TO: Distribution

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XF: 1603

FROM: T. G. Grumbles
DATE: August 28, 1991

VISTA

Int roffice Communication

SUBJ: EPA REQUEST FOR INFORMATION ON EDC

Attached is a memo from EPA informing us that they are concerned about EDC emissions and exposures and requesting "any additional hazard or exposure data .... that would be useful to the agency in more fully assessing the risks of EDC." This letter is from the Office of Toxic Substances (OTS) and is a result of a new effort by the Agency to review TRI data, identify high volume chemicals, screen for multi-media exposure potential, and then more complete risk assessments by obtaining data from industry and/or requiring testing be done with their TSCA authority.

I'm providing this for your review and am not proposing any action at this time. I am currently working to determine who else received the letter, determine if trade association (VI or CMA) action will occur, and to get more information on this new OTS initiative.

After the above is completed, I'll contact you regarding our next steps in response to the letter. Please call me with any comments or questions.

Tom

T. G. Grumbles

dlj
.313

Attachment

Distribution: David Booth, P. Carrico-LCVCM, M. G. Hayes-LCCC, D. Penney-Austin

(EPA Cover Letter Only)
T. H. Huffman, R. D. Gamblin, J. Friend

SAL 000066779

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Mr. Thomas Grumbles
Manager of Environmental Affairs
Vista Chemical Company, Inc.
900 Threadneedle
Houston, TX 77079

Dear Mr. Grumbles:

The EPA Office of Toxic Substances (OTS) recently conducted a preliminary review of readily available data on the chemical 1,2-dichloroethane. The purpose of this letter is to inform you of the results of OTS' review. Background materials OTS has prepared on 1,2-dichloroethane are enclosed.

The Agency is concerned that there is a potential risk of cancer to persons exposed to 1,2-dichloroethane. 1,2-Dichloroethane has been classified by EPA as a "probable human carcinogen." During the OTS preliminary review, possible routes of human exposure were evaluated, including workplace exposures, end-use exposures, and exposures resulting from releases to the environment during manufacture, processing, use, and disposal. This multi-media review indicated several possible exposure scenarios which could contribute to a risk.

This review also indicates that more careful consideration of 1,2-dichlorethane by EPA is necessary. OTS will therefore continue to assess exposures to 1,2-dichlorethane and consider whether and what risk reduction actions may be appropriate. Therefore, the Agency is taking this chemical substance to the next level of risk management review, where we will address hazard and exposure issues as well as pollution prevention.

While OTS is pursuing this more intensive assessment of 1,2-dichlorethane, I want to encourage your company to undertake voluntary pollution prevention measures within those parts of your operation where the manufacture, processing, use, or disposal of 1,2-dichlorethane is performed. Pollution prevention is the use of processes, practices, or products that reduce or eliminate the

generation of pollutants and wastes.[1] Because OTS has not evaluated specific details of site operations within your company, EPA is not recommending specific pollution prevention measures at this time. As a general matter, facilities are in the best position to identify pollution prevention opportunities that should be explored.

As your company may well be aware, this is not the first nor the only pollution prevention activity being undertaken by the Agency at this time. EPA, through the Office of Toxic Substances, is also actively promoting a voluntary effort targeted at reducing the emissions of 17 TRI chemicals through pollution prevention opportunities. Your CEO has probably already been contacted by the Agency with information about this program - the 33/50 initiative.

I have also enclosed a copy of the recently enacted Pollution Prevention Act of 1990, which outlines the pollution prevention goals the Agency will be pursuing in the near future. I would especially like to draw your attention to section 7 of the Act, which details the data necessary to evaluate pollution prevention activities and plan for their implementation. The first reports under the Pollution Prevention Act are not required until 1992 for calendar year 1991. However, I believe that immediate voluntary implementation of all feasible pollution prevention actions would be prudent.

I would like to offer you the opportunity to submit additional hazard or exposure data on 1,2-dichlorethane that you believe would be useful to the Agency in more fully assessing the risks of 1,2-dichloroethane. I would also be interested in learning of any actions your firm has or plans to engage in to reduce exposures to 1,2-dichloroethane, or to implement pollution prevention practices. OTS will incorporate information submitted by your company in further Agency assessments.

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[1] Within the industrial sector, pollution prevention is often referred to as source reduction and, according to the Pollution Prevention Act of 1990, includes those activities which "reduce the amount of any hazardous substance, pollutant, or contaminant entering any waste stream or otherwise released in the environment (including fugitive emissions) prior to recycling, treatment or disposal. The term includes equipment or technology modifications, process or procedure modifications, reformulation or redesign of products, substitution of raw materials, and improvements in housekeeping, maintenance, training or inventory control." The term does not include any practice which "alters the physical, chemical, or biological characteristics or the volume of a hazardous substance, pollutant, or contaminant through a process or activity which itself is not integral to and necessary for the production of a product or the providing of a service."

A copy of this letter, as well as the background material on 1,2-dichloroethane enclosed with this letter, has been placed in a publicly accessible administrative record for this chemical. Please send any responses to this letter to:

OTS Document Processing Center (TS-790)
(Attn: RM1 Process/1,2-Dichloroethane File)
Office of Toxic Substances
U.S. Environmental Protection Agency
401 "M" Street, S.W.
Washington D.C. 20460

All responses and correspondence submitted by your firm will be placed in this administrative record unless confidentiality is claimed at the time of submission of the information in accordance with the procedures outlined in 40 CFR Part 2 Subpart B, and 41 FR 36902, September 1, 1976, as amended at 43 FR 40000, September 8, 1978 and 50 FR 51661, December 18, 1985. If no claim of confidentiality accompanies the information, the information may be made available to the public without further notice. If a claim for confidentiality is made on all or part of the provided information, you must also substantiate the claim by submitting a full written response to each question posed in the enclosed item entitled "Support Information for Confidentiality Claims." EPA will determine whether the information in your submission is entitled to confidential treatment and such information will only be disclosed by EPA to the extent, and by means of the procedures, set forth in the cited regulations. Please note that failure to include the responses to the substantiation questions for each claim of confidentiality will be construed by EPA as a waiver of your claim.

Should you have any questions on the information contained in this letter, please contact the TSCA Assistance Information Service (Hotline) at (202) 554-1404 for further information. The Hotline also has a package of pollution prevention guidance information available upon request.

Sincerely,

Mark A. Greenwood

Mark A. Greenwood
Director
Office of Toxic Substances

cc: 1,2-Dichloroethane Administrative Record
EPA Regional Offices

Enclosures:
1,2-Dichloroethane Background Materials
Pollution Prevention Act of 1990
Support Information for Confidentiality Claims

Support Information for Confidentiality Claims

Information submitted under specific reporting requirements of the Toxic Substances Control Act (TSCA) or in support of such is subject to the provisions of Section 14 of TSCA and to EPA's Regulations on the Confidentiality of Business Information (see 40 CFR Part 2). You must comply with the following procedures to assert a claim of confidentiality for the information solicited in the attached letter. Failure to follow these procedures fully at the time you submit the information to EPA will be interpreted by the Agency as a waiver of your claim of confidentiality.

Asserting a Claim

Information claimed as confidential must be clearly marked by boxing, circling or underlining. All pages containing such information should also be stamped **"CONFIDENTIAL"**. Care should be taken to ensure that these markings do not obscure the submission's text.

Sanitized Copy

Two copies must be submitted of any documents containing information claimed as confidential. One copy should be complete, with the information being claimed as confidential marked in the manner described in the preceding paragraph. The other copy should have all of the information claimed as confidential excised. This version will be placed in EPA's Public Files.

Substantiating Claims of Confidentiality

Detailed written responses to the following questions must be provided at the time you submit information for any portion of the information you claim as confidential. Your responses should be as specific as possible, with examples as appropriate, and should provide substantiation arguments for all types of information (e.g., sales or production/importation volumes, chemical identity, company identity) you claim as confidential.

1. For what period of time do you assert this claim of confidentiality? If a claim is to extend until a certain event or point in time, please indicate that event or time period. Explain why the information should remain confidential until such event or time.

2. Have there been any confidentiality determinations made by EPA, other Federal agencies, or courts in connection with this information? If so, please enclose copies.

(over)

3. Has any of the information that you are claiming as confidential been disclosed to individuals outside your company? Will it be disclosed to such persons in the future? If so, what restrictions, if any, apply to use or further disclosure of the information?

4. Briefly describe any physical or procedural restrictions within your company relating to the use and storage of the information you are claiming as confidential. What other steps, if any, have you taken to prevent undesired disclosure of the information during its use or when an employee leaves your company?

5. Does the information claimed as confidential appear or is it referred to in any of items listed below:

   - advertising or promotional materials for the chemical or the end product containing it;

   - safety data sheets or other similar materials for the chemical or the end product containing it;

   - professional or trade publications; or

   - any other media available to the public or to your competitors.

   If you answered yes to any of the above questions, you must indicate where the information appears and explain why it should nonetheless be treated as confidential.

6. Would disclosure of this information be likely to result in substantial harm to your competitive position? If so, you must specifically describe the alleged harmful effects and indicate why they should be considered to be substantial. Also, you must describe how disclosure of the information would cause the harm.

7. If the information in question is "health and safety data" pursuant to 40 CFR Part 2.306(3)(i), do you assert that disclosure of the information you are claiming as confidential would reveal:

   a) confidential process information;

   b) confidential proportions of a mixture; or

   c) information unrelated to the effects of the substance on human health or the envir nment?

   If your answer to any of the above questions is yes, you must explain how such information would be rev aled.

RM1 Meeting Summary

Date: June 21, 1990
Subject: 1,2-Dichloroethane
Chairman: Jim Willis
Coordinator: Nancy Chiu
Supporting Docs.: RM1 Briefing Package on 1,2-dichloroethane

1,2-dichloroethane (DCE) is recommended for follow-up in the STARR process. The major hazard concern identified is carcinogenicity. It was recomended that DCE be added to the Risk Reduction Candidate List for Occupational exposure, and ambient air exposure.

The worker exposure value (81,227 workers at 2,154 plant sites) was questioned. It appears that this value includes all of the work rs at the facilities, however, it may be that only a few are actually exposed.

The decision was made to send letters of concern to those facilities which show the most significant releases, using the same criteria as in past letter cases.

The decision was made to evaluate optional criteria for determining which facilities will receive letters in this and similar cases. This analysis should be performed by the Existing Chemicals Assessment Division (ECAD) and the Exposure Evaluation Division (EED) within six weeks, and a paper summarizing the results circulated. The case will be brought back to RM1 in 8 weeks.

It appears that there is there is not enough data on Immuno tox and hemato tox. HERD should examine these areas.

The effect on the Margin of Exposure (MOE) for the most sensitive endpoints (othe than cancer) if controls for cancer risk are set in place was questioned; such controls will raise the MOE to >100.

A decision was made for HERD to look at the mutagenicity, and to determine whether there is a need to go to Tier III. The results should be reported back to RM1.

I. SELECTION RATIONALE

1,2-Dichloroethane ($C_2H_4Cl_2$, CASRN 107-06-2) was identified during TRI screening as a chemical with very large production volumes and environmental releases. DCE is toxic to humans and animals if inhaled, ingested, or dermally absorbed. It is classified by EPA as a B1 "probable human carcinogen" based on sufficient evidence from animal studies.

II. CONCLUSION AND RECOMMENDATION

1,2-Dichloroethane (DCE) is recommended for follow-up in the STARR Process. The major hazard concern identified is carcinogenicity. DCE should be added to the Risk Reduction Candidate List.

Based on the 1987 TRI release data and the chemical/fate properties, the exposure potential of DCE to environment (air, water and soil) and general public is estimated to be high. Preliminary quantitative risk assessment, using the environmental model estimates and EPA established cancer slope factors (inhalation and oral), suggests that approximately 66 and 83 excess life time cancer cases can result among populations being exposed to DCE contaminated air (72 million persons) and drinking water (40 thousand persons), respectively. The highest daily inhalation and drinking water intake estimates are 0.06 and 0.022 mg/kg/d, respectively. Limited animal studies indicate that possible immunological and hematological effects can be resulted at these exposure levels.

Additional modeling studies can include verification of site-specific model key parameters (e.g. air emission stack height, actual release days), intermittent/batch/accidental release scenarios, removal rate during drinking water treatment, ground water exposure through leaching, and acute aquatic toxicity due to DCE releases at low flow conditions. Testing recommendation for immunotoxicity and blood effects can be made since there are very limited data in these areas available in the literature.

III. BASIS FOR THE CONCLUSION

Chemical/Physical Properties

DCE has molecular weight of 98.96 daltons (conversion factor 4.04)and is in the form of a colorless liquid. It is very soluble in water (8.69×10^3 mg/l) and organic solvents (log Kow 1.48) and adsorbs moderately to organic sediments (log Koc 1.14). The Henry constant and vapor pressure at 25 °C are 4.5×10^{-2} atm-m^3/mol and 61 mm Hg, respectively.

Exposure Aspects Summary

Production/Use

DCE is produced commercially either by the direct catalytic vapor or liquid-phase chlorination of ethylene or by catalyzed reaction of ethylene, HCl, and O_2. Production in the United States has increased from 7.3 billion lb in 1985 to 12.9 billion lb 1986. Importation of DCE in 1985 is 14.3 million lb.

DCE is mainly used as a chemical intermediate. It is also added to leaded gasoline as a lead scavenger. Approximately 84% is used to produce vinyl chloride. DCE is also used in synthesis of 1,1,1-trichloroethane, aziridine, trichloroethylene, tetrachloroethylene, and ethylene diamines. Other miscellaneous applications include use in solvents for various extraction and cleaning purposes in organic synthesis, as a dispersant in rubber and plastics, as wetting and penetrating agents, in ore floatation and as a grain fumigant.

Occupational Exposure

The 1990 NOES survey by NIOSH shows that 81,227 workers at 2,154 plant sites could be exposed to DCE. The occupational exposure areas include food processing, textile mill and textile products processing, chemical/petroleum/rubber products production, primary metal industry, electrical/mechanical and transportation equipment industry, business and health services, and museum/botanical/zoological gardens. Between 1979 to 1990, OSHA documented 41 screen values and 105 OSHA personal values. Among the personal values, one ceiling value of 160 ppm (at J.T. BAker Chemicals, N.J.) and one TWA value of 59 ppm (at Plastics Products, Texas) exceeded the OSHA recommended standards (ceiling 100 ppm and 8-hr TWA 50 ppm).

Environmental Fate

DCE is very volatile from all media. The estimated half-life of DCE in air ranges (via photooxidation) from 12.2 to 122 days. DCE is biodegradable by aerobic microorganisms in water and soil with estimated half-life of 100 days to 6 months. The low estimated log BCF value (0.85) indicates that DCE bioconcentrates poorly in aquatic organisms. Since DCE is soluble and adsorbs poorly to the soil and sediments, it can be expected to leach easily into the ground water.

Environmental Exposure

According to the 1987 TRI data, a total of 6.13 million lbs/yr of DCE was released to atmosphere from 75 facilities. About 3.56 million lbs was released from ponit sources and 2.58

million lbs was released from nonpoint sources. About 1.47 million lbs/yr were released to water media: 72,775 lbs were directly discharged from 39 facilities to navigable waterways, and 139,428 lbs were indirectly discharged via offsite transfers to 22 POTWs or private waste water treatment facilities. The indirect discharge is based on the assumption of 90% removal of the originally transferred amount (1,394,278 lbs) prior to releases. About 3,173 lbs were directly released to the land and 1.31 million lbs was released to land via underground injection.

Using the Industrial Source Complex Long-Term (ISCLT) model in the GEMS Atmospheric Modeling Subsystem (GAMS), EED estimated the air concentrations within a 50 km diameter of all air release sources. Assumptions used in the modeling efforts include 1) 99.9% destruction efficiency for off-site transfers and 2) no decomposition or transformation of DCE in the ambient air after release since the travel time (3 hr) to reach 50 km distance is smaller than the half-life (122 days) of DCE in air. The estimated air concentrations range from 9.7×10^{-12} ug/m^3 to 210 ug/m^3 d pending on the specific site release amounts and the distances from the emission sources.

EED also estimated surface water and drinking water concentrations downstream from the water release sites using the Routing Graphic Display System. Removal of DCE via absorption and biodegradation in the stream during the travel time was taken into consideration. The ten highest estimated DCE concentrations in surface water are in the range of 13.26 ppb to 798.05 ppb. The highest estimated DCE concentration at a drinking water utility intake is 798 ug/l.

Since DCE is expected to leach easily in the ground, the potential for ground water contamination can be high if the land release controls are not effective.

Health Aspects Summary

Pharmacokinetics

DCE is easily absorbed by humans and animals via various exposure routes (inhalation, dermal, ingestion) and rapidly distributed to body tissues.

Conjugation of DCE and metabolite 1,2-dichloroethanol with glutathione is the preferred metabolic pathway with S-(2-hydroxyethyl)-cysteine and thiodiglycolic acid as the two end metabolic products. Urine excretion is the major route for elimination of DCE and its metabolites.

Cases of fatality in humans were reported via inhalation or oral route. In animals, acute inhalation and oral exposure to

DCE in sufficient concentrations result in death. The acute inhalation LC50 in rats is 1,000 ppm (0.1- 8 hr) and oral LD50 in rats and mice were 680 and 413 mg/kg/d, respectively. Gross observations at necropsy revealed liver and kidney effects.

Longer term exposure to DCE led to immnunoligical, hematological, hepatic, renal, cardiological and adrenal gland effects in various animals.

The inhalation NOAEL and LOAEL for immunological effects (increased susceptibility to bacteria) in mice were 2.5 and 5 ppm (5 d, 3 h/d) which are equivalent to 1.6 and 3.5 mg/kg/d, respectively. The oral LOAEL (via gavage) for immunological effects (reduced antibody forming cell response) in mice was 4.9 mg/kg/d (14 d).

The inhalation NOAEL and LOAEL for hematological effects (increased plasma prothrombin clotting time) in monkeys were 100 and 400 ppm (8-12 d, 5 d/wk, 7 h/d, which are equivalent to 33 and 131 mg/kg/d). The oral NOAEL and LOAEL for hematological effects (decrease in leukocytes) in mice were 4.9 and 49 mg/kg/d (14 d).

The inhalation NOAEL and LOAEL for hepatic effects in monkey were 100 and 400 ppm (8-12 d, 5 d/wk, 7 hr/d), resepectively. The inhalation LOAELs for liver weight increase and liver degeneration in guinea pigs were 100 and 200 ppm (246 d, 5 d/wk, 7 hr/d, equiv. to 42 and 84 mg/kg/d). The oral NOAEL and LOAEL for hepatic effects in rats were 30 and 80 mg/kg/d (5-7 wk).

The inhalation NOAEL and LOAEL for renal effects in monkeys were 100 ppm and 400 ppm (8-12 d, 5 d/wk, 7 h/d), respectively. The inhalation renal NOAEL in monkeys and rabbits, at longer exposure (25 wk, 5d/wk, 7 h/d) was 200 ppm. In rats, the chronic oral NOAEL for renal effects in rats was 25 mg/kg/d (2 yr).

The inhalation LOAEL for cardiological (fatty) and adrenal medulla calcification in monkeys was 200 ppm (25 wk, 5 d/wk, 7 h/d) which is equivalent to 65 mg/kg/d.

There were no respiratory effects observed in mice exposed at oral dose of 49 mg/kg/d for 14 d, or 189 mg/kg/d for 90 d, or at air concentration of 100 ppm for 4 wk, 5 d/wk, 7 hr/d (equiv. to 145 mg/kg/d). No respiratory effects were observed in rabbits and monkeys at 200 ppm for 25 wk, 5 d/wk, 7 h/d.

No neurological effects were observed in dogs exposed to 400 ppm for 8 months, 5d/wk, 7 h/d (equiv. to 116 mg/kg/d).

Carcinogenicity

EPA classified DCE as a B1 "probable human carcinogen" based on the observation of sufficient evidence of carcinogenicity from animal studies. DCE in corn oil was administered by gavage to rats for 78 weeks at TWA dosages of 47 and 95 mg/kg/d. The incidences of hemangiosarcoma and forestomach squamous-cell carcinomas were significantly increased and were dose-related (NCI, 1978). Based on this study and the assumption of 100% absorption at the low dose, EPA developed oral and inhalation slope factor of 9.1×10^{-2} $(mg/kg/d)^{-1}$.

Mutagenicity

The mutagenic activity of DCE has been tested in bacteria, plants, D melanogaster, mammalian cells in vitro and in vivo rodent assays. In S. typhimurium testing system, DCE has generally elicited marginally positive mutagenesis without metabolic activation and stronger mutagenic responses when exogenous metabolic systems were added.

Positive mutagenic responses have been reported for DCE in several assays using D melanogaster. These include sex-linked recessive lethal assay (inhalation exposure, 0.07% vapor for 4.6 or 8 hrs and food exposure 50 mM) and somatic cell mutations (larvae food exposure 0.1, 0.5% in food). DCE induced a dose-related increase in mutation at HGPT (hypoxanthine-guanine phosphorilosyl transferase) locus in cultured CHO cells. Dose-related hepatocyte DNA damage was observed in mice treated via various routes (intraperitoneal, oral, inhalation).

Developmental and Reproductive Effects

No studies were located regarding reproductive effects in humans following oral or inhalation exposure to DCE. No reproductive effects were observed in rats exposed to 150 ppm (1 generation, 7 d/wk, 6 h/d (equiv. to 132 mg/kg/d) or at 25 mg/kg/d (oral administration) for 2 yr. No significantly increased incidence of malformations was observed among the offspring of rats exposed to 100 ppm DCE (NOAEL) during days 6-15 of gestation. Exposure to 300 ppm produced high maternal mortality. Only one dam of six survivors had implantation sites, all of which were resorbed. Administration of 510 mg/kg/d (NOAEL) in drinking water to pregnant mice during days 7-14 of gestation produced no developmental effects and few discernible effects on maternal health; no skeletal or visceral anomalies in the fetus could be attributed to treatment. No dose-dependent effects on fertility, gestation, litter size, viability, or lactation indices were observed in mice exposed to doses of 5-50 mg/kg/d (NOAEL) in drinking water for 24-49 weeks.

Environmental Effects

The 24-, 48-, 72- and 96-hour LC_{50} values for fathead minnows were 141, 118, 116 and 116 mg/l, respectively. The 7-day LC_{50} in guppies was 106 mg/l. The EC_0, EC_{50}, and EC_{100} were 1.3, 1.8 and 2.4 mg/l in the golden orfe (duration not specific). In the marine dab, a 96-hr LC_{50} of 115 mg/l was reported.

The 24- and 48-hr LC_{50} in D. magna, have resulted in 24- and 48- hour LC_{50} values of 246 and 218 mg/l and a NOEC of < 68 mg/l. In the mysid shrimp, 24-, 48-, 72- and 96- hr LC_{50} values were 108, 110, 112 and 113 mg/l. The 32-day MATC in fathead minnows were 29 and 59 mg/l. The LOELs for reproduction and growth in D. magna were 21 and 72 mg/l, respectively.

In algae, S. capricornutum the 7-d toxicity threshold for decreased cell multiplication was 710 mg/l. An EC50 of 130 mg/l for algae H. pluialis was reported.

An average MATC of 41 mg/l for parental fish weight reduction was identified in a 32-day reproduction bioassay of DCE using fathead minnows. The NOECs and LOELs for reproduction and growth in D. magna were 11-42 and 21-72 mg/l, respectively. Based on these two studies, EEB/HERD recommended the chronic concern level of 16 ppm. The OWRS documented fresh chronic LOEL of 20 ppm. The OWRS also documented LOELs for fresh and marine acute of 118 and 113 ppm, respectively.

Preliminary Quantitative Cancer Risk Estimates

Ambient Air & Drinking Water

EED has estimated risk levels and lifetime excess cancer cases due to DCE air emissions. Data used in the estimations included the EPA established cancer risk slope factor of 9.1 x 10^{-2} $(mg/kg/day)^{-1}$, model-estimated ambient air concentrations, and population data within GAMS. The estimates are summarized in Table I.

The model estimates that there are 65.7 excess life time cancer cases among a total 72 million persons exposed. The annual incidence is 0.939 cases per year.

EED has also estimated the lifetime excess cancer risk of populations served by water supplies containing DCE using the model estimates, the EPA established slope factor (oral) of 9.1 x 10^{-2} $(mg/kg/day)^{-1}$, and census data within RGDS. The ten highest estimates are summarized in Table II.

Table I. Cancer Risk via Air Contamination

risk level	population at risk	life time cases
5.48E-03	1,165	6.39E+00
5.48E-03 - 1.00E-03	1,847	2.63E+00
1.00E-03 - 1.00E-04	50,650	1.09E+01
1.00E-04 - 1.00E-05	726,412	1.69E+01
1.00E-05 - 1.00E-06	6,917,031	1.85E+01
1.00E-06 - 1.00E-07	27,235,465	9.59E+00
1.00E-07 - 1.00E-08	16,668,806	7.72E-01
1.00E-08 - 1.00E-09	12,778,101	4.72E-02
1.00E-09 - 1.00E-10	8,075,259	4.35E-03
TOTAL	72,454,736	65.7

Table II. Cancer Risk via Drinking Water Contamination

concentration (ug/l)	risk level	population at risk	lifetime cases
798.050	2.07E-3	39,800	8.266E+01
0.048	1.31E-8	61,020	7.623E-03
0.046	1.31E-8	8,000	9.578E-04
0.046	1.31E-8	50,000	5.986E-03
0.037	1.06E-8	60,000	5.778E-03
0.029	8.29E-9	3,200	2.415E-04
0.027	7.71E-9	10,488	7.916E-04
0.024	6.86E-9	228,000	1.424E-02
0.024	6.86E-9	600,000	3.748E-02
0.023	6.57E-9	6,000	3.592E-04
	TOTAL	1,066,508	82.733

TABLE III

highest daily intake via drinking water: 0.022 mg/kg/d
highest daily intake via inhalation: 0.06 mg/kg/d

		repro-	terato-	immuno-	hemato-	hepatic	renal	cardio-	adrenal	neuro-
oral										
	NOAEL	25	50		4.9	30	25			
	LOAEL			4.9	49	80		65	65	
inhal										
	NOAEL	50		1.6	33		32			
	LOAEL			3.3	131	42	131			116
MOE*										
	via DW	1136	2272	72	72	1363	1136	2954	2954	5272
	via inhal	416	833	27	27	500	416	1083	1083	1933

* Lowest NOAEL (or LOAEL if no NOAEL available) was used in the MOE calculations under each health effect category

** All NOAELs and LOAELs are expressed in mg/kg/d.

As indicated in the table II, approximately 40 thousand persons consume drinking water (from one Indiana facility) containing DCE estimate of 798 ppb. This may result in an excess of 82.66 lifetime cancer cases.

The lowest NOAELs and LOAELs for various health effects are listed in Table III. The MOEs of the highest daily DCE inhalation intake for various effects are also summarized in Table III. The low MOE values for immunological and hematological effects suggests further testing needs for DCE.

Surface Water

The ten highest mean flow estimates range from 3.26 to 798.05 ppb. The estimates are lower than the freshwater chronic concern level of 16 ppm recommended by EEB/HERD.

EED estimated that the potential of DCE leaching to the ground water from the landfill sites can be high because of the high water solubility and low absorbability of DCE.

Regulatory Activities

DCE has several state and federal environmental regulations and activities including two under SARA Title III (EPCRA, 1986). DCE is listed as a Toxic Release Inventory (TRI) chemical under EPCRA Section 313. Under CERCLA, releases of DCE at or above the reportable quantity (RQ) of 5,000 lb must be reported to the Region or National Response Center. It is also selected for a Toxicological Profile under CERCLA Section 104. DCE is on the RCRA Appendix IX list of chemicals for which ground water at RCRA hazardous waste sites is required to be monitored.

DCE is considered as a toxic pollutant under the Toxic Pollutant Effluent Standard of CWA. In 1980, OWRS recommended LOEL (Lowest Observed Effect Level) of 118 ppm and 20 ppm for acute and chronic freshwater aquatic life. OWRS estimated that ingesting water and organisms containing 0.94 ppb DCE may result in a cancer risk of 1×10^{-6}. Consumption of aquatic organisms at 243 ppb concentration may result in a cancer risk of 1×10^{-6}. The Maximum Contaminant Level drinking water standard for DCE is 5 ug/l. The ODW health advisories for 1-day, 10-day, and long-term are 0.74, 0.74, and 2.6 ug/l, respectively.

Nine states have maximum acceptable concentration standards for drinking water ranging from 0.38 to 5 ppb. Eleven states have maximum acceptable ambient air concentration standards ranging from 0.038 to 1,000 ug/m^3.

DCE is a pesticide active ingredient under FIFRA. Under OSHA, the Permissible Exposure Limits (PEL) for 8-hr TWA,

SECTION 1. SHORT TITLE AND TABLE OF CONTENTS.

This Act may be cited as the ``Pollution Prevention Act of 1990''.

TABLE OF CONTENTS

SEC. 2. FINDINGS AND POLICY.

(a) FINDINGS.--The Congress finds that:

(1) The United States of America annually produces millions of tons of pollution and spends tens of billions of dollars per year controlling this pollution.

(2) There are significant opportunities for industry to reduce or prevent pollution at the source through cost-effective changes in production, operation, and raw materials use. Such changes offer industry substantial savings in reduced raw material, pollution control, and liability costs as well as help protect the environment and reduce risks to worker health and safety.

(3) The opportunities for source reduction are often

not realized b cause existing regulations, and the industrial resources they require for compliance, focus upon treatment and disposal, rather than source reduction; existing regulations do not emphasize multi-media management of pollution; and businesses n ed information and technical assistance to overcome institutional barriers to the adoption of source reduction practices.

(4) Source reduction is fundamentally different and more desirable than waste management and pollution control. The Environmental Protection Agency needs to address the historical lack of attention to source reduction.

(5) As a first step in preventing pollution through source reduction, the Environmental Protection Agency must establish a source reduction program which collects and disseminates information, provides financial assistance to States, and implements the other activities provided for in this Act.

(b) POLICY.--The Congress hereby declares it to be the national policy of the United States that pollution should be prevented or reduced at the source whenever feasible; pollution that cannot be prevented should be recycled in an environmentally safe manner, whenever feasible; pollution that cannot be prevented or recycled should be treated in an

environmentally safe manner whenever feasible; and disposal or other release into the environment should be employed only as a last resort and should be conducted in an environmentally safe manner.

SEC. 3. DEFINITIONS.

For purposes of this Act--

(1) The term ``Administrator'' means the Administrator of the Environmental Protection Agency.

(2) The term ``Agency'' means the Environmental Protection Agency.

(3) The term ``toxic chemical'' means any substance on the list described in section 313(c) of the Superfund Amendments and Reauthorization Act of 1986.

(4) The term ``release'' has the same meaning as provided by section 329(8) of the Superfund Amendments and Reauthorization Act of 1986.

(5)(A) The term ``source reduction'' means any practice which--

(i) reduces the amount of any hazardous substance, pollutant, or contaminant entering any waste stream or otherwise released into the environment (including fugitive emissions) prior to recycling, treatment, or disposal; and

(ii) reduces the hazards to public health and the environment associated with the release of such

substances, pollutants, or contaminants. The term includes equipment or technology modifications, process or procedure modifications, reformulation or redesign of products, substitution of raw materials, and improvements in housekeeping, maintenance, training, or inventory control.

(B) The term ``source reduction'' does not include any practice which alters the physical, chemical, or biological characteristics or the volume of a hazardous substance, pollutant, or contaminant through a process or activity which itself is not integral to and necessary for the production of a product or the providing of a service.

(6) The term ``multi-media'' means water, air, and land.

(7) The term ``SIC codes'' refers to the 2-digit code numbers used for classification of economic activity in the Standard Industrial Classification Manual.

SEC. 4. EPA ACTIVITIES.

(a) AUTHORITIES.--The Administrator shall establish in the Agency an office to carry out the functions of the Administrator under this Act. The office shall be ind pendent of the Agency's single-medium program offices but shall have the authority to review and advise such offices on their activities to promote a multi-media approach to source

reduction. The office shall be under the directi n of such officer of the Agency as the Administrator shall designate.

(b) FUNCTIONS.--The Administrator shall develop and implement a strategy to promote source reduction. As part of the strategy, the Administrator shall--

(1) establish standard methods of measurement of source reduction;

(2) ensure that the Agency considers the effect of its existing and proposed programs on source reduction efforts and shall review regulations of the Agency prior and subsequent to their proposal to determine their effect on source reduction;

(3) coordinate source reduction activities in each Agency Office and coordinate with appropriate offices to promote source reduction practices in other Federal agencies, and generic research and development on techniques and processes which have broad applicability;

(4) develop improved methods of coordinating, and assuring public access to data collected under Federal environmental statutes;

(5) facilitate the adoption of source reduction techniques by businesses. This strategy shall include the use of the Source Reduction Clearinghouse and Stat matching grants provided in this Act to foster the exchange of information regarding source reduction

techniques, the dissemination of such information to businesses, and the provision of technical assistance to businesses. The strategy shall also consider the capabilities of various businesses to make use of source reduction techniques;

(6) identify, where appropriate, measurable goals which reflect the policy of this Act, the tasks necessary to achieve the goals, dates at which the principal tasks are to be accomplished, required resources, organizational responsibilities, and the means by which progress in meeting the goals will be measured;

(7) establish an advisory panel of technical experts comprised of representatives from industry, the States, and public interest groups, to advise the Administrator on ways to improve collection and dissemination of data;

(8) establish a training program on multimedia source reduction opportunities, including workshops and guidance documents, for State and Federal permit issuance, enforcement, and inspection officials working within all agency program offices.

(9) identify and make recommendations to Congress to eliminate barriers to source reduction including the use of incentives and disincentives;

(10) identify opportunities to use Federal procurement to encourage source reduction;

(11) develop, test and disseminate model source reduction auditing procedures designed to highlight source reduction opportunities; and

(12) establish an annual award program to recognize a company or companies which operate outstanding or innovative source reduction programs.

SEC. 5. GRANTS TO STATES FOR STATE TECHNICAL ASSISTANCE PROGRAMS.

(a) GENERAL AUTHORITY.--The Administrator shall make matching grants to States for programs to promote the use of source reduction techniques by businesses.

(b) CRITERIA.--When evaluating the requests for grants under this section, the Administrator shall consider, among other things, whether the proposed State program would accomplish the following:

(1) Make specific technical assistance available to businesses seeking information about source reduction opportunities, including funding for experts to provide onsite technical advice to business seeking assistance and to assist in the development of source reduction plans.

(2) Target assistance to businesses for whom lack of information is an impediment to source reduction.

(3) Provide training in source reduction techniques. Such training may be provided through local engineering

schools or any other appropriate means.

(c) MATCHING FUNDS.--Federal funds used in any State program under this section shall provide no more than 50 per centum of the funds made available to a State in each year of that State's participation in the program.

(d) EFFECTIVENESS.--The Administrator shall establish appropriate means for measuring the effectiveness of the State grants made under this section in promoting the use f source reduction techniques by businesses.

(e) INFORMATION.--States receiving grants under this section shall make information generated under the grants available to the Administrator.

SEC. 6. SOURCE REDUCTION CLEARINGHOUSE.

(a) AUTHORITY.--The Administrator shall establish a Source Reduction Clearinghouse to compile information including a computer data base which contains information n management, technical, and operational approaches to source reduction. The Administrator shall use the clearinghouse to--

(1) serve as a center for source reduction technol gy transfer;

(2) mount active outreach and education programs by the States to further the adoption of source reduction technologies; and

(3) collect and compile information reported by States receiving grants under section 5 on the operati n

and success of State source reduction programs.

(b) PUBLIC AVAILABILITY.--The Administrator shall make available to the public such information on source reduction as is gathered pursuant to this Act and such other pertinent information and analysis regarding source reduction as may be available to the Administrator. The data base shall permit entry and retrieval of information to any person.

SEC. 7. SOURCE REDUCTION AND RECYCLING DATA COLLECTION.

(a) REPORTING REQUIREMENTS.--Each owner or operator of a facility required to file an annual toxic chemical release form under section 313 of the Superfund Amendments and Reauthorization Act of 1986 (``SARA'') for any toxic chemical shall include with each such annual filing a toxic chemical source reduction and recycling report for the preceeding calendar year. The toxic chemical source reduction and recycling report shall cover each toxic chemical required to be reported in the annual toxic chemical release form filed by the owner or operator under section 313(c) of that Act. This section shall take effect with the annual report filed under section 313 for the first full calendar year beginning after the enactment of this Act.

(b) ITEMS INCLUDED IN REPORT.--The toxic chemical source reduction and recycling report required under subsection (a) shall set forth each of the following on a facility-by-facility basis for each toxic chemical:

(1) The quantity of the chemical entering any waste stream (or otherwise released into the environment) prior to recycling, treatment, or disposal during the calendar year for which the report is filed and the percentage change from the previous year. The quantity reported shall not include any amount reported under paragraph (7). When actual measurements of the quantity of a toxic chemical entering the waste streams are not readily available, reasonable estimates should be made based on best engineering judgment.

(2) The amount of the chemical from the facility which is recycled (at the facility or elsewhere) during such calendar year, the percentage change from the previous year, and the process of recycling used.

(3) The source reduction practices used with respect to that chemical during such year at the facility. Such practices shall be reported in accordance with the following categories unless the Administrator finds other categories to be more appropriate:

(A) Equipment, technology, process, or procedure modifications.

(B) Reformulation or redesign of products.

(C) Substitution of raw materials.

(D) Improvement in management, training, inventory control, materials handling, or other

general operational phases of industrial facilities.

(4) The amount expected to be reported under paragraph (1) and (2) for the two calendar years immediately following the calendar year for which the report is filed. Such amount shall be expressed as a percentage change from the amount reported in paragraphs (1) and (2).

(5) A ratio of production in the reporting year to production in the previous year. The ratio should be calculated to most closely reflect all activities involving the toxic chemical. In specific industrial classifications subject to this section, where a feedstock or some variable other than production is the primary influence on waste characteristics or volumes, the report may provide an index based on that primary variable for each toxic chemical. The Administrator is encouraged to develop production indexes to accommodate individual industries for use on a voluntary basis.

(6) The techniques which were used to identify source reduction opportunities. Techniques listed should include, but are not limited to, employee recommendations, external and internal audits, participative team management, and material balance audits. Each type of source reduction listed under paragraph (3) should be associated with the techniques or

multiples of techniques used to identify the source reduction technique.

(7) The amount of any toxic chemical released into the environment which resulted from a catastrophic event, remedial action, or other one-time event and is not associated with production processes during the reporting year.

(8) The amount of the chemical from the facility which is treated (at the facility or elsewhere) during such calendar year and the percentage change from the previous year.

For the first year of reporting under this subsection, comparison with the previous year is required only to th extent such information is available.

(c) SARA PROVISIONS.--The provisions of sections 322, 325(c), and 326 of the Superfund Amendments and Reauthorization Act of 1986 shall apply to the reporting requirements of this section in the same manner as to the reports required under section 313 of that Act. The Administrator may modify the form required for purposes of reporting information under section 313 of that Act to the extent he deems necessary to include the additional information required under this section.

(d) ADDITIONAL OPTIONAL INFORMATION.--Any person filing a report under this section for any year may include with the

report additional information regarding source reduction, recycling, and other pollution control techniques in earlier years.

(e) AVAILABILITY OF DATA.--Subject to section 322 of th Superfund Amendments and Reauthorization Act of 1986, th Administrator shall make data collected under this section publicly available in the same manner as the data collected under section 313 of the Superfund Amendments and Reauthorization Act of 1986.

SEC. 8. EPA REPORT.

(a) BIENNIAL REPORTS.--The Administrator shall provide Congress with a report within eighteen months after enactment of this Act and biennially thereafter, containing a detailed description of the actions taken to implement the strategy to promote source reduction developed under section 4(b) and of the results of such actions. The report shall include an assessment of the effectiveness of the clearinghouse and grant program established under this Act in promoting the goals of the strategy, and shall evaluate data gaps and data

duplication with respect to data collected under Fed ral environmental statutes.

(b) SUBSEQUENT REPORTS.--Each biennial report submitted under subsection (a) after the first report shall contain each of the following:

(1) An analysis of the data collected under section 7 on an industry-by-industry basis for not less than five SIC codes or other categories as the Administrator deems appropriate. The analysis shall begin with those SIC codes or other categories of facilities which generate the largest quantities of toxic chemical waste. The analysis shall include an evaluation of trends in source reduction by industry, firm size, production, or other useful means. Each such subsequent report shall cover five SIC codes or other categories which were not c vered in a prior report until all SIC codes or other categories have been covered.

(2) An analysis of the usefulness and validity of the data collected under section 7 for measuring trends in source reduction and the adoption of source reduction by business.

(3) Identification of regulatory and nonregulatory barriers to source reduction, and of opportunities for using existing regulatory programs, and incentives and disincentives to promote and assist source reduction.

(4) Identification of industries and pollutants that require priority assistance in multi-media source reduction.

(5) Recommendations as to incentives needed t encourage investment and research and development in source reduction.

(6) Identification of opportunities and devel pment of priorities for research and development in source reduction methods and techniques.

(7) An evaluation of the cost and technical feasibility, by industry and processes, of source reduction opportunities and current activities and an identification of any industries for which there are significant barriers to source reduction with an analysis of the basis of this identification.

(8) An evaluation of methods of coordinating, streamlining, and improving public access to data collected under Federal environmental statutes.

(9) An evaluation of data gaps and data duplication with respect to data collected under Federal environmental statutes.

In the report following the first biennial report provided for under this subsection, paragraphs (3) through (9) may be included at the discretion of the Administrator.

SEC. 9. SAVINGS PROVISIONS.

F-12-603

DRAFT NTP TECHNICAL REPORT

ON THE

TOXICITY STUDIES OF 1,2-DICHLOROETHANE IN F344/N RATS, SPRAGUE DAWLEY RATS, OSBORNE-MENDEL RATS, AND B6C3F$_1$ MICE

(DRINKING WATER AND GAVAGE STUDIES)

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June 1989

NTP TOX 4

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

These studies were supported in part or whole by funds from the Comprehensive Environmental Response, Compensation, and Liability Act trust fund by interagency agreement with the Agency for Toxic Substances and Disease Registry, U.S. Public Health Service.

FOREWORD

These studies were performed under the direction of the National Institute of Environmental Health Sciences (NIEHS) as a function of the National Toxicology Program (NTP). The NTP, established in 1978, develops and evaluates 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. By bringing together the relevant programs, staff, and resources from the Public Health Service, U.S. Department of Health and Human Services (DHHS), the NTP has centralized and strengthened activities relating to basic and applied research, biological assay development and validation, and the dissemination of toxicological information to the public and to the scientific and regulatory communities.

The NTP is made up of four charter DHHS agencies: the National Cancer Institute (NCI), National Institutes of Health; the NIEHS, National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS.

TOXICITY STUDIES

OF

1,2-DICHLOROETHANE
(ETHYLENE DICHLORIDE)

(CAS NO. 107-06-2)

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

(DRINKING WATER AND GAVAGE STUDIES)

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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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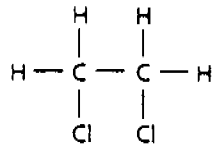
CONTENTS

APPENDIX



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

Studies were conducted to compare the toxicity of 1,2-dichloroethane in F344/N rats, Sprague Dawley rats, Osborne-Mendel rats, and B6C3F$_1$ mice. Rats and mice 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, 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.

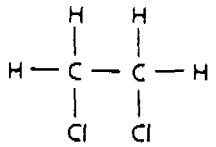
Kidney and liver weights were increased in dosed rats of all three strains. No chemical-related lesions were observed except for a dose-related incidence of renal tubular regeneration in female F344/N rats.

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 (milliliters per kilogram body weight), 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 (in milligrams per kilogram per day) by gavage.



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

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

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

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 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 1.5 million workers could be at

risk (Gold, 1980). 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 tissue 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 at 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) 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 1,2-dichloroethane-exposed rats (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)

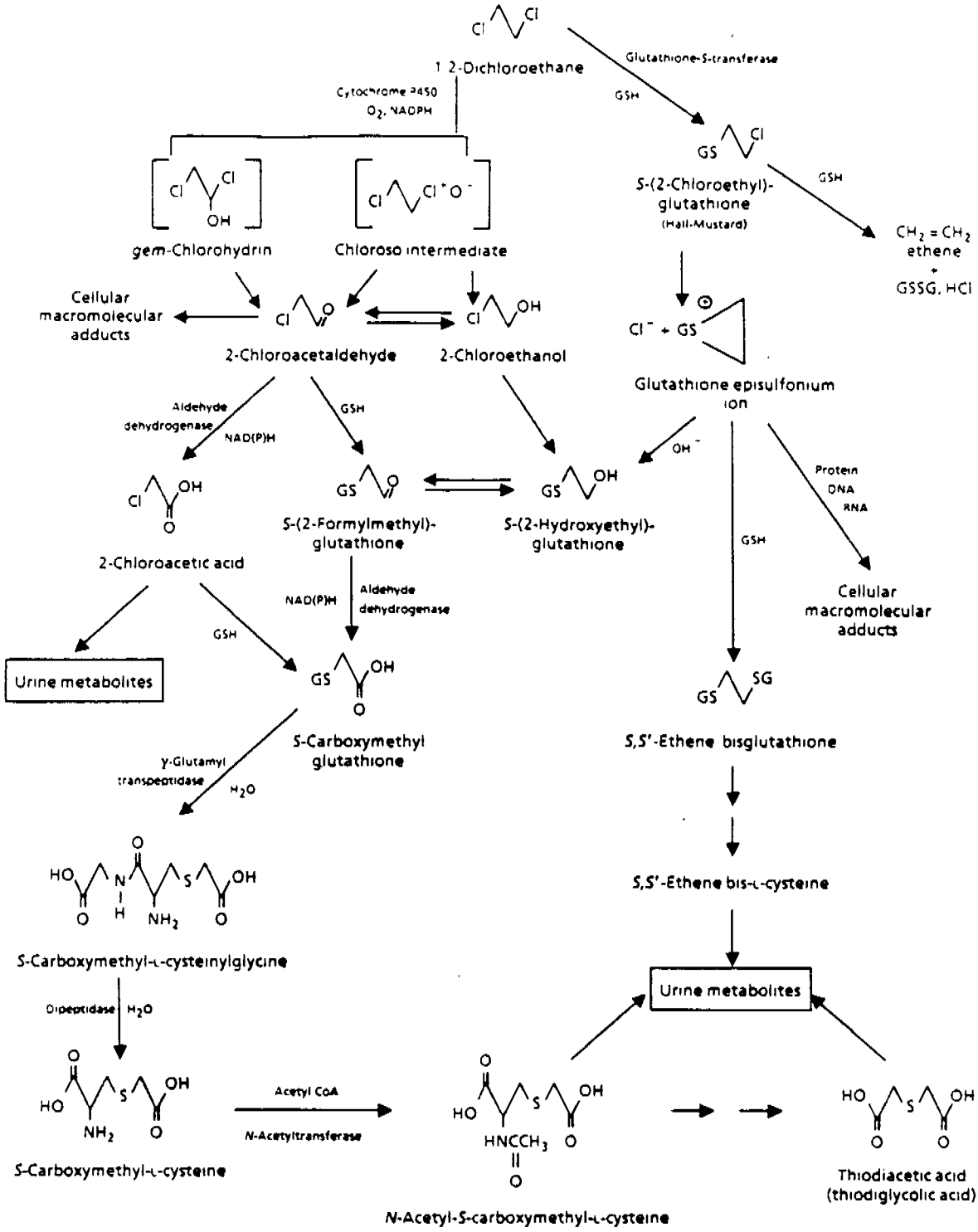

FIGURE 1. PROPOSED PATHWAYS FOR 1,2-DICHLOROETHANE METABOLISM
(from IPCS, 1987)

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 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 at 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 at 57 ± 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 was carcinogenic and caused neoplasms at multiple sites with metastases (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, species 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.

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

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 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

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.

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 fr

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 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. 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 NTP 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 rats 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).

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

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.

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 at 4,000 ppm or more and of females exposed at 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

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)	Estimated Intake Dose (e)
MALE							
0	10/10	134 ± 2	358 ± 4	+223 ± 3		25	
500	10/10	133 ± 2	359 ± 7	+226 ± 6	100	24	49
1,000	10/10	133 ± 2	358 ± 5	+225 ± 5	100	21	86
2,000	10/10	132 ± 2	358 ± 3	+226 ± 3	100	18	147
4,000	10/10	134 ± 1	329 ± 3	+195 ± 3	92	15	259
8,000	10/10	133 ± 2	302 ± 4	+168 ± 4	84	14	515
FEMALE							
0	10/10	109 ± 2	202 ± 2	+93 ± 2		19	
500	10/10	108 ± 1	204 ± 3	+96 ± 2	101	18	58
1,000	10/10	108 ± 1	207 ± 2	+99 ± 1	102	16	102
2,000	10/10	108 ± 2	199 ± 3	+92 ± 1	99	14	182
4,000	10/10	105 ± 3	195 ± 1	+90 ± 3	97	12	320
8,000	10/10	106 ± 1	187 ± 2	+81 ± 2	93	11	601

(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.
(e) Milligrams per kilogram per day based on the mean of the initial and final body weights

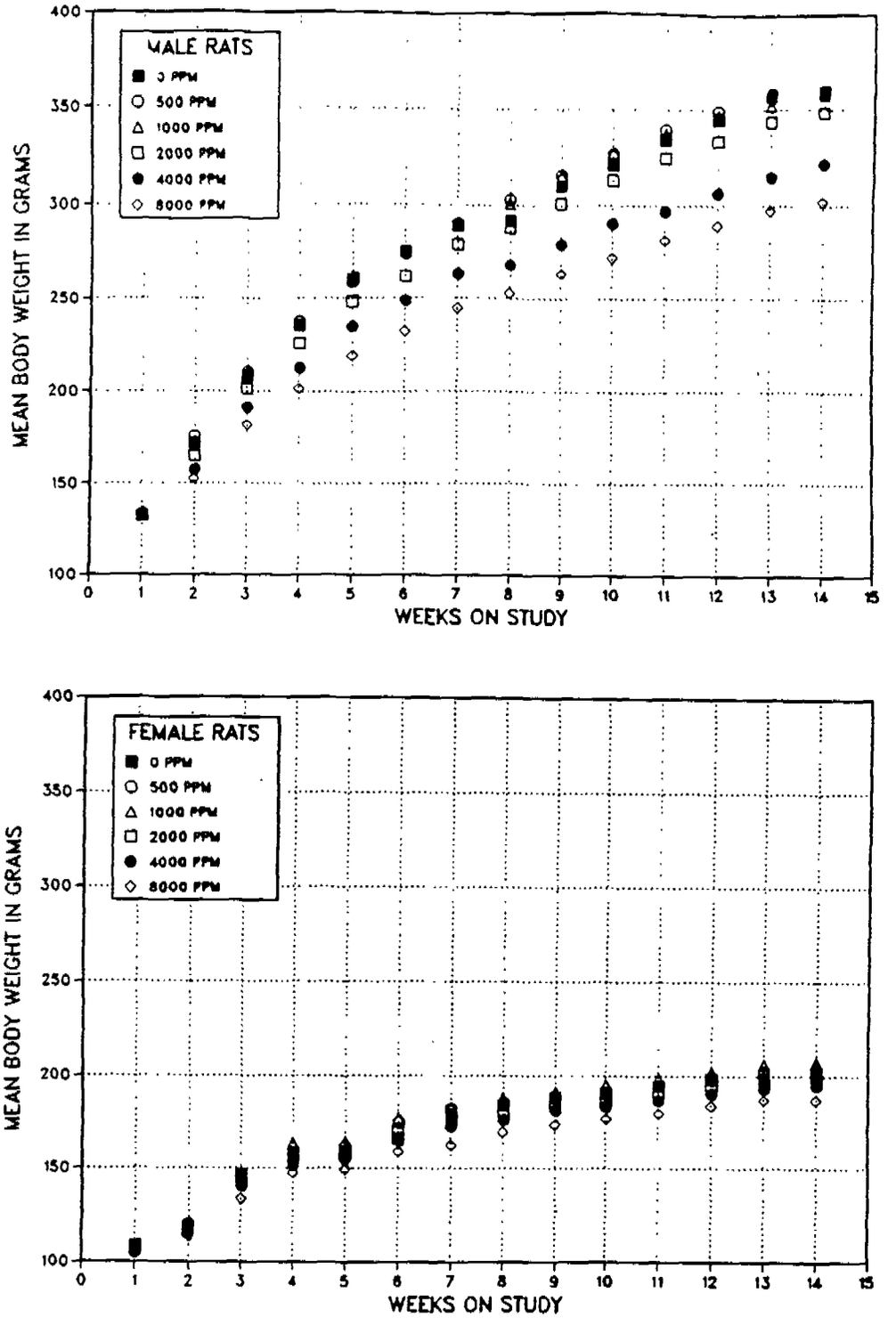

FIGURE 2. GROWTH CURVES FOR F344/N RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE

in the high dose male rats are all indicative of animal dehydration (Table A3). The decrease in mean cell volume (hemoglobin/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

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	1,856 ± 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 ± 810	**21,080 ± 940	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 studies						
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 ± 18	**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 ± 0.81
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 ± 18
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 ± 0.28
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 studies						
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	**998 ± 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	*9,000 ± 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

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.

Sprague Dawley Rats: All Sprague Dawley rats lived to the end of the studies (Table 8). Mean body weights of males and females exposed at 4,000 ppm or more were lower than those of controls throughout the studies (Figure 3). Water consumption by the three highest dosed 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

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)	Estimated Intake Dose (e)
MALE							
0	10/10	170 ± 2	457 ± 11	+288 ± 10		43	
500	10/10	169 ± 2	452 ± 7	+283 ± 7	99	37	60
1,000	10/10	169 ± 2	439 ± 6	+270 ± 6	96	30	99
2,000	10/10	169 ± 2	436 ± 12	+267 ± 12	95	25	165
4,000	10/10	168 ± 2	440 ± 8	+272 ± 7	96	21	276
8,000	10/10	169 ± 3	418 ± 9	+248 ± 7	91	19	518
FEMALE							
0	10/10	139 ± 2	281 ± 6	+141 ± 5		44	
500	10/10	144 ± 2	291 ± 8	+147 ± 8	104	33	76
1,000	10/10	143 ± 2	290 ± 5	+147 ± 4	103	23	106
2,000	10/10	143 ± 2	276 ± 5	+133 ± 4	98	18	172
4,000	10/10	141 ± 2	270 ± 7	+128 ± 6	96	16	311
8,000	10/10	135 ± 2	257 ± 5	+123 ± 4	91	13	531

(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.
(e) Milligrams per kilogram per day based on the mean of the initial and final body weights

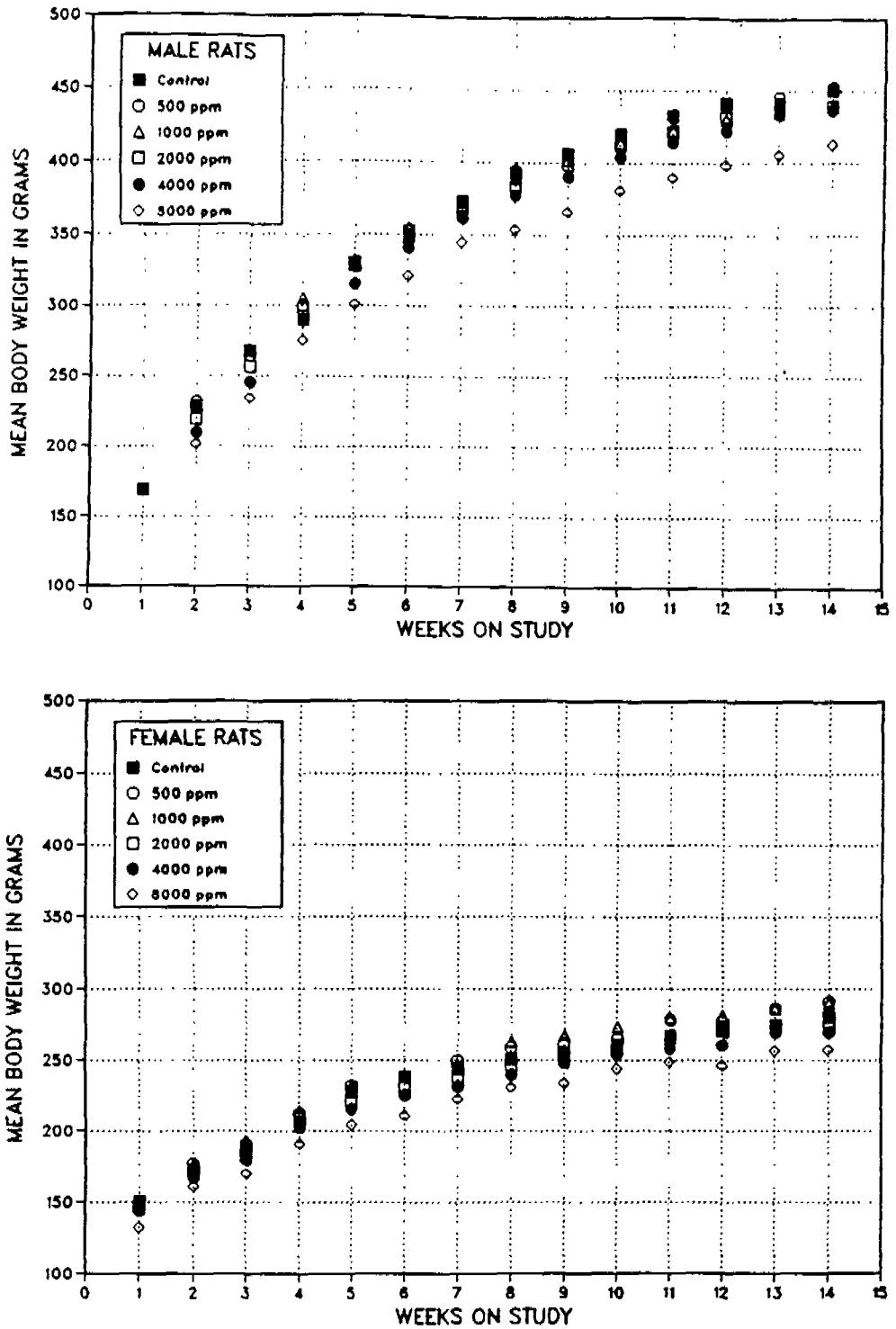

FIGURE 3. GROWTH CURVES FOR SPRAGUE DAWLEY RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE

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.

Osborne-Mendel Rats: No compound-related deaths occurred in Osborne-Mendel rats (Table 9). Mean body weights of males exposed at 2,000 ppm or more and of females exposed at 1,000 ppm or more were lower than those of controls throughout the studies (Figure 4). Water consumption by the three highest

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)	Estimated Intake Dose (e)
MALE							
0	(f) 9/10	172 ± 3	452 ± 15	+281 ± 16		42	
500	10/10	171 ± 4	482 ± 13	+311 ± 14	107	35	54
1,000	10/10	170 ± 3	468 ± 17	+298 ± 18	104	28	88
2,000	10/10	169 ± 3	435 ± 14	+266 ± 14	96	22	146
4,000	10/10	172 ± 3	399 ± 12	+227 ± 14	88	19	266
8,000	10/10	171 ± 3	382 ± 11	+211 ± 12	85	17	492
FEMALE							
0	10/10	138 ± 3	278 ± 12	+140 ± 12		43	
500	10/10	139 ± 3	277 ± 6	+137 ± 5	100	34	82
1,000	10/10	138 ± 3	275 ± 5	+138 ± 3	99	26	126
2,000	10/10	137 ± 3	261 ± 4	+124 ± 3	94	23	213
4,000	10/10	136 ± 2	275 ± 7	+139 ± 5	99	22	428
8,000	10/10	138 ± 2	258 ± 5	+121 ± 4	93	18	727

(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) Milligrams per kilogram per day based on the mean of the initial and final body weights
(f) Week of death: 7

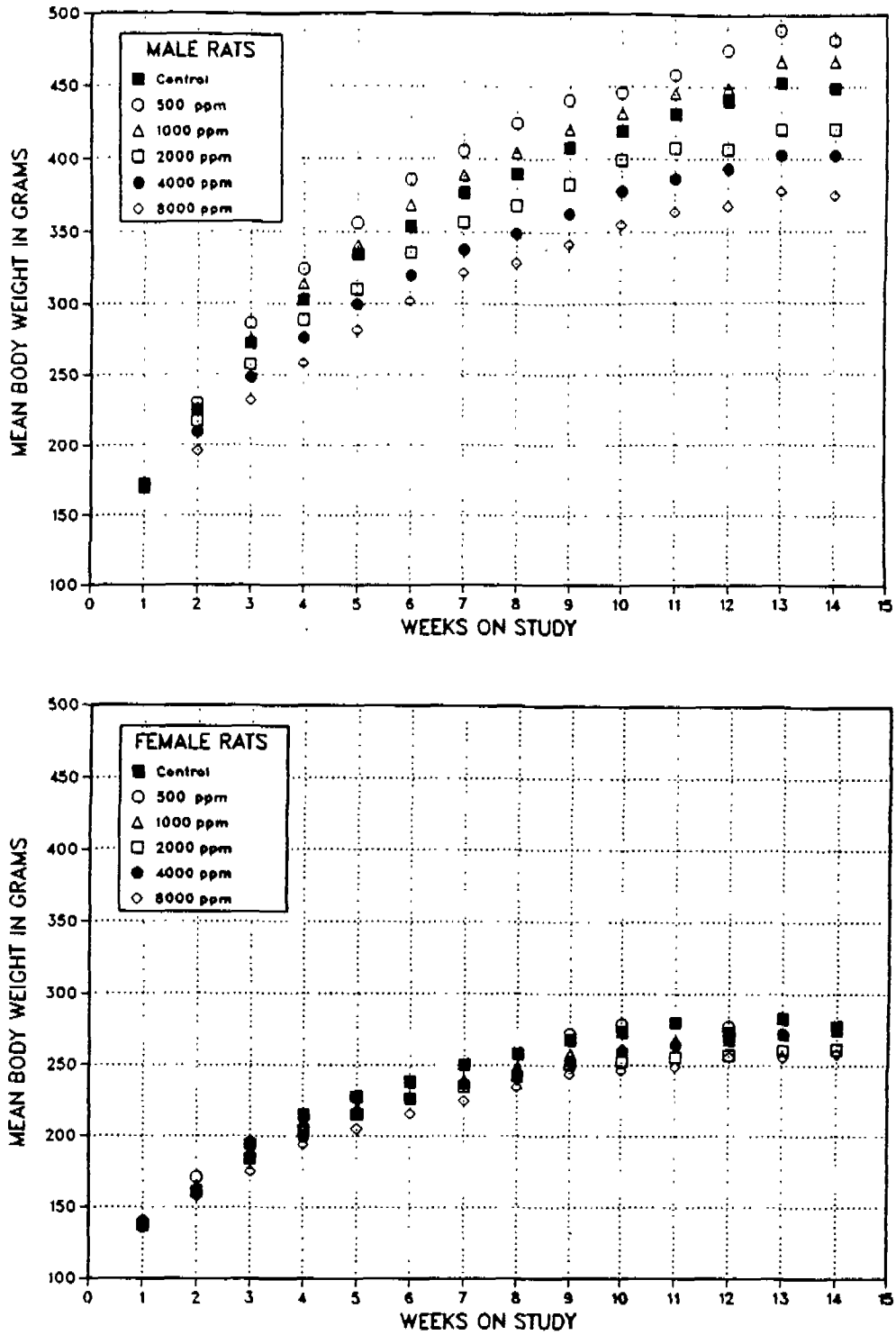

FIGURE 4. GROWTH CURVES FOR OSBORNE-MENDEL RATS IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE

dosed 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

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

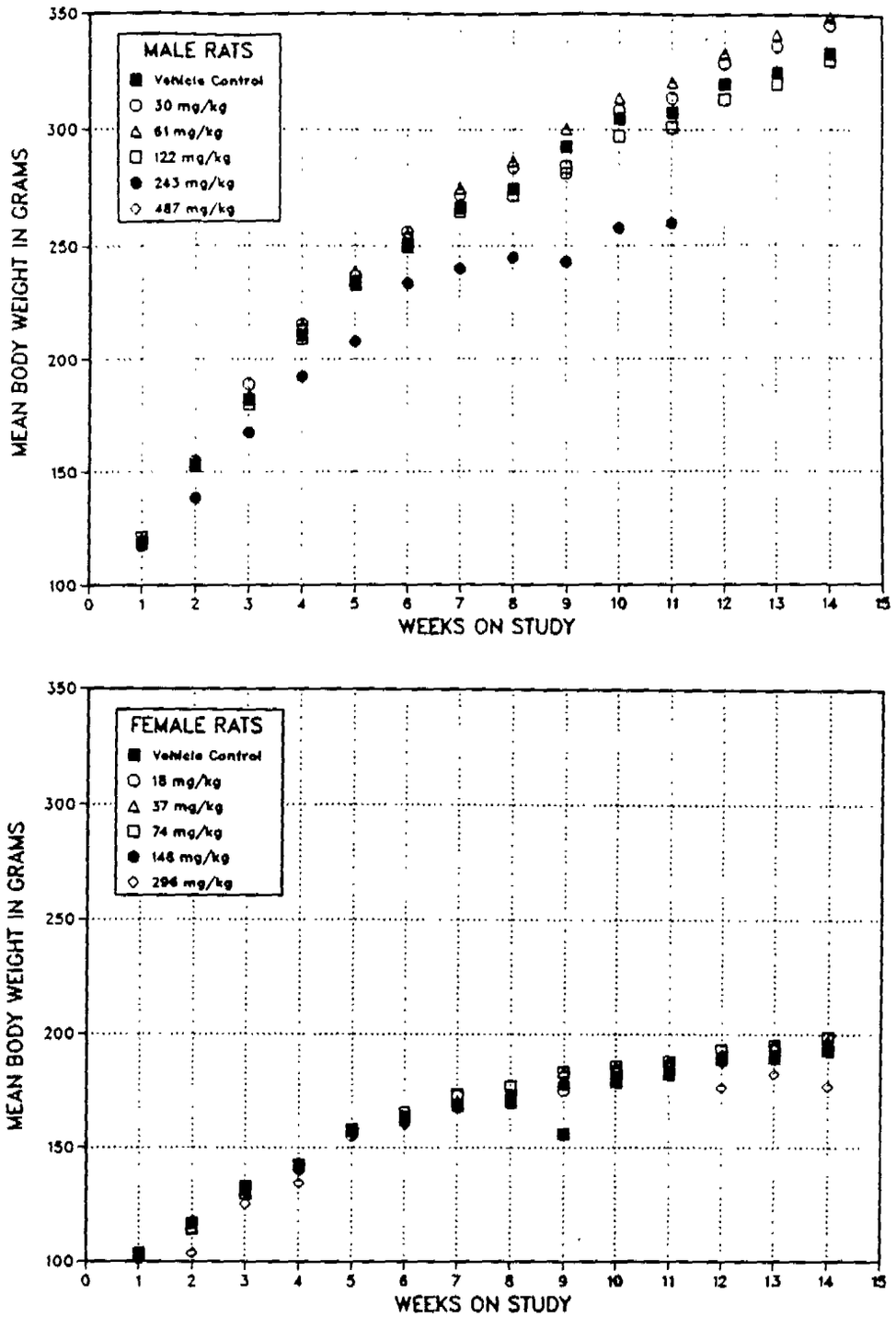

FIGURE 5. GROWTH CURVES FOR F344/N RATS ADMINISTERED 1,2-DICHLOROETHANE IN CORN OIL BY GAVAGE FOR THIRTEEN WEEKS

sometimes seen with hyperplasia and inflammation. Necrosis of the cerebellum and of the thymus 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 at 8,000 ppm died before the end of the studies (Table 12). Mean body weights of males exposed at 500 ppm or more and of females exposed at 1,000 ppm or more were lower than those of controls throughout most of the studies (Figure 6).

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)	Estimated Intake Dose (e)
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	249
1,000	10/10	21.1 ± 0.4	29.3 ± 0.5	+8.2 ± 0.6	93.3	11.3	448
2,000	10/10	20.8 ± 0.4	29.4 ± 0.8	+8.6 ± 0.7	93.6	9.8	781
4,000	10/10	20.3 ± 0.2	28.6 ± 0.7	+8.3 ± 0.6	91.1	16.6	2,710
8,000	10/10	20.5 ± 0.3	25.9 ± 0.7	+5.4 ± 0.8	82.5	12.2	4,207
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	244
1,000	10/10	16.9 ± 0.2	23.2 ± 0.6	+6.3 ± 0.5	89.6	13.0	647
2,000	10/10	16.9 ± 0.3	23.7 ± 0.5	+6.8 ± 0.4	91.5	12.0	1,182
4,000	10/10	17.1 ± 0.3	23.8 ± 0.6	+6.7 ± 0.5	91.9	12.7	2,478
8,000	(f) 1/10	17.2 ± 0.4	23.4	+4.7	90.3	12.5	4,926

(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) Milligrams per kilogram per day based on the mean of the initial and final body weights
(f) Week of death: 1,1,5,5,9,10,10,11,13

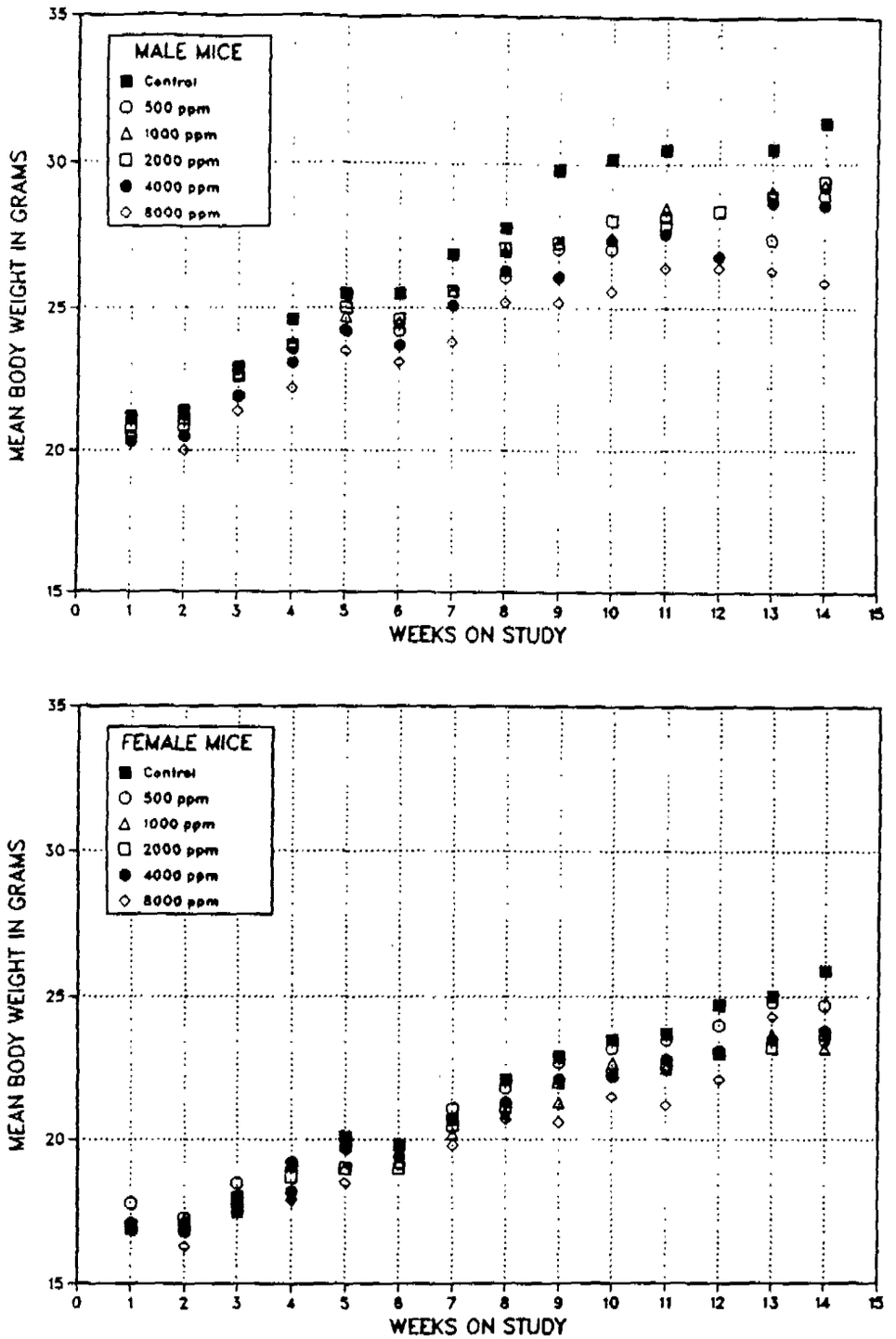

FIGURE 6. GROWTH CURVES FOR MICE IN THE THIRTEEN-WEEK DRINKING WATER STUDIES OF 1,2-DICHLOROETHANE

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

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

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.

IV. DISCUSSION AND CONCLUSIONS

1,2-Dichloroethane administered at up to 8,000 ppm in drinking water for 13 weeks appeared to be relatively nontoxic for 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 dos 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 dosed 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 level 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, 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 level 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 an 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 tenfold 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 for males, based on kidney lesions, and 4,000 ppm for females, based on mortality.

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APPENDIX A

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 ± 0.06	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