± 0.16	**4 3 ± 0.12
Thymus	1.1 ± 0.03	(c) 1 2 ± 0.06	1 2 ± 0 06	1.2 ± 0.03	(d) 1.3 ± 0.06	1 0 ± 0 07
FEMALE						
Number weighed	10	8	10	9	10	(e) 1
Body weight (grams)	24.0 ± 0.59	23 7 ± 0.52	22.5 ± 0 54	22.8 ± 0.57	23.2 ± 0.57	23.0
Brain	19.3 ± 0.41	20 1 ± 0.35	20.7 ± 0 43	19.7 ± 0.24	19.8 ± 0.65	19 0
Heart	5.2 ± 0.13	5.2 ± 0.16	5.8 ± 0 18	5.6 ± 0.25	5.7 ± 0.23	5.3
Right kidney	8.0 ± 0.23	**9.4 ± 0.21	**9.4 ± 0 17	**9.3 ± 0.24	**9.3 ± 0.22	9 4
Liver	52.5 ± 0.85	51.5 ± 0.95	*56.0 ± 0 67	*56.1 ± 1.18	**59.7 ± 1.01	60.5
Lung	8.0 ± 0.34	8.7 ± 0.21	9.5 ± 0.57	9.1 ± 0.38	9.8 ± 0.94	8.3
Thymus	2.0 ± 0.12	1.9 ± 0.08	2 0 ± 0 13	1.9 ± 0.10	1.8 ± 0.08	1.7

(a) Mean ± standard error in milligrams per gram unless otherwise specified; P values vs. the controls by Dunn's test (Dunn, 1964) or Shirley's test (Shirley, 1977).
(b) Unless otherwise specified
(c) Eight thymuses were weighed.
(d) Seven thymuses were weighed.
(e) Not included in statistical analysis
*P<0.05
**P<0.01