National Cancer Institute
CARCINOGENESIS
Technical Report Series
No. 86
1978

BIOASSAY OF 1,2-DIBROMOETHANE FOR POSSIBLE CARCINOGENICITY

CAS No. 106-93-4

NCI-CG-TR-86

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

BIOASSAY OF

1,2-DIBROMOETHANE

FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

DHEW Publication No. (NIH) 78-1336

REPORT ON THE BIOASSAY OF 1,2-DIBROMOETHANE
FOR POSSIBLE CARCINOGENICITY

CARCINOGENESIS TESTING PROGRAM
DIVISION OF CANCER CAUSE AND PREVENTION
NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH

FOREWORD: This report presents the results of the bioassay of 1,2-dibromoethane conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. Negative results, in which the test animals do not have a significantly greater incidence of cancer than control animals, do not necessarily mean the test chemical is not a carcinogen because the experiments are conducted under a limited set of circumstances. Positive results demonstrate that the test chemical is carcinogenic for animals under the conditions of the test and indicate a potential risk to man. The actual determination of the risk to man from animal carcinogens requires a wider analysis.

CONTRIBUTORS: This bioassay of 1,2-dibromoethane was conducted by Hazleton Laboratories America, Inc., Vienna, Virginia, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., prime contractor for the NCI Carcinogenesis Testing Program.

The experimental design was determined by the NCI Project Officers, Dr. J. H. Weisburger (1,2) and Dr. E. K. Weisburger (1). The principal investigators for the contract were Dr. M. B. Powers (3), Dr. R. W. Voelker (3), Dr. W. A. Olson (3,4) and Dr. W. M. Weatherholtz (3). Chemical analysis was performed by Dr. C. L. Guyton (3,5) and the analytical results were reviewed by Dr. N. Zimmerman (6); the technical supervisor of animal treatment and observation was Ms. K. J. Petrovics (3).

Histopathologic examinations were performed by Dr. D. A. Banas (3) and Dr. R. H. Habermann (3) and reviewed by Dr. R. W. Voelker (3) at the Hazleton Laboratories America, Inc., and the diagnoses included in this report represent the interpretation of these pathologists. Histopathology findings and reports were reviewed by Dr. R. L. Schueler (7).

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute (8); the statistical analysis was performed by Mr. W. W. Belew (6) and Dr. J. R. Joiner (7), using methods selected for the Carcinogenesis Testing Program by Dr. J. J. Gart (9).

This report was prepared at METREK, a Division of The MITRE Corporation (6) under the direction of the NCI. Those responsible for this report at METREK are the project coordinator, Dr. L. W. Thomas (6), task leader Dr. M. R. Kornreich (6), senior biologist Ms. P. Walker (6), biochemist Dr. B. Fuller (6), and technical editor Ms. P. A. Miller (6). The final report was reviewed by members of the participating organizations.

The following other scientists at the National Cancer Institute were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. K. C. Chu (1), Dr. C. Cueto, Jr. (1), Dr. J. F. Douglas (1), Dr. D. G. Goodman (1), Dr. R. A. Griesemer (1), Dr. H. A. Milman (1), Dr. T. W. Orme (1), Dr. R. A. Squire (1,10), Dr. J. M. Ward (1), and Dr. C. E. Whitmire (1).

---

1. Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

2. Now with the Naylor Dana Institute for Disease Prevention, American Health Foundation, Hammon House Road, Valhalla, New York.

3. Hazleton Laboratories America, Inc., 9200 Leesburg Turnpike, Vienna, Virginia.

4. Now with the Center for Regulatory Services, 2347 Paddock Lane, Reston, Virginia.

5. Now with Rhodia, Inc., 23 Belmont Drive, Somerset, New Jersey.

6. The MITRE Corporation, METREK Division, 1820 Dolley Madison Boulevard, McLean, Virginia.

7. Tracor Jitco, Inc., 1776 East Jefferson Street, Rockville, Maryland.

8. EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

9. Mathematical Statistics and Applied Mathematics Section, Biometry Branch, Field Studies and Statistics Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

10. Now with the Division of Comparative Medicine, Johns Hopkins University, School of Medicine, Traylor Building, Baltimore, Maryland.

SUMMARY

A bioassay for possible carcinogenicity of technical-grade 1,2-dibromoethane was conducted using Osborne-Mendel rats and B6C3F1 mice. 1,2-Dibromoethane in corn oil was administered by gavage, at either of two dosages, to groups of 50 male and 50 female animals of each species. The time-weighted average high and low doses of 1,2-dibromoethane used in the chronic bioassay were, respectively, 41 and 38 mg/kg/day for male rats, 39 and 37 mg/kg/day for female rats and 107 and 62 mg/kg/day for mice of both sexes. For each species 20 animals of each sex were placed on test as vehicle controls. These animals were gavaged with corn oil with the same frequency that dosed animals were gavaged with 1,2-dibromoethane mixtures. Twenty animals of each sex were placed on test as untreated controls for each species. These animals were not intubated.

There was a positive association between increased dosage and accelerated mortality in rats and mice of both sexes. All surviving dosed male rats were sacrificed in week 49 and all surviving dosed female rats were sacrificed after 61 weeks of compound administration. All male mice and high dose female mice died or were sacrificed by week 78, while the low dose mice were observed for an additional 37 weeks after a 53-week period of chemical administration.

In rats squamous-cell carcinomas of the forestomach were observed in 45/50, 33/50, 40/50 and 29/50 of the low dose males, high dose males, low dose females and high dose females, respectively, while none were observed in controls. Each of these incidences was statistically significant. These lesions were seen as early as week 12 in rats and week 24 in mice; they invaded locally and eventually metastasized. Increased incidences of hepatocellular carcinomas were observed in dosed rats, but the incidence of this neoplasm was significant only in females. Increased incidences of hemangiosarcomas were observed in each dosed rat group, but was statistically significant only in males, where they appeared as early as week 26.

Early development of squamous-cell carcinomas which invaded and metastasized was also observed among mice. Squamous-cell carcinomas were found in 45/50, 29/49, 46/49 and 28/50 of the low dose males, high dose males, low dose females and high dose females, respectively, but none were found in controls. Each of these incidences was statistically significant. Incidences of alveolar/bronchiolar adenomas were significant for male and female dosed mice.

Under the conditions of this bioassay, 1,2-dibromoethane was carcinogenic to Osborne-Mendel rats and B6C3F1 mice. The compound

induced squamous-cell carcinomas of the forestomach in rats of both sexes, hepatocellular carcinomas in female rats, and hemangiosarcomas in male rats. In mice of both sexes the compound induced squamous-cell carcinomas of the forestomach and alveolar/bronchiolar adenomas.

TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

LIST OF TABLES

LIST OF TABLES (Continued)

LIST OF TABLES (Concluded)

I. INTRODUCTION

1,2-Dibromoethane (NCI No. C00522), a volatile saturated brominated hydrocarbon, is used principally as a lead scavenger in tetraalkyl lead gasoline and antiknock preparations (Fishbein, 1976) but also as a soil and grain fumigant, a chemical intermediate, and a solvent (International Agency for Research on Cancer, 1977). This chemical was selected for bioassay by the National Cancer Institute because of the extensive potential for human exposure.

The Chemical Abstracts Service (CAS) Ninth Collective Index (1977) name for this compound is 1,2-dibromoethane.* It is also called DBE; sym-dibromoethane, ethylene dibromide; EDB; and glycol dibromide.

Domestic production figures were first reported for 1,2-dibromoethane in 1923 (U.S. Tariff Commission, 1924) and in 1974 U.S. production was approximately 330 million pounds (U.S. International Trade Commission, 1976). Although more than 200 million pounds of the 1974 domestic production were utilized in tetraalkyl lead antiknock formulations, consumption of 1,2-dibromoethane via this application has been declining since the early 1970s in response to the decreased use of leaded fuels (Chemical and Engineering News, 1976). The efficacy of application of the compound as a fumigant was first reported in 1925 by Neifert (Spencer, 1973) and it has been used in fumigant mixtures

*The CAS registry number is 106-93-4.

for disinfecting fruits, vegetables, grains, tobacco, seeds, mills, and warehouses (Berck, 1974). There have been more than 100 pesticides registered by the U.S. Environmental Protection Agency which include 1,2-dibromoethane as a constituent (U.S. Environmental Protection Agency, 1975). In determining use of 1,2-dibromoethane as a pesticide, it was estimated that 1 million pounds were used by U.S. farmers in 1971 and 230 thousand pounds were used in California in 1974 to combat insects (California Department of Food and Agriculture, 1975).

The most ubiquitous source of potential exposure of the general population to 1,2-dibromoethane is through inhalation of automobile emissions (i.e., evaporation from the fuel tank and carburetor of vehicles using leaded gasoline). Preliminary air monitoring data revealed 1,2-dibromoethane concentrations of approximately 0.01 ppb in the vicinity of gasoline stations on traffic arteries, 0.1 ppb at an oil refinery, and 10 to 15 ppb at 1,2-dibromoethane manufacturing sites (U.S. Environmental Protection Agency, 1975); therefore, it is apparent that employees of these enterprises may be exposed to 1,2-dibromoethane. In addition, use of the compound as a fumigant indicates the probable exposure of agricultural workers or those individuals fumigating crops in storage facilities.

1,2-Dibromoethane is a severe irritant, inducing blisters subsequent to dermal exposure. Upon inhalation 1,2-dibromoethane causes

delayed pulmonary lesions and mild central nervous system depression (Gosselin et al., 1976).

Prior to this study, no evidence for the carcinogenicity of 1,2-dibromoethane was found in the literature. The compound has been shown to induce mutations in bacteria, plants, and fruit flies (International Agency for Research on Cancer, 1977).

II. MATERIALS AND METHODS

A. Chemicals

One batch of technical-grade 1,2-dibromoethane (Figure 1) was purchased from Dow Chemical Company by Hazleton Laboratories America, Inc., Vienna, Virginia. The purity of the compound was initially determined at Hazleton Laboratories using gas-liquid chromatography (GLC) internal standard and total-area analyses. GLC analysis, using the internal standard method, revealed the technical-grade compound to be 96.3 percent pure. Using GLC total-area analysis, the 1,2-dibromoethane peak occupied 88.3 percent of the total area, while a second major peak accounted for 10.1 percent, and ten other peaks each accounted for less than 1 percent of the total area.

Second and third purity determinations were performed by Hazleton Laboratories to establish the stability of 1,2-dibromoethane under storage conditions. The second analysis, performed approximately 16 months after the initial analysis and using both GLC internal standard and total-area analyses, indicated that the technical-grade compound was 99.1 percent pure. The third analysis, performed approximately 5 months after the second analysis and using GLC total-area analysis, indicated that the technical-grade 1,2-dibromoethane was 99.6 percent pure. Infrared spectra from both the second and third chemical characterizations were comparable to the spectrum of the analytical standard.

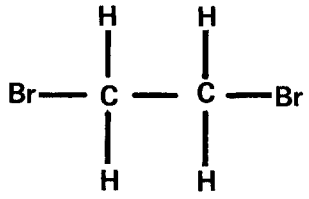


FIGURE 1
CHEMICAL STRUCTURE OF 1,2-DIBROMOETHANE

Although the results of the first GLC total-area analysis disagreed with the manufacturer's stated minimum purity of 99.5 percent (based on the results of a total-area analysis), subsequent stability tests indicated that the purity was over 99 percent.

Throughout this report the term 1,2-dibromoethane is used to represent this technical-grade material.

B. Dosage Preparation

Fresh solutions of 1,2-dibromoethane in Duke's® corn oil (S. F. Sauer Company, Richmond, Virginia) were prepared weekly, sealed, and stored in dark bottles at 1°C. These solutions were considered generally stable for 10 days under the indicated storage conditions. The concentrations of 1,2-dibromoethane in corn oil were 4 percent for the rat bioassay and 1 to 2 percent for the mouse bioassay.

C. Animals

Two animals species, rats and mice, were used in the carcinogenicity bioassay. The Osborne-Mendel rat was selected on the basis of a comparative study of the tumorigenic responsiveness to carbon tetrachloride of five different strains of rats (Reuber and Glover, 1970). The B6C3F1 mouse was selected because it has been used by the NCI for carcinogenesis bioassays and has proved satisfactory in this capacity.

Rats and mice of both sexes were obtained through contracts of the Division of Cancer Treatment, National Cancer Institute. The Osborne-Mendel rats and the B6C3F1 mice were obtained from the Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts. Upon

receipt, animals were quarantined for at least 10 days, observed for visible signs of disease or parasites, and assigned to the various treated and control groups.

D. Animal Maintenance

All animals were housed by species in temperature- and humidity-controlled rooms. The temperature range was 20° to 24°C and the relative humidity was maintained between 45 and 55 percent. The air conditioning system in the laboratory provided filtered air at a rate of 12 to 15 complete changes of room air per hour. Fluorescent lighting was provided on a 12-hour-daily cycle.

The rats were individually housed in suspended galvanized-steel wire-mesh cages with perforated floors, while mice were housed by sex in groups of 10 in solid-bottom polypropylene cages equipped with filter tops. Sanitized cages with fresh bedding (Sanichips®, Pinewood Sawdust Company, Moonachie, New Jersey) were provided once each week for mice. Rats received sanitized cages with no bedding with the same frequency. Food hoppers were changed and heat-sterilized once a week for the first 10 weeks and once a month thereafter. Fresh heat-sterilized glass water bottles and sipper tubes were provided three times a week. Food (Wayne Lab-Blox®, Allied Mills, Inc., Chicago, Illinois) and water were available ad libitum.

Rats treated with 1,2-dibromoethane and the untreated and vehicle control rats were housed in the same room as other rats intubated

with* 1,1,2,2-tetrachloroethane (79-34-5); allyl chloride (107-05-1); carbon tetrachloride (56-23-5); and chloroform (67-66-3). The mice treated with 1,2-dibromoethane and their controls were housed in the same room as other mice intubated with 1,1,2,2-tetrachloroethane (79-34-5); chloroform (67-66-3); allyl chloride (107-05-1); chloropicrin (76-06-2); dibromochloropropane (96-12-8); 1,2-dichloroethane (107-06-2); 1,1-dichloroethane (75-34-3); trichloroethylene (79-01-6); 3-sulfolene (77-79-2); iodoform (75-47-8); methylchloroform (71-55-6); 1,1,2-trichloroethane (79-00-5); tetrachloroethylene (127-18-4); carbon disulfide (75-15-0); hexachloroethane (67-72-1); trichlorofluoromethane (75-69-4); and carbon tetrachloride (56-23-5).

E. Gastric Intubation

Intubation was performed for five consecutive days per week on a mg/kg body weight basis utilizing the most recently observed group mean body weight as a guide for determining the dose. Mean body weights for each group were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. All animals of one sex within a treated group received the same dose. Animals were gavaged with test solutions under a hood to minimize extraneous exposure of other animals and laboratory personnel to the chemical.

F. Selection of Initial Dose Levels

In order to establish the maximum tolerated dosages of 1,2-dibromoethane for administration to treated animals in the chronic studies, subchronic toxicity tests were conducted with both rats and mice.

*CAS registry numbers are given in parentheses.

Animals of each species were distributed among six groups, each consisting of five males and five females. 1,2-Dibromoethane mixed with corn oil was introduced by gavage to five of the six rat groups and five of the six mouse groups at dosages of 40, 63, 100, 163, and 251 mg/kg/day. The sixth group of each species served as a control group, receiving only the corn oil by gavage. Intubation was performed 5 consecutive days per week for 6 weeks, followed by a 2-week observation period to detect any delayed toxicity.

A dosage inducing no mortality and resulting in a depression in mean group body weight of approximately 20 percent relative to controls was selected as the initial high dose. When weight gain criteria were not applicable, mortality data alone were utilized.

At 63 mg/kg/day none of the rats died during the 8-week period. At dosages of 100 mg/kg/day one male and one female rat died. Mean group body weight of dosed rats at the end of the 8-week period was within 10 percent of that of control rats at dosages of 63 mg/kg/day or less. At dosages of 100 mg/kg/day mean body weight for male rats was 75 percent that of controls, and for female rats, was 82 percent of that for controls. The initial high dose selected for use in the chronic bioassay was 80 mg/kg/day for male and female rats.

All the male mice receiving dosages of 159 mg/kg/day or less survived the 8-week study. All female mice survived except one treated with 100 mg/kg/day and two receiving 251 mg/kg/day. At dosages of 159 mg/kg/day or less mean body weight in treated mice

was greater than that in control mice, except in males receiving 63 and 159 mg/kg/day. Mean body weight was 71 and 91 percent that of controls in males treated with 63 and 159 mg/kg/day, respectively. The initial high dose selected for use in the chronic bioassay was 120 mg/kg/day for male and female mice.

G. Experimental Design

The experimental design parameters for the chronic study (species, sex, group size, dosages administered, duration of treated and untreated observation periods, and the time-weighted average dosages) are summarized in Tables 1 and 2.

The treated and vehicle control rats were placed on test simultaneously and were all approximately 8 weeks old at the time the experiment began. The untreated control rats were placed on test 15 weeks later at the age of 5 weeks. Intubation was performed 5 consecutive days per week. The initial doses utilized for male and female rats were 80 and 40 mg/kg/day. Throughout this report those rat groups initially receiving the formed dosage are referred to as the high dose groups, while those rat groups initially receiving the latter dosage are referred to as the low dose groups. In week 17 intubation of the high dose rats was discontinued as a result of the deaths of 18 high dose males and 20 high dose females during or immediately after intubation in week 15. During the 13 weeks when 1,2-dibromoethane dosing was suspended, the high dose rats received no corn oil intubations. In week 30 the high dose rats were again

TABLE 1

DESIGN SUMMARY FOR OSBORNE-MENDEL RATS
1,2-DIBROMOETHANE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	1,2-DIBROMO-ETHANE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE OVER WEEKS OF TEST PERIOD[b]
MALE					
UNTREATED CONTROL	20	--	--	107	--
VEHICLE CONTROL	20	0	49	14	0
LOW DOSE	50	40	41		38
		40[c]	6	2	
HIGH DOSE	50	80	16		41
		0		13	
		40	12		
		40[c]	6	2	
FEMALE					
UNTREATED CONTROL	20	--	--	107	--
VEHICLE CONTROL	20	0	61	2	0
LOW DOSE	50	40	41		37
		40[c]	16	4	
HIGH DOSE	50	80	16		39
		0		13	
		40	12		
		40[c]	16	4	

[a] Dosages, given in mg/kg body weight, were administered by gavage 5 consecutive days per week.

[b] Time-weighted average dosage = $\frac{\Sigma \text{ (dosage X weeks received)}}{\Sigma \text{ (weeks of test period)}}$

Male rats were on test for 49 weeks and female rats were on test for 61 weeks.

[c] These dosages were cyclically administered with a pattern of 1 dosage-free week followed by 4 weeks (5 days per week) of dosage at the level indicated.

TABLE 2

DESIGN SUMMARY FOR B6C3F1 MICE
1,2-DIBROMOETHANE GAVAGE EXPERIMENT

	INITIAL GROUP SIZE	1,2-DIBROMO-ETHANE DOSAGE[a]	OBSERVATION PERIOD TREATED (WEEKS)	OBSERVATION PERIOD UNTREATED (WEEKS)	TIME-WEIGHTED AVERAGE DOSAGE[b]
MALE					
UNTREATED CONTROL	20	--	--	78	--
VEHICLE CONTROL	20	0	53	6	0
LOW DOSE	50	60	10		62
		100	2		
		60	41		
		0		25	
HIGH DOSE	50	120	10		107
		200	2		
		120	27		
		60	14		
		0		24	
FEMALE					
UNTREATED CONTROL	20	--	--	90	--
VEHICLE CONTROL	20	0	53	7	0
LOW DOSE	50	60	10		62
		100	2		
		60	41		
		0		37	
HIGH DOSE	50	120	10		107
		200	2		
		120	27		
		60	14		
		0		25	

[a] Dosages, given in mg/kg body weight, were administered by gavage 5 consecutive days per week.

[b] Time-weighted average dosage = $\frac{\Sigma \text{ (dosage X weeks received)}}{\Sigma \text{ (weeks receiving chemical)}}$

intubated, but this time at the same dosage that the low dose animals were receiving. In week 42 all intubations of low and high dose rats ceased for 1 week followed by 4 weeks of dose administration. All surviving treated male rats were sacrificed in week 49; all surviving treated females were sacrificed in week 61. For both males and females the surviving vehicle control rats were sacrificed in week 63. Corn oil gavage of male vehicle controls was suspended after 49 weeks, followed by a 14-week observation period. Gavage of female vehicle controls was suspended after 61 weeks, followed by a 2-week observation period. There were no untreated observation periods for dosed rats.

The treated and control mice were all approximately 5 weeks old at the time the bioassay was started. Intubation was performed 5 consecutive days per week. The initial dosages utilized for male and female mice were 120 and 60 mg/kg/day. Throughout this report those mice initially receiving the former dosage are referred to as the high dose groups, while those mice initially receiving the latter dosage are referred to as the low dose groups. In week 11 high and low dosages for both sexes were increased to 200 and 100 mg/kg/day, respectively. In week 13 dosages for all mice were decreased to initial levels. In week 40 the dosage administered to the high dose groups was decreased to 60 mg/kg/day, the same dosage being administered to the low dose groups. Compound administration to high and low dose mice and corn oil gavage of vehicle controls were discontinued in week 54. All surviving male mice and high dose female mice

were sacrificed by week 78. Low dose females were observed for 37 weeks after intubation ceased.

The untreated controls received no 1,2-dibromoethane or corn oil, while the vehicle controls were intubated with corn oil.

H. Clinical and Histopathologic Examinations

Animals were weighed immediately prior to initiation of the experiment. Body weights, food consumption, and data concerning appearance, behavior, signs of toxic effects, and incidence, size, and location of tissue masses were recorded at weekly intervals for the first 10 weeks and at monthly intervals thereafter. From the first day, all animals were inspected daily for mortality. The presence of tissue masses was determined by observation and palpation of each animal.

A necropsy was performed on each animal regardless of whether it died, was killed when moribund, or was sacrificed at the end of the bioassay. The animals were euthanized by exsanguination under sodium pentobarbital anesthesia, and were immediately necropsied. The histopathologic examination consisted of gross and microscopic examination of major tissues, organs, and gross lesions taken from sacrificed animals and, whenever possible, from animals found dead.

Tissues were preserved in 10 percent buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin prior to microscopic examination. An occasional section was subjected to special staining techniques for more definitive diagnosis.

Slides were prepared from the following tissues: skin, subcutaneous tissue, lungs and bronchi, trachea, bone marrow, spleen, lymph nodes, thymus, heart, salivary gland, liver, gallbladder (mice), pancreas, esophagus, stomach, small intestine, large intestine, kidney, urinary bladder, pituitary, adrenal, thyroid, parathyroid, testis, prostate, seminal vesicle, brain, eye, muscle, uterus, mammary gland, and ovary.

A few tissues were not examined for some animals, particularly for those that died early. Also, some animals were missing, cannibalized, or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation. Thus, the number of animals for which particular organs, tissues, or lesions were examined microscopically varies and does not necessarily represent the number of animals that were placed on experiment in each group.

I. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the statistical techniques described in this section. Those analyses of the experimental results

that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) when testing two groups for equality and used Tarone's (1975) extensions of Cox's methods when testing a dose-related trend. One-tailed P-values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P-value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site was examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970, pp. 48-52) was used to compare the tumor incidence of a control group to that of a group of treated animals at each dose level. When results for a number of treated groups, k, are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966, pp. 6-10) requires that the P-value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the narrative section. It is not, however, presented in the tables, where the Fisher exact P-values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971, pp. 362-365), was also used when appropriate. Under the assumption of a linear trend, this test determined if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend was a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first

tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which animals died naturally or were sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity ($P < 0.05$, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a treated group of animals

and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a treated group and the proportion in a control group corresponds to a relative risk of unity. Values in excess of unity represent the condition of a larger proportion in the treated group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95 percent of a large number of identical experiments, the true ratio of the risk in a treated group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (a $P < 0.025$ one-tailed test when the control incidence is not zero, $P < 0.050$ when the control incidence is zero) has occurred. When the lower limit is less than unity but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical which could not be detected under the conditions of this test.

III. CHRONIC TESTING RESULTS: RATS

A. Body Weights and Clinical Observations

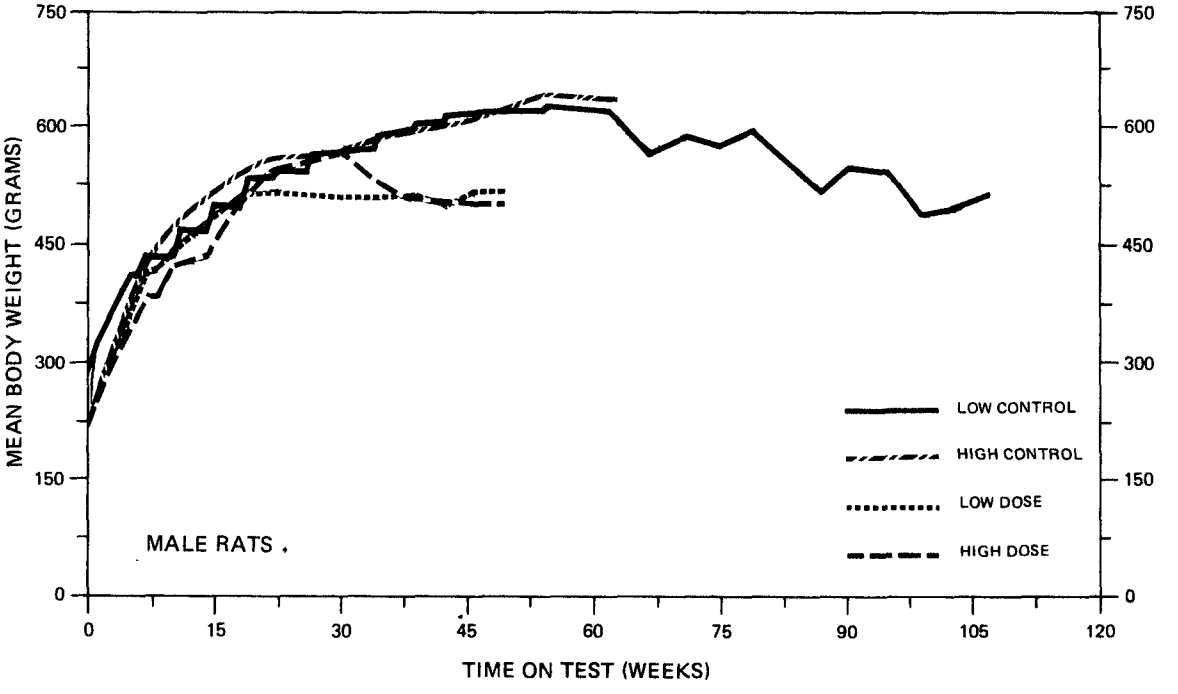
Compound-related mean group body weight depression was apparent in male and female rats after the first 10 weeks of the study (Figure 2). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

Reddened ears and a hunched appearance were observed in all treated groups by week 5. Firm distended abdomens and abdominal urine stains were noted in the treated groups by week 38.

B. Survival

The estimated probabilities of survival for male and female rats in the control and 1,2-dibromoethane-dosed groups are shown in Figure 3.

For male rats the Tarone test for positive association between increased dosage and accelerated mortality was significant ($P < 0.001$). Although the study was originally scheduled to last 110 weeks, the bioassay of male rats was terminated in week 49 due to excessive deaths among both the high dose and low dose treated groups: the remaining 5 high dose and 19 low dose males were sacrificed at that point. In the vehicle control rats, 9 were sacrificed in week 49 and the remaining 9 were sacrificed in week 63. In the untreated control group, 5 males were sacrificed in week 59 and the remaining 4 in week 107. Of the 18 high dose males that died in week



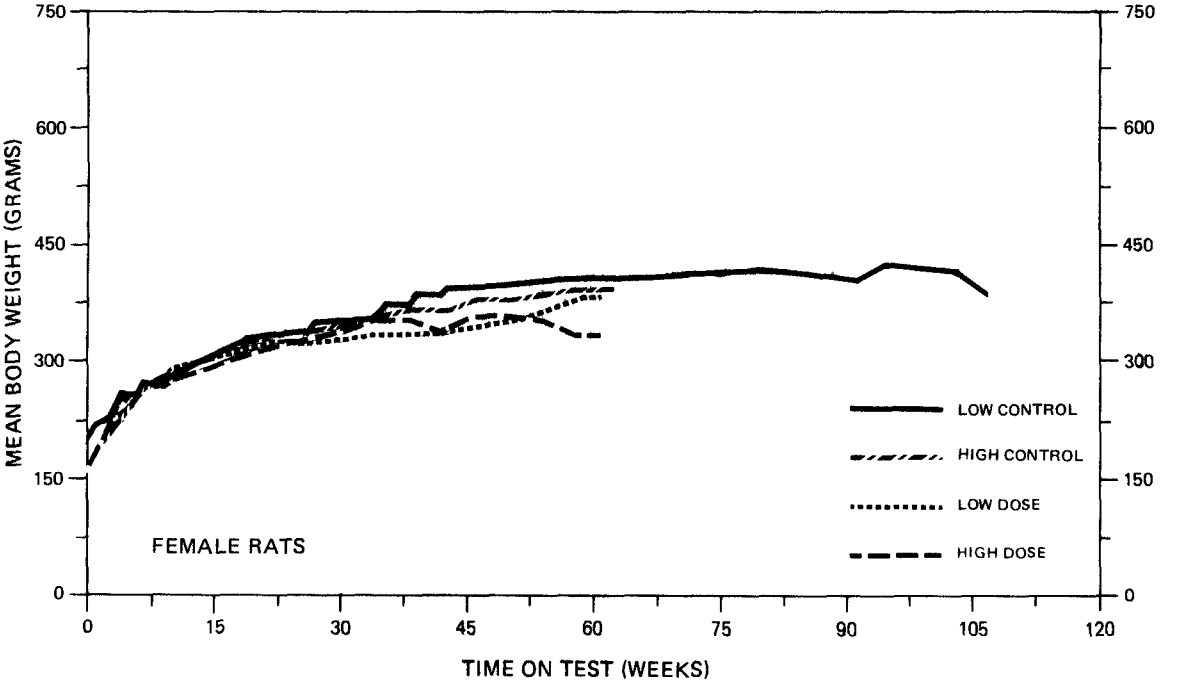
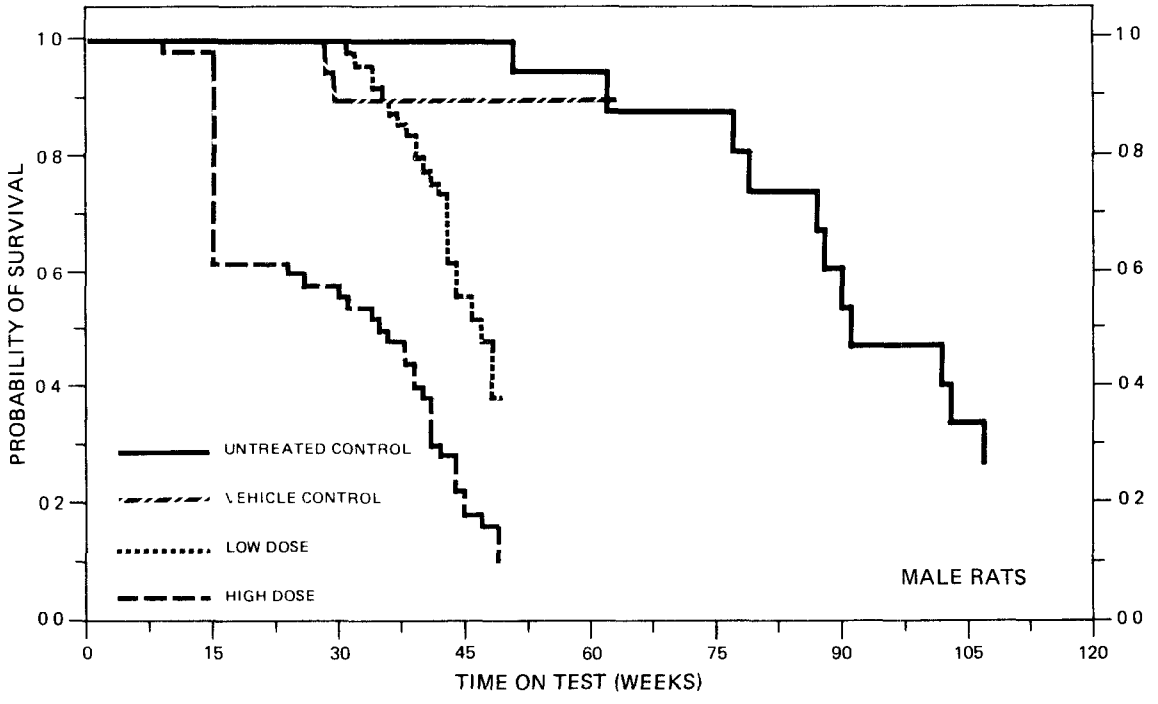


FIGURE 2
GROWTH CURVES FOR 1,2-DIBROMOETHANE CHRONIC STUDY RATS



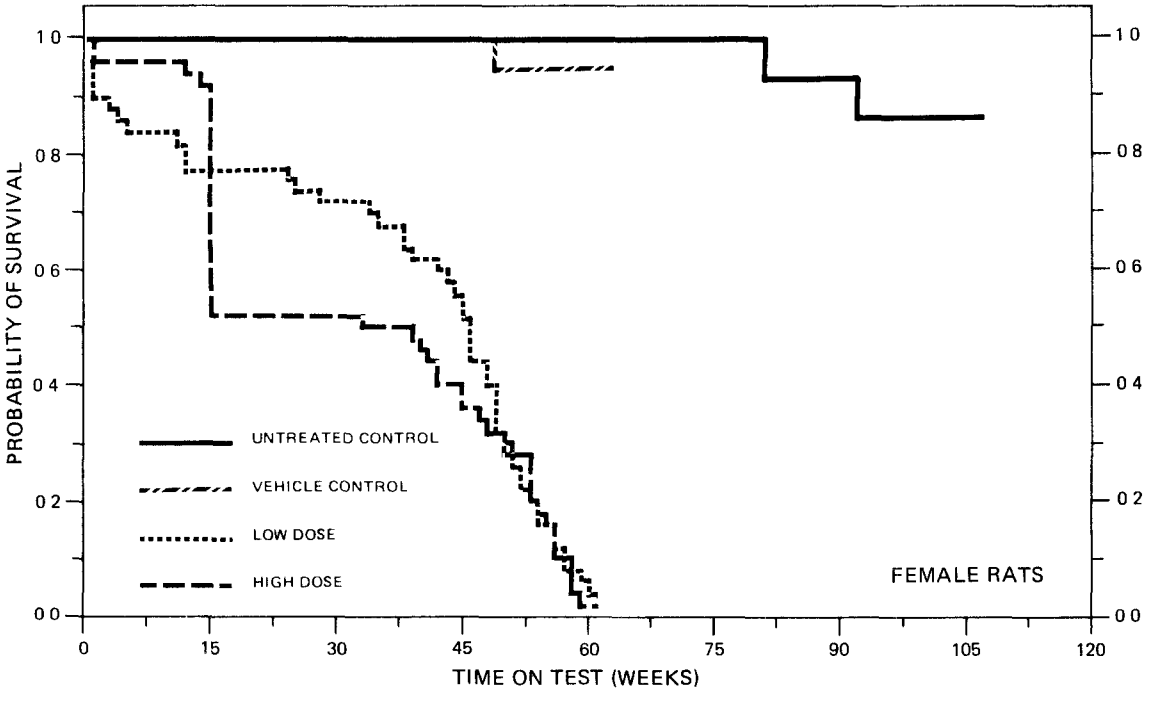


FIGURE 3
SURVIVAL COMPARISONS OF 1,2-DIBROMOETHANE CHRONIC STUDY RATS

15, 11 had both acanthosis and hyperkeratosis of the forestomach. Three rats in the high dose treated group showed evidence of gastric squamous-cell carcinomas as early as week 15. Thirty of the thirty-one high dose male rats living over 15 weeks developed squamous-cell carcinomas of the stomach. A high incidence of early-developing squamous-cell carcinomas was also observed in the low dose treated group but no squamous-cell carcinomas were detected in the stomachs of any of the rats from either control group. Thus, mortality may have been associated with tumor incidence.

For female rats the Tarone test for positive association between increased dosage and accelerated mortality was also significant ($P < 0.001$). In the high dose group, 20/50 females (40 percent) died in week 15 either during intubation or shortly thereafter, suggesting acute toxic reactions. High mortality in both treated groups led to sacrificing all remaining dosed rats in week 61, when the 1 remaining high dose and 2 remaining low dose rats were sacrificed. All of the surviving vehicle control rats were sacrificed in week 63. Five of the untreated control rats were sacrificed in week 59 with the remainder sacrificed in week 107. In the high dose group one rat showed evidence of stomach squamous-cell carcinoma as early as week 12 and two additional high dose rats showed evidence of this tumor in week 15. All females that survived beyond week 15 showed evidence of squamous-cell carcinomas. Results were similar in the low dose rats where the first squamous-cell carcinoma was observed in week 12 and

100 percent of those surviving beyond week 15 showed evidence of this tumor; this tumor was absent in the control groups. Thus, mortality may have been associated with tumor incidence.

C. Pathology

Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2).

Exposure of rats to 1,2-dibromoethane by gavage was associated with a dramatically increased incidence of squamous-cell carcinomas originating in the forestomach in male and female rats. This malignant neoplasm occurred in 45/50 (90 percent) low dose males, 40/50 (80 percent) low dose females, 33/50 (66 percent) high dose males, and 29/50 (58 percent) high dose females. None were observed in untreated or vehicle control animals. Microscopically, these tumors were characterized by acanthosis and hyperkeratosis of squamous epithelium, downward growth of basal epithelium in papillary cords, and sequestered nests of anaplastic cells invading the lamina propria, muscularis mucosa, submucosa, tunica muscularis and serosa of the stomach and spreading to the peritoneal cavity. Metastases, by peritoneal seeding or through blood vessels, were widespread and usually multiple, involving nearly every organ of the abdominal cavity in some animals. Several tumors metastasized to the lung.

An increased incidence of hepatic neoplastic nodules and carcinomas also occurred in treated animals. In animals fed high doses,

1/50 (2 percent) males and 1/48 (2 percent) females had neoplastic nodules; and 1/50 (2 percent) males and 5/48 (10 percent) females had hepatocellular carcinomas. In animals fed low doses, 2/50 (4 percent) males had neoplastic nodules and 1/50 (2 percent) males and 1/47 (2 percent) females had hepatocellular carcinomas. In untreated animals, 1/20 (5 percent) females had hepatocellular carcinoma, while no hepatic neoplasms were observed in the vehicle control groups. These neoplasms occurred in numbers greater than anticipated for Osborne-Mendel rats as a group, particularly in the high dose females; consequently, these lesions are considered to be related to the intake of 1,2-dibromoethane.

An increased incidence of hemangiosarcomas was observed in treated animals. This malignant neoplasm occurred in the spleen of 10/50 (20 percent) low dose and 3/49 (6 percent) high dose males and 1/49 (2 percent) low dose and 3/48 (6 percent) high dose females. A small number of other primary sites in male rats were involved: liver, 3/50 (6 percent) low dose and 1/50 (2 percent) high dose; pancreas, 2/49 (4 percent) low dose; kidney, 1/50 (2 percent) high dose; and abdominal cavity, 1/50 (2 percent) high dose. Microscopically, most appeared as large cavernous structures although some were small and highly cellular, forming slit-like vascular clefts lined by large anaplastic mesenchymal cells.

Induction of nonneoplastic lesions by 1,2-dibromoethane was recognized in several instances. In animals receiving high doses,

hyperkeratosis and acanthosis of the forestomach in 12/50 (24 percent) males and 18/50 (36 percent) females were observed, while 4/50 (8 percent) low dose females and 1/20 (5 percent) untreated females had this change. This is considered to be part of the spectrum of induced lesions of the forestomach. Also, degenerative changes in the liver (peliosis hepatis) and adrenal gland (cortical-cell degeneration) were observed in a small number of treated males and females. Early development of testicular atrophy was observed in dosed rats.

Results of this histopathologic examination indicate that administration of 1,2-dibromoethane was carcinogenic in male and female Osborne-Mendel rats, inducing squamous-cell carcinomas of the forestomach in both sexes, hemangiosarcomas (primarily of the spleen) in males and hepatocellular carcinomas in females.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in rats are summarized in Tables 3 and 4. The analysis is included for every type of tumor in either sex where at least two such tumors were observed in at least one of the control or 1,2-dibromoethane-dosed groups and where such tumors were observed in at least 5 percent of the group.

In both male and female rats significant incidences of stomach squamous-cell carcinomas (often with metastases) were observed. For both sexes the Cochran-Armitage tests indicated significant ($P < 0.001$) positive associations between dosage and tumor incidence.

TABLE 3

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE RATS TREATED WITH 1,2-DIBROMOETHANE[a]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Circulatory System: Hemangiosarcoma[b]	0/20(0.00)	11/50(0.22)	4/50(0.08)
P Values[c]	N.S.	P = 0.017	N.S.
Departure from Linear Trend[e]	P = 0.006	---	---
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	1.384	0.386
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	31	26
Liver: Hepatocellular Carcinoma or Neoplastic Nodule[b]	0/20(0.00)	3/50(0.06)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.250	0.123
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	48	47
Stomach: Squamous-Cell Carcinoma[b]	0/20(0.00)	45/50(0.90)	33/50(0.66)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P < 0.001	---	---
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	6.636	4.627
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	31	15

TABLE 3 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Kidney: Hamartoma* or Mixed Tumor Malignant[b]	0/20(0.00)	2/49(0.04)	4/50(0.08)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.125	0.386
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	37	41
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b]	0/20(0.00)	5/50(0.10)	8/49(0.16)
P Values[c]	P = 0.042	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.525	0.972
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	44	15

*This is considered to be a benign form of the malignant mixed tumor of the kidney and consists of proliferative lipocytes, tubular structures, fibroblasts, and vascular spaces in varying proportions.

TABLE 3 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 38 or 41 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated groups(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 4

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE RATS TREATED WITH 1,2-DIBROMOETHANE[a]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Circulatory System: Hemangiosarcoma[b]	0/20(0.00)	1/49(0.02)	3/48(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.023	0.261
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	38	42
Liver: Hepatocellular Carcinoma[b]	0/20(0.00)	1/47(0.02)	5/48(0.10)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.023	0.547
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	61	33
Liver: Hepatocellular Carcinoma or Neoplastic Nodule[b]	0/20(0.00)	1/41(0.02)	6/48(0.13)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.027	0.695
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	61	33

TABLE 4 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Stomach: Squamous-Cell Carcinoma[b]	0/20(0.00)	40/50(0.80)	29/50(0.58)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P < 0.001	---	---
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	5.737	4.021
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	12	12
Adrenal: Cortical Adenoma or Cortical Carcinoma[b]	0/20(0.00)	0/44(0.00)	4/45(0.09)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	---	Infinite
Lower Limit	---	---	0.429
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	47
Mammary Gland: Adenoma NOS or Adeno-carcinoma NOS[b]	1/20(0.05)	0/50(0.00)	2/50(0.04)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	0.000	0.800
Lower Limit	---	0.000	0.045
Upper Limit	---	7.475	46.273
Weeks to First Observed Tumor	---	---	33

TABLE 4 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Adenoma NOS or Fibroadenoma[b]	0/20(0.00)	0/50(0.00)	3/50(0.06)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	---	Infinite
Lower Limit	---	---	0.250
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	33

[a]Treated groups received time-weighted average doses of 37 or 39 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

For both male and female rats the Fisher exact tests supported these findings with significant ($P < 0.001$) comparisons of both high and low dose to control. Based upon these results, the administration of 1,2-dibromoethane was associated with an increased incidence of squamous-cell carcinomas of the stomach in both male and female rats.

Because of the early mortality noted in treated rats, additional, time-adjusted analyses were conducted for selected tumors. These analyses, which included only those rats surviving at least until the time of the appearance of the first tumor of that type, are included in Tables 5 and 6.

For females when incidences were combined so that the numerator represented rats with either a hepatocellular carcinoma or a neoplastic nodule of the liver, the Cochran-Armitage test using the time-adjusted incidences showed a significant ($P = 0.014$) positive association between dosage and tumor incidence. This was supported by a significant ($P = 0.022$) Fisher exact test comparison of high dose to vehicle control. Based upon these results, the administration of 1,2-dibromoethane was associated with the combined incidence of hepatocellular carcinomas and neoplastic nodules of the liver in female rats.

In male rats the incidence of hemangiosarcomas was increased in the low dose group compared to the controls. For the time-adjusted data the Fisher exact test showed a significant ($P = 0.018$) comparison of the low dose group to the vehicle control. The Cochran-Armitage test, however, was not significant. Although the incidence rate in

TABLE 5

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE RATS TREATED WITH 1,2-DIBROMOETHANE[a]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma or Neoplastic Nodule[b,e]	0/18(0.00)	3/26(0.12)	2/9(0.22)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.438	0.627
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	48	47
Kidney: Hamartoma* or Mixed Tumor Malignant[b,e]	0/18(0.00)	2/44(0.05)	4/28(0.14)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.126	0.628
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	37	41
Circulatory System: Hemangiosarcoma[b,e]	0/20(0.00)	11/50(0.22)	4/27(0.15)
P Values[c]	N.S.	P = 0.018	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	1.384	0.718
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	31	26

*This is considered to be a benign form of the malignant mixed tumor of the kidney and consists of proliferative lipocytes, tubular structures, fibroblasts, and vascular spaces in varying proportions.

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Thyroid: Follicular-Cell Adenoma or Follicular-Cell Carcinoma[b,e]	0/20(0.00)	5/50(0.10)	8/48(0.17)
P Values[c]	P = 0.040	N.S.	N.S.
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.525	0.992
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	44	15

[a]Treated groups received time-weighted average doses of 38 or 41 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]These analyses were based solely upon animals surviving at least 52 weeks, except for sites where the first tumor of interest was observed earlier than 52 weeks in any group of this sex and species, where the analyses were based upon all animals that survived until or past the date that the first tumor was observed.

TABLE 6

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE RATS TREATED WITH 1,2-DIBROMOETHANE[a]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b,f]	0/20(0.00)	1/35(0.03)	5/25(0.20)
P Values[c]	P = 0.028	N.S.	P = 0.043
Departure from Linear Trend[e]	P = 0.016	---	---
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.032	1.058
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	61	33
Liver: Hepatocellular Carcinoma or Neoplastic Nodule[b,f]	0/20(0.00)	1/35(0.03)	6/25(0.24)
P Values[c]	P = 0.014	N.S.	P = 0.022
Departure from Linear Trend[e]	P = 0.006	---	---
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.032	1.345
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	61	33
Adrenal: Cortical Adenoma or Cortical Carcinoma[b,f]	0/20(0.00)	0/19(0.00)	4/17(0.24)
P Values[c]	N.S.	N.S.	P = 0.036
Departure from Linear Trend[e]	P = 0.008	---	---
Relative Risk (Vehicle Control)[d]	---	---	Infinite
Lower Limit	---	---	1.150
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	47

TABLE 6 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 37 or 39 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

[f]These analyses were based solely upon animals surviving at least 52 weeks, except for sites where the first tumor of interest was observed earlier than 52 weeks in any group of this sex and species, where the analyses were based upon all animals that survived until or past the date that the first tumor was observed.

the high dose was 4/27 (15 percent) compared to 0/20 in the control, the high dose to control Fisher exact test was not significant.

In female rats increases in the combined incidence of cortical adenomas or cortical carcinomas of the adrenal gland were observed. Neither the Cochran-Armitage test nor the Fisher exact tests, however, were significant under the Bonferroni criterion.

In male rats the treated groups showed an increased incidence of thyroid tumors. For the time-adjusted statistical analysis, the Cochran-Armitage test showed a significant ($P = 0.040$) positive association between dosage and the combined incidence of follicular-cell adenomas or follicular-cell carcinomas of the thyroid.

IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

Dose-related mean body weight depression was apparent in both male and female mice from week 10 through the remainder of the bioassay (Figure 4). Fluctuations in the growth curve may be due to mortality; as the size of the group diminishes, the mean body weight may be subject to wide variations.

In week 7 alopecia was observed among treated animals. Nine high dose males and 13 high dose females died between weeks 12 and 14 and at that time all surviving animals had soft feces, alopecia, and body sores. These observations, as well as a thin, hunched appearance, increased in high dose groups as the study progressed. In week 42 small inguinal nodules were observed on some of the low dose males.

B. Survival

The estimated probabilities of survival for male and female mice in the control and 1,2-dibromoethane-dosed groups are shown in Figure 5.

For male mice the Tarone test for positive association between increased dosage and accelerated mortality was significant ($P < 0.001$). Due to excessive deaths among the treated animals, the study was terminated in week 78: only 20 percent (10/50) of the high dose and 40 percent (20/50) of the low dose mice survived for at least 58 weeks. The 18/20 vehicle control mice (90 percent) surviving to week 59 were sacrificed at that time. Mortality was somewhat higher than

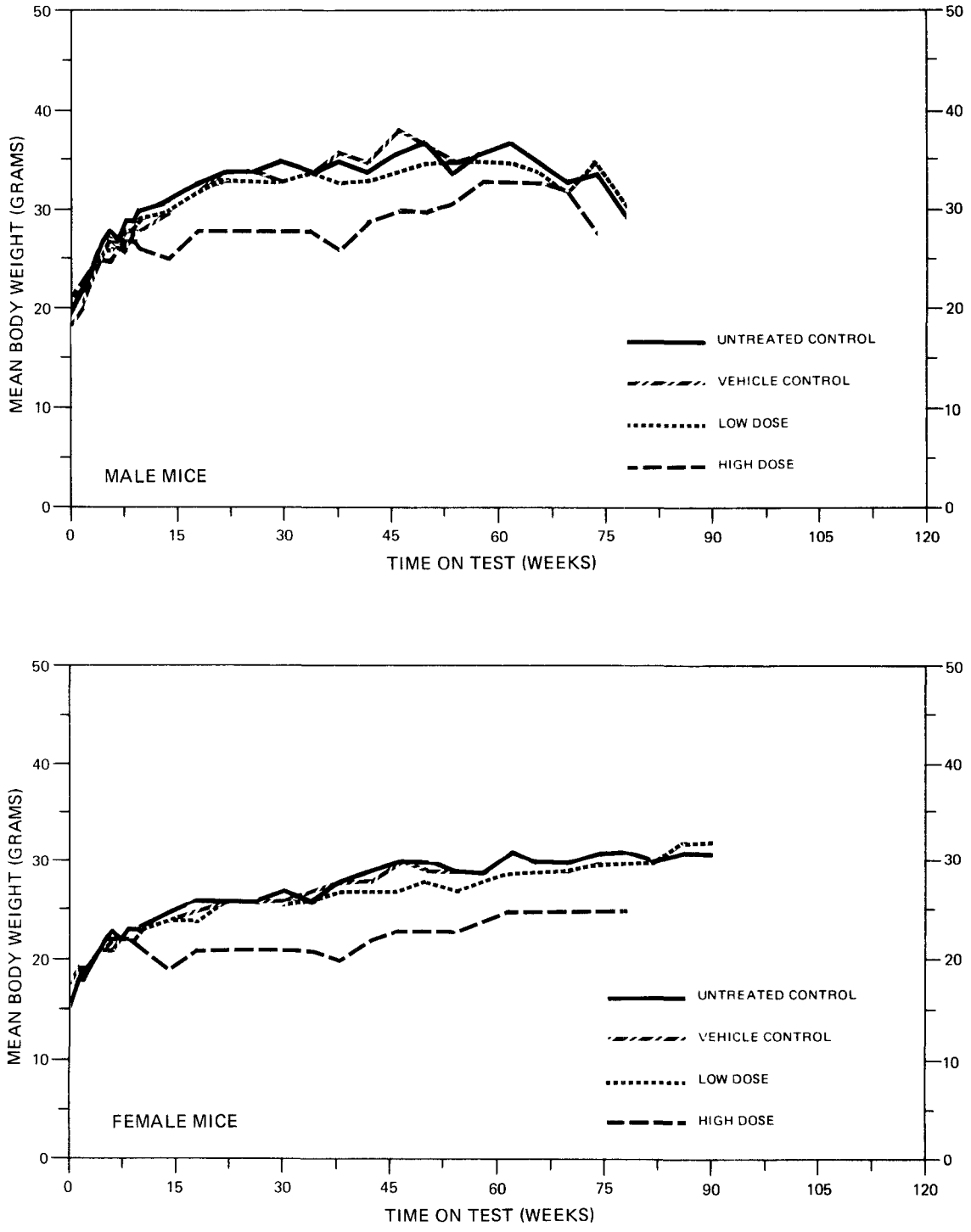
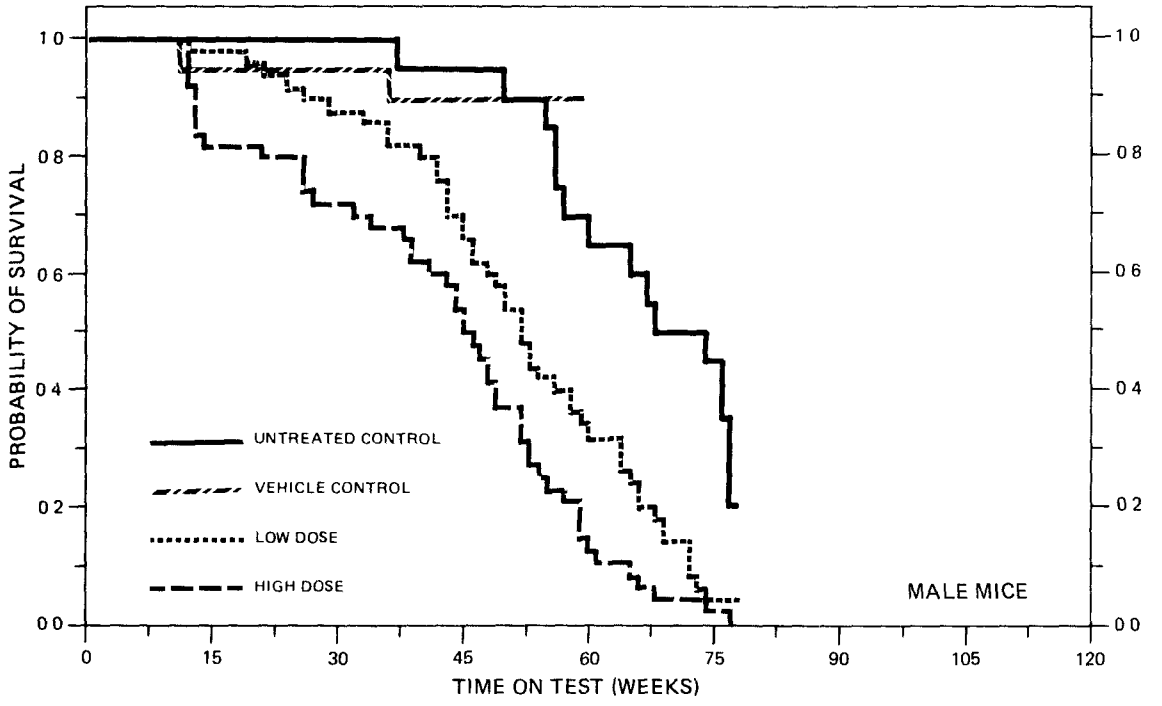


FIGURE 4
GROWTH CURVES FOR 1,2-DIBROMOETHANE CHRONIC STUDY MICE



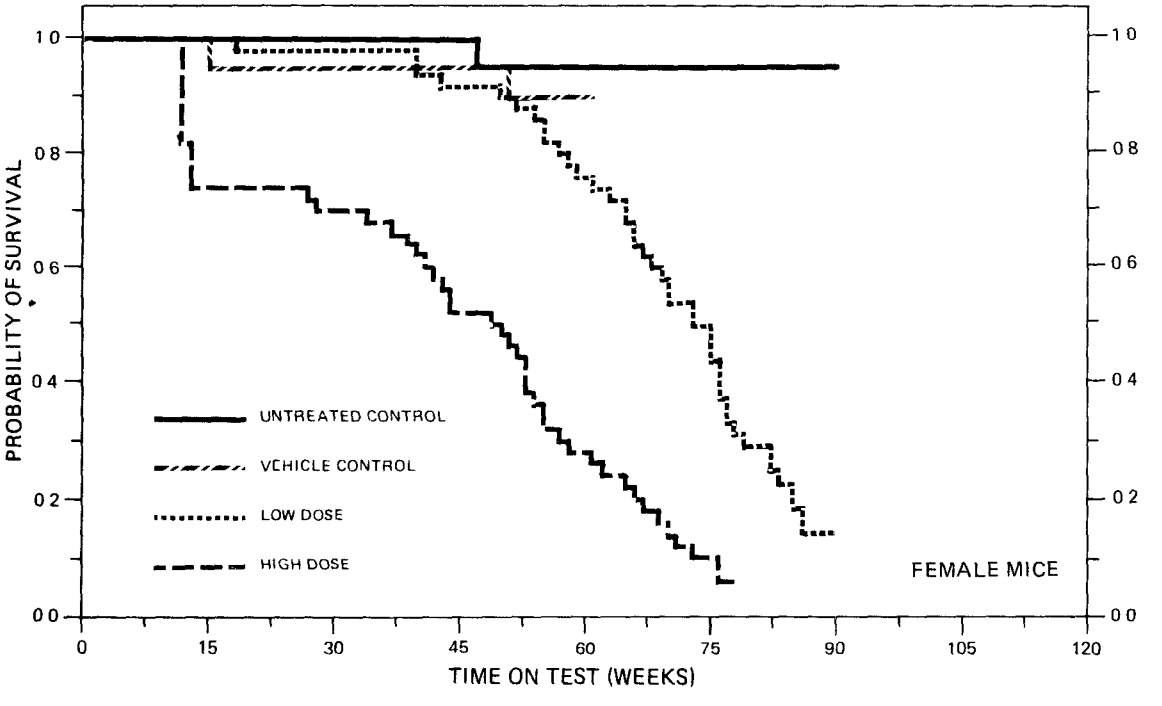


FIGURE 5
SURVIVAL COMPARISONS OF 1,2-DIBROMOETHANE CHRONIC STUDY MICE

expected among the untreated controls, with only 70 percent (14/20) remaining alive by week 58. Seventy-eight percent (31/40) of the high dose males and 92 percent (42/46) of the low dose males surviving at least 26 weeks developed a squamous-cell carcinoma of the forestomach. This tumor was not observed in male mice of either control group.

For female mice the Tarone test showed a significant ($P < 0.001$) positive association between dosage and mortality. The high dose group was terminated in week 78, while the low dose group was not terminated until week 90. Sixteen percent (8/50) of the high dose, 56 percent (28/50) of the low dose, and 95 percent (19/20) of the untreated control animals survived at least 70 weeks. The 18 vehicle controls (90 percent) remaining alive in week 58 were sacrificed in weeks 59 and 60. Seventy-six percent (28/37) of the high dose female mice alive in week 14 developed a squamous-cell carcinoma of the forestomach. In the low dose group, all mice surviving longer than week 18 for which tissues were available for examination developed a forestomach squamous-cell carcinoma. No control mice developed this tumor.

C. Pathology

Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2).

Exposure of mice to 1,2-dibromoethane by gavage was associated with a dramatically increased incidence of squamous-cell carcinomas of the forestomach of male and female mice. This malignant gastric neoplasm was observed in 29/49 (59 percent) high dose males, 28/50 (56 percent) high dose females, 45/50 (90 percent) low dose males, and 46/49 (94 percent) low dose females; none were observed in the untreated or vehicle controls. The microscopic appearance and distribution of metastases of this neoplasm to the peritoneal cavity and lung were similar to those described in rats. In addition, squamous-cell papillomas of the forestomach were recognized in 2/49 (4 percent) high dose males and 1/49 (2 percent) low dose females that did not have carcinomas. These are considered to be part of the spectrum of induced gastric lesions.

Increased numbers of primary lung neoplasms were also noted in treated animals. Alveolar/bronchiolar adenomas occurred in 10/47 (21 percent) high dose males, 6/46 (13 percent) high dose females, 4/45 (9 percent) low dose males, and 10/43 (23 percent) low dose females. Additionally, an alveolar/bronchiolar carcinoma occurred in 1/43 (2 percent) low dose females. No pulmonary neoplasms were observed in control mice; consequently, the tumors are considered to be compound-related.

Nonneoplastic lesions related to intake of 1,2-dibromoethane were observed in several instances. In the forestomach, acanthosis was recognized in 5/49 (10 percent) high dose males, 9/50 (18 percent) high

dose females, and 1/50 (2 percent) low dose males. Hyperkeratosis occurred in the stomach of 13/49 (27 percent) high dose males, 12/50 (24 percent) high dose females, and 1/49 (2 percent) low dose females. These two related changes are considered to be part of the spectrum of gastric lesions induced by 1,2-dibromoethane.

Additionally, testicular atrophy related to compound administration occurred in males receiving high doses.

The histopathologic examination indicated that under the conditions of this experiment administration of 1,2-dibromoethane was carcinogenic in male and female B6C3F1 mice, inducing squamous-cell carcinomas of the forestomach and pulmonary adenomas.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 7 and 8. The analysis is included for every type of tumor in either sex where at least two such tumors were observed in at least one of the control or 1,2-dibromoethane-dosed groups and where such tumors were observed in at least 5 percent of the group.

In both male and female mice significant incidences of stomach squamous-cell carcinomas (often with metastases) were observed. For both sexes the Cochran-Armitage tests indicated significant ($P < 0.011$) positive associations between dosage and tumor incidence using either the untreated or the vehicle controls. The Fisher exact tests confirmed these findings with significant ($P < 0.001$) comparisons of

TABLE 7

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN MALE MICE TREATED WITH 1,2-DIBROMOETHANE[a]

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	3/20(0.15)	0/20(0.00)	1/50(0.02)	2/49(0.04)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.025	---	---	---
Relative Risk (Untreated Control)[d]	---	---	0.133	0.272
Lower Limit	---	---	0.003	0.025
Upper Limit	---	---	1.568	2.233
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.022	0.125
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	76	---	72	59
Lung: Alveolar/Bronchiolar Adenoma[b]	0/18(0.00)	0/20(0.00)	4/45(0.09)	10/47(0.21)
P Values[c]	P = 0.011	P = 0.009	N.S.	P = 0.029* P = 0.021**
Relative Risk (Untreated Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.389	1.197
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.429	1.320
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	58	26

TABLE 7 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Stomach: Squamous-Cell Carcinoma[b]	0/20(0.00)	0/20(0.00)	45/50(0.90)	29/49(0.59)
P Values[c]	P = 0.003	P = 0.003	P < 0.001* P < 0.001**	P < 0.001* P < 0.001**
Departure from Linear Trend[e]	P < 0.001	P < 0.001	---	---
Relative Risk (Untreated Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	6.638	4.108
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	6.638	4.108
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	24	26
Stomach: Squamous-Cell Papilloma or Squamous-Cell Carcinoma[b]	0/20(0.00)	0/20(0.00)	45/50(0.90)	31/49(0.63)
P Values[c]	P = 0.001	P = 0.001	P < 0.001* P < 0.001**	P < 0.001* P < 0.001**
Departure from Linear Trend[e]	P < 0.001	P < 0.001	---	---
Relative Risk (Untreated Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	6.636	4.411
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	6.636	4.411
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	24	26

TABLE 7 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 62 or 107 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage tes6 is given beneath the incidence of tumors in the corresponding control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the untreated control group (*) or the vehicle control group (**) is given beneath the incidence of tumors in that treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

TABLE 8

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH 1,2-DIBROMOETHANE[a]

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Hematopoietic System: Malignant Lymphoma[b]	5/20(0.25)	0/20(0.00)	1/48(0.02)	0/50(0.00)
P Values[c]	P < 0.001	N.S.	P = 0.007*(N)	P < 0.001*(N)
Departure from Linear Trend[e]	P = 0.123	P = 0.226	---	---
Relative Risk (Untreated Control)[d]	---	---	0.083	0.000
Lower Limit	---	---	0.002	0.000
Upper Limit	---	---	0.690	0.313
Relative Risk (Vehicle Control)[d]	---	---	0.417	0.000
Lower Limit	---	---	0.006	0.000
Upper Limit	---	---	32.057	7.475
Weeks to First Observed Tumor	90	---	85	---
Lung: Alveolar/Bronchiolar Adenoma[b]	0/20(0.00)	0/20(0.00)	10/43(0.23)	6/46(0.13)
P Values[c]	N.S.	N.S.	P = 0.015* P = 0.015**	N.S.
Departure from Linear Trend[e]	P = 0.020	P = 0.020	---	---
Relative Risk (Untreated Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	1.445	0.725
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	1.445	0.725
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	50	49

TABLE 8 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma[b]	0/20(0.00)	0/20(0.00)	11/43(0.26)	6/46(0.13)
P Values[c]	N.S.	N.S.	P = 0.009* P = 0.009**	N.S.
Departure from Linear Trend[e]	P = 0.010	P = 0.010	---	---
Relative Risk (Untreated Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	1.614	0.725
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	1.614	0.725
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	50	49
Stomach: Squamous-Cell Carcinoma[b]	0/20(0.00)	0/20(0.00)	46/49(0.94)	28/50(0.56)
P Values[c]	P = 0.011	P = 0.011	P < 0.001* P < 0.001**	P < 0.001* P < 0.001**
Departure from Linear Trend[e]	P < 0.001	P < 0.001	---	---
Relative Risk (Untreated Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	7.101	3.880
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	7.101	3.880
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	40	34

TABLE 8 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	UNTREATED CONTROL	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Mammary Gland: Adenocarcinoma,NOS[b]	0/20(0.00)	0/20(0.00)	3/48(0.06)	1/50(0.02)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.261	0.022
Upper Limit	---	---	Infinite	Infinite
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.261	0.022
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	---	---	82	54
Uterus: Endometrial Stromal Polyp[b]	1/20(0.05)	0/20(0.00)	1/38(0.03)	3/44(0.07)
P Values[c]	N.S.	N.S.	N.S.	N.S.
Relative Risk (Untreated Control)[d]	---	---	0.526	1.364
Lower Limit	---	---	0.007	0.120
Upper Limit	---	---	40.260	69.919
Relative Risk (Vehicle Control)[d]	---	---	Infinite	Infinite
Lower Limit	---	---	0.029	0.284
Upper Limit	---	---	Infinite	Infinite
Weeks to First Observed Tumor	90	---	90	67

TABLE 8 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 62 or 107 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the corresponding control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the compa rison of a treated group with the untreated control group (*) or the vehicle control group (**) is given beneath the incidence of tumors in that treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

both high and low dose to each control for both male and female mice. A significant ($P < 0.001$) departure from linearity was also observed for both sexes since there was a sharp increase in this tumor incidence in the dosed mice. Based upon these results, the administration of 1,2-dibromoethane was associated with the incidence of squamous-cell carcinomas of the stomach in both male and female mice.

In female mice, the Cochran-Armitage and Fisher exact tests indicated a negative association between dosage and the incidence of malignant lymphomas. This result appears related to the shorter survival of dosed mice.

Because of the poor survival noted in the treated mice and because of the sacrifice of all male and female vehicle control mice (the controls of choice) in weeks 59 and 60, additional, time-adjusted analyses were conducted. In performing these time-adjusted analyses, it was necessary first to adjust for the numerous deaths before the mice had been at risk of developing neoplasms for an adequate period. This was done by including only those mice which survived at least 52 weeks or, if the tumor of interest occurred earlier, at least until the first tumor of that type was observed. Due to the sacrifice of the vehicle controls it was also necessary to adjust for those dosed mice which survived longer than (and hence were at risk longer than) the vehicle controls. When the vehicle controls were sacrificed it was principally because these mice were approaching a moribund stage. To adjust for this problem, only those mice surviving less than 64

weeks were used in these analyses. The results of these analyses are presented in Tables 9 and 10 for selected tumors.

In both male and female mice the incidence of alveolar/bronchiolar adenomas was increased in the treated groups compared to the control groups. Using the time-adjusted analysis for males, the Cochran-Armitage test showed a significant (P = 0.004) positive association between dosage and incidence. This was supported by a significant Fisher exact test result in comparing the high dose to the vehicle control (P = 0.020). For females, using the time-adjusted analysis, the Cochran-Armitage test was also significant (P = 0.018). The Fisher exact test was significant for the comparisons of the high dose to vehicle control (P = 0.024). Historically, corn oil vehicle control B6C3F1 mice at Hazelton Laboratories used in the NCI Carcinogenesis Testing Progam showed incidence levels of 7/180 (4 percent) alveolar/bronchiolar adenomas in males and 6/180 (3 percent) in females. Based on these results, the administration of 1,2-dibromoethane was associated with the incidence of alveolar/bronchiolar adenomas in both male and female B6C3F1 mice.

TABLE 9

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH 1,2-DIBROMOETHANE[a,f]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	0/19(0.00)	1/30(0.03)	8/34(0.24)
P Values[c]	P = 0.004	N.S.	P = 0.020
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.035	1.341
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	58	26
Stomach: Squamous-Cell Carcinoma[b]	0/19(0.00)	29/31(0.94)	24/34(0.71)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P < 0.001	---	---
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	6.743	4.690
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	24	26

TABLE 9 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 62 or 107 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

[f]These time-adjusted analyses include those mice surviving less than 64 weeks but surviving at least as long as the earliest time at which the tumor of interest was observed in any of the groups.

TABLE 10

TIME-ADJUSTED ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN FEMALE MICE TREATED WITH 1,2-DIBROMOETHANE[a,f]

TOPOGRAPHY:MORPHOLOGY	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Adenoma[b]	0/19(0.00)	2/10(0.20)	4/14(0.29)
P Values[c]	P = 0.018	N.S.	P = 0.024
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.592	1.338
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	50	49
Stomach: Squamous-Cell Carcinoma[b]	0/19(0.00)	9/10(0.90)	11/14(0.79)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P = 0.004	---	---
Relative Risk (Vehicle Control)[d]	---	Infinite	Infinite
Lower Limit	---	5.914	5.051
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	40	34

TABLE 10 (CONCLUDED)

[a]Treated groups received time-weighted average doses of 62 or 107 mg/kg by gavage.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when $P < 0.05$; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when $P < 0.05$.

[f]These time-adjusted analyses include those mice surviving less than 64 weeks but surviving at least as long as the earliest time at which the tumor of interest was observed in any of the groups.

V. DISCUSSION

Under the conditions of this bioassay there was a significant positive association between increased dosage and accelerated mortality in rats and mice of both sexes. Although the study was originally designed to last 110 weeks for rats and 90 weeks for mice, these bioassays were terminated early due to poor survival and the early onset of cancer. The accelerated mortality in both species appeared to be associated with cancer of the forestomach. A preliminary report of some of these findings from the same study reported here has already been published (Olson et al., 1973).

In both species there were dramatically increased incidences of squamous-cell carcinomas of the forestomach. These tumors appeared early, invaded locally, and eventually metastasized throughout the abdominal cavity. In addition, hyperkeratosis and acanthosis, considered to be components of the spectrum of chemically induced gastric lesions, were present in many of the high dose rats and mice. In rats squamous-cell carcinomas of the forestomach occurred in 45/50 (90 percent), 33/50 (66 percent), 40/50 (80 percent), and 29/50 (58 percent) of the low dose males, high dose males, low dose females, and high dose females, respectively, and in mice they were detected in 45/50 (90 percent), 29/49 (59 percent), 46/49 (94 percent), and 28/50 (56 percent) of the low dose males, high dose males, low dose females, and high dose females. These lesions were seen as early as week 12 in rats and week 24 in mice. None were observed in untreated or

vehicle control rats or mice. For each sex of both species the Cochran-Armitage tests indicated a significant positive association between dosage and tumor incidence. These associations were substantiated in each case by Fisher exact comparisons of the high and low dose group to both types of controls.

Increased incidences of hepatic lesions (i.e., neoplastic nodules and hepatocellular carcinomas) were observed in dosed rats, particularly among high dose females. When the incidences of hepatocellular carcinoma in females were adjusted to include only those surviving at least until the first hepatocellular carcinoma was observed (33 weeks), the Cochran-Armitage test indicated a significant positive association between dosage and incidence, and this association was substantiated by the high dose to control Fisher exact comparison. Increased incidences of hemangiosarcomas were observed in all dosed rat groups, but the incidence was statistically significant only for low dose males. These lesions appeared as early as week 26 in male rats. That the incidence in the low dose group exceeded that in the high dose group may be due to the higher rate of early deaths among high dose rats.

The incidences of alveolar/bronchiolar adenomas in mice dosed with 1,2-dibromoethane were elevated relative to controls. These pulmonary neoplasms were detected in 4/45 (9 percent) low dose and 10/47 (21 percent) high dose males and in 10/43 (23 percent) low dose and 6/46 (13 percent) high dose females, but in no controls of either

sex. The Cochran-Armitage test indicated significant positive associations between dosage and incidence for male and female mice. These associations were supported by the high dose to control Fisher exact comparisons for both sexes.

Under the conditions of this bioassay 1,2-dibromoethane was carcinogenic to Osborne-Mendel rats and B6C3F1 mice. The compound induced squamous-cell carcinomas of the forestomach in rats of both sexes, hepatocellular carcinomas in female rats and hemangiosarcomas in male rats. In mice of both sexes the compound induced squamous-cell carcinomas of the forestomach and alveolar/bronchiolar adenomas.

VI. BIBLIOGRAPHY

Armitage, P., Statistical Methods in Medical Research, Chapter 14. J. Wiley & Sons, New York, 1971.

Berck, B., "Fumigant Residues of Carbon Tetrachloride, Ethylene Dichloride, and Ethylene Dibromide in Wheat, Flour, Bran, Middlings and Bread." Journal of Agricultural Food Chemistry 22:977-984, 1974.

Berenblum, I., editor, Carcinogenicity Testing. International Union Against Cancer, Technical Report Series, Vol. 2. International Union Against Cancer, Geneva, 1969.

Berg, G.L., editor, Farm Chemicals Handbook, 1976. Meister Publishing Company, Willoughby, Ohio, p. D111, 1976.

California Department of Food and Agriculture, Pesticide Use Report, 1974. Sacramento, California, pp. 77-78, 1975; as cited in IARC, 1977.

Chemical Abstracts Service, The Chemical Abstracts Service (CAS) Ninth Collective Index, Volumes 76-85, 1972-1976. American Chemical Society, Washington, D.C., 1977.

Chemical and Engineering News. "Industry/Business," Vol. 54, p. 9, 1976.

Cox, D.R., Analysis of Binary Data, Chapters 4 and 5. Methuen and Co., Ltd., London, 1970.

Cox, D.R., "Regression Models and Life-Tables." Journal of the Royal Statistical Society, Series "B" 34:187-220, 1972.

Fishbein, L., "Industrial Mutagens and Potential Mutagens: I. Halogenated Aliphatic Derivatives." Mutation Research 32:267-308, 1976.

Gart, J.J.. "The Comparison of Proportions: A Review of Significance Tests, Confidence Limits, and Adjustments for Stratification." International Statistical Institute Review 39:148-169, 1971.

Gosslin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason, Clinical Toxicology of Commercial Products, 4th edition. The Williams and Wilkins Company, Baltimore, Maryland, 1976.

International Agency for Research on Cancer (IARC), IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. Volume 15: Some Fumigants, the Herbicides 2,4-D and 2,4,5-T,

Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals. United Nations World Health Organization, Geneva, Switzerland, pp. 195-209, August 1977.

Kaplan, E.L., and P. Meier, "Nonparametric Estimation from Incomplete Observations." Journal of the American Statistical Association 53:457-481, 1958.

Linhart, M.S., J.A. Cooper, R.L. Martin, N.P. Page, and J.A. Peters, "Carcinogenesis Bioassay Data System." Computers and Biomedical Research 7:230-248, 1974.

Miller, R.G., Simultaneous Statistical Inference. McGraw-Hill Book Co., New York, 1966.

Olson, W.A., R.T. Habermann, E.K. Weisburger, J.M. Ward, and J.H. Weisburger, "Induction of Stomach Cancer in Rats and Mice by Halogenated Aliphatic Fumigants." Journal of the National Cancer Institute 51(6):1993-1995, December 1973.

Reuber, M.D., and E.L. Glover, "Cirrhosis and Carcinoma of the Liver in Male Rats Given Subcutaneous Carbon Tetrachloride." Journal of the National Cancer Institute 44:419-423, 1970.

Saffiotti, U., R. Montesano, A.R. Sellakumar, F. Cefis, and D.G. Kaufman, "Respiratory Tract Carcinogenesis in Hamsters Induced by Different Numbers of Administration of Benzo (a) Pyrene and Ferric Oxide." Cancer Research 32:1073-1079, 1972.

Spencer, E.Y., Guide to the Chemicals Used in Crop Protection, 6th edition. University of Western Ontario, Research Branch, Agriculture Canada, Publication 1093. London, Ontario, p. 263, 1973.

Tarone, R.E., "Tests for Trend in Life-Table Analysis." Biometrika 62:679-682, 1975.

U.S. Environmental Protection Agency, Sampling and Analysis of Selected Toxic Substances, Task II: Ethylene Dibromide, Final Report. Office of Toxic Substances, Washington, D.C., September 1975.

U.S. International Trade Commissin, Synthetic Organic Chemicals, U.S. Production and Sales, 1974. USITC Publication 776, Washington, D.C., 1976.

U.S. Tariff Commission, Census of Dyes and Other Synthetic Organic Chemicals, 1923. Tariff Information Series, No. 32, Washington, D.C., 1924.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS TREATED WITH 1,2-DIBROMOETHANE

TABLE A1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS TREATED WITH 1,2-DIBROMOETHANE (EDB)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-061M	LOW DOSE 01-062M	HIGH DOSE 01-063M
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
FIBROSARCOMA	1 (5%)			
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			5 (10%)	1 (2%)
MIXED TUMOR, METASTATIC				1 (2%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(20)	(50)	(50)
LYMPHOCYTIC LEUKEMIA	1 (5%)			
GRANULOCYTIC LEUKEMIA				1 (2%)
#SPLEEN	(20)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			4 (8%)	10 (20%)
HEMANGIOSARCOMA			10 (20%)	3 (6%)
#MESENTERIC L. NODE	(19)	(20)	(47)	(46)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)	2 (4%)
#THYMUS	(13)	(6)	(32)	(20)
SQUAMOUS CELL CARCINOMA, METASTA			1 (3%)	
THYMOMA				1 (5%)
MIXED TUMOR, METASTATIC				1 (5%)
CIRCULATORY SYSTEM				
*HEART	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-061M	LOW DOSE 01-062M	HIGH DOSE 01-063M
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(14)	(1)		
CARCINOMA,NOS	1 (7%)			
#LIVER	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			18 (36%)	14 (28%)
NEOPLASTIC NODULE			2 (4%)	1 (2%)
HEPATOCELLULAR CARCINOMA			1 (2%)	1 (2%)
MIXED TUMOR, METASTATIC				1 (2%)
HEMANGIOSARCOMA			2 (4%)	1 (2%)
HEMANGIOSARCOMA, METASTATIC			1 (2%)	
#PANCREAS	(20)	(20)	(49)	(46)
SQUAMOUS CELL CARCINOMA, METASTA			10 (20%)	9 (20%)
MIXED TUMOR, METASTATIC				1 (2%)
HEMANGIOSARCOMA			1 (2%)	
HEMANGIOSARCOMA, METASTATIC			1 (2%)	
#ESOPHAGUS	(15)	(16)	(46)	(41)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)	1 (2%)
#STOMACH	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA			45 (90%)	33 (66%)
MIXED TUMOR, METASTATIC				1 (2%)
#SMALL INTESTINE	(20)	(20)	(45)	(43)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)	
ADENOCARCINOMA, NOS				1 (2%)
FIBROSARCOMA	1 (5%)			
#DUODENUM	(20)	(20)	(45)	(43)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	1 (2%)
#COLON	(19)	(20)	(48)	(48)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(49)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			3 (6%)	1 (2%)
MIXED TUMOR, MALIGNANT			1 (2%)	4 (8%)
HEMANGIOSARCOMA				1 (2%)
HAMARTOMA+			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
+ THIS IS CONSIDERED TO BE A BENIGN FORM OF THE MALIGNANT MIXED TUMOR OF THE KIDNEY AND CONSISTS OF PROLIFERATIVE LIPOCYTES, TUBULAR STRUCTURES, FIBROBLASTS, AND VASCULAR SPACES IN VARYING PROPORTIONS.

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-061M	LOW DOSE 01-062M	HIGH DOSE 01-063M
#URINARY BLADDER	(19)	(20)	(49)	(44)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(20)	(20)	(50)	(46)
CHROMOPHOBE ADENOMA	2 (10%)			
#ADRENAL	(20)	(20)	(48)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	2 (4%)
CORTICAL ADENOMA			1 (2%)	
CORTICAL CARCINOMA	2 (10%)		1 (2%)	
MIXED TUMOR, METASTATIC				1 (2%)
#THYROID	(19)	(20)	(50)	(49)
FOLLICULAR-CELL ADENOMA			4 (8%)	7 (14%)
FOLLICULAR-CELL CARCINOMA	1 (5%)		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(50)
ADENOCARCINOMA, NOS	1 (5%)			
FIBROADENOMA	1 (5%)			
#PROSTATE	(20)	(14)	(30)	(20)
SQUAMOUS CELL CARCINOMA, METASTA				1 (5%)
#TESTIS	(20)	(20)	(49)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	1 (2%)
INTERSTITIAL-CELL TUMOR			1 (2%)	
*EPIDIDYMIS	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-061M	LOW DOSE 01-062M	HIGH DOSE 01-063M
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	1 (2%)
BODY CAVITIES				
*MEDIASTINUM	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
*ABDOMINAL CAVITY	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)	
HEMANGIOSARCOMA				1 (2%)
*MESENTERY	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	11	2	28	44
MORIBUND SACRIFICE			3	1
SCHEDULED SACRIFICE	5	9		
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	4	9	19	5
ANIMAL MISSING				

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1 (CONCLUDED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-061M	LOW DOSE 01-062M	HIGH DOSE 01-063M
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	6		46	35
TOTAL PRIMARY TUMORS	11		72	56
TOTAL ANIMALS WITH BENIGN TUMORS	2		6	8
TOTAL BENIGN TUMORS	3		7	8
TOTAL ANIMALS WITH MALIGNANT TUMORS	6		45	34
TOTAL MALIGNANT TUMORS	8		63	47
TOTAL ANIMALS WITH SECONDARY TUMORS#			25	19
TOTAL SECONDARY TUMORS			57	52
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			2	1
TOTAL UNCERTAIN TUMORS			2	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS TREATED WITH 1,2-DIBROMOETHANE (EDB)

	CONTROL(UNTR) 01-031F	CONTROL(VEH) 01-061F	LOW DOSE 01-064F	HIGH DOSE 01-065F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY **	20	20	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(50)	(48)
CARCINOMA, NOS, METASTATIC				1 (2%)
SQUAMOUS CELL CARCINOMA, METASTA			4 (8%)	4 (8%)
HEPATOCELLULAR CARCINOMA, METAST				1 (2%)
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(20)	(49)	(48)
SQUAMOUS CELL CARCINOMA, METASTA			11 (22%)	4 (8%)
HEMANGIOSARCOMA			1 (2%)	3 (6%)
#LYMPH NODE	(20)	(20)	(39)	(39)
SQUAMOUS CELL CARCINOMA, METASTA			3 (8%)	
#MESENTERIC L. NODE	(20)	(20)	(39)	(39)
SQUAMOUS CELL CARCINOMA, METASTA				1 (3%)
CIRCULATORY SYSTEM				
#HEART	(20)	(20)	(50)	(47)
MIXED TUMOR, METASTATIC	1 (5%)			
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(47)	(48)
SQUAMOUS CELL CARCINOMA, METASTA			21 (45%)	12 (25%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-061F	LOW DOSE 01-064F	HIGH DOSE 01-065F
NEOPLASTIC NODULE				1 (2%)
HEPATOCELLULAR CARCINOMA	1 (5%)		1 (2%)	5 (10%)
HEMANGIOSARCOMA, METASTATIC				1 (2%)
*BILE DUCT	(20)	(20)	(50)	(50)
CARCINOMA,NOS				1 (2%)
#PANCREAS	(20)	(20)	(45)	(47)
CARCINOMA, NOS, METASTATIC				1 (2%)
SQUAMOUS CELL CARCINOMA, METASTA			11 (24%)	8 (17%)
#ESOPHAGUS	(15)	(14)	(43)	(41)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	1 (2%)
#STOMACH	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA			40 (80%)	29 (58%)
#SMALL INTESTINE	(20)	(20)	(47)	(46)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(47)	(48)
SQUAMOUS CELL CARCINOMA, METASTA			4 (9%)	4 (8%)
MIXED TUMOR, MALIGNANT	1 (5%)		2 (4%)	1 (2%)
HAMARTOMA +	2 (10%)		1 (2%)	1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(19)	(20)	(39)	(40)
CHROMOPHOBE ADENOMA	6 (32%)	1 (5%)		
#ADRENAL	(20)	(20)	(44)	(45)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	3 (7%)
CORTICAL ADENOMA				2 (4%)
CORTICAL CARCINOMA				2 (4%)
#THYROID	(20)	(20)	(43)	(43)
FOLLICULAR-CELL ADENOMA				1 (2%)
FOLLICULAR-CELL CARCINOMA				1 (2%)
C-CELL ADENOMA	2 (10%)			
C-CELL CARCINOMA	2 (10%)			
#PANCREATIC ISLETS	(20)	(20)	(45)	(47)
ISLET-CELL ADENOMA	1 (5%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
+ THIS IS CONSIDERED TO BE A BENIGN FORM OF THE MALIGNANT MIXED TUMOR OF THE KIDNEY AND CONSISTS OF PROLIFERATIVE LIPOCYTES, TUBULAR STRUCTURES, FIBROBLASTS, AND VASCULAR SPACES IN VARYING PROPORTIONS.

TABLE A2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-061F	LOW DOSE 01-064F	HIGH DOSE 01-065F
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(50)	(50)
ADENOMA, NOS				1 (2%)
ADENOCARCINOMA, NOS	2 (10%)	1 (5%)		1 (2%)
FIBROADENOMA	2 (10%)			2 (4%)
*UTERUS	(20)	(20)	(45)	(45)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)
ENDOMETRIAL STROMAL POLYP		1 (5%)	2 (4%)	1 (2%)
HEMANGIOMA	1 (5%)			
*OVARY/OVIDUCT	(20)	(20)	(45)	(45)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
*OVARY	(20)	(20)	(47)	(48)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
CYSTADENOCARCINOMA, NOS	1 (5%)			
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*MESENTERY	(20)	(20)	(50)	(50)
SQUAMOUS CELL CARCINOMA, METASTA				2 (4%)
ALL OTHER SYSTEMS				
ADIPOSE TISSUE				
SQUAMOUS CELL CARCINOMA, METASTA				2

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2 (CONCLUDED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-061F	LOW DOSE 01-064F	HIGH DOSE 01-065F
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	2		45	49
MORIBUND SACRIFICE		1	3	
SCHEDULED SACRIFICE	5			
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	13	19	2	1
ANIMAL MISSING				
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	14	2	40	29
TOTAL PRIMARY TUMORS	21	3	47	52
TOTAL ANIMALS WITH BENIGN TUMORS	12	2	3	6
TOTAL BENIGN TUMORS	14	2	3	8
TOTAL ANIMALS WITH MALIGNANT TUMORS	6	1	40	29
TOTAL MALIGNANT TUMORS	7	1	44	43
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		29	18
TOTAL SECONDARY TUMORS	1		59	47
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT				1
TOTAL UNCERTAIN TUMORS				1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE TREATED WITH 1,2-DIBROMOETHANE

TABLE B1
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE TREATED WITH 1,2-DIBROMOETHANE (EDB)

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M062	HIGH DOSE 02-M063
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	19	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	20	50	49
INTEGUMENTARY SYSTEM				
*SKIN	(19)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
*SUBCUT TISSUE	(19)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)	1 (2%)
FIBROSARCOMA	1 (5%)			
RESPIRATORY SYSTEM				
#LUNG/BRONCHUS	(18)	(20)	(45)	(47)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)
#LUNG	(18)	(20)	(45)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			3 (7%)	1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA			4 (9%)	10 (21%)
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(19)	(20)	(50)	(49)
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (5%)			
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (5%)			
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)	
GRANULOCYTIC LEUKEMIA	1 (5%)			1 (2%)
#SPLEEN	(19)	(20)	(45)	(33)
SQUAMOUS CELL CARCINOMA, METASTA			18 (40%)	16 (48%)
#BRONCHIAL LYMPH NODE	(18)	(18)	(41)	(32)
SQUAMOUS CELL CARCINOMA, METASTA			5 (12%)	4 (13%)
#MESENTERIC L. NODE	(18)	(18)	(41)	(32)
SQUAMOUS CELL CARCINOMA, METASTA			12 (29%)	7 (22%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M062	HIGH DOSE 02-M063
#STOMACH	(20)	(20)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE				1 (2%)
#THYMUS	(12)	(19)	(37)	(31)
SQUAMOUS CELL CARCINOMA, METASTA			1 (3%)	
CIRCULATORY SYSTEM				
NONE				
DIGESTIVE SYSTEM				
#LIVER	(19)	(20)	(45)	(48)
SQUAMOUS CELL CARCINOMA, METASTA			18 (40%)	20 (42%)
NEOPLASTIC NODULE		1 (5%)		
HEPATOCELLULAR CARCINOMA		1 (5%)	1 (2%)	1 (2%)
*GALLBLADDER	(19)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			4 (8%)	4 (8%)
#PANCREAS	(19)	(19)	(44)	(36)
SQUAMOUS CELL CARCINOMA, METASTA			23 (52%)	24 (67%)
#ESOPHAGUS	(18)		(40)	(45)
SQUAMOUS CELL CARCINOMA, METASTA			1 (3%)	2 (4%)
#STOMACH	(20)	(20)	(50)	(49)
SQUAMOUS CELL PAPILLOMA				2 (4%)
SQUAMOUS CELL CARCINOMA			45 (90%)	29 (59%)
#SMALL INTESTINE	(18)	(19)	(42)	(42)
SQUAMOUS CELL CARCINOMA, METASTA			9 (21%)	4 (10%)
#DUODENUM	(18)	(19)	(42)	(42)
SQUAMOUS CELL CARCINOMA, METASTA				7 (17%)
#LARGE INTESTINE	(19)	(19)	(42)	(40)
SQUAMOUS CELL CARCINOMA, METASTA			4 (10%)	3 (8%)
URINARY SYSTEM				
#KIDNEY	(19)	(20)	(45)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			10 (22%)	5 (11%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M062	HIGH DOSE 02-M063
#URINARY BLADDER	(17)	(19)	(40)	(45)
SQUAMOUS CELL CARCINOMA, METASTA			3 (8%)	6 (13%)
ENDOCRINE SYSTEM				
#ADRENAL	(19)	(20)	(43)	(46)
SQUAMOUS CELL CARCINOMA, METASTA			13 (30%)	16 (35%)
#THYROID	(18)	(20)	(34)	(35)
FOLLICULAR-CELL ADENOMA				1 (3%)
REPRODUCTIVE SYSTEM				
#PROSTATE	(18)	(20)	(37)	(35)
SQUAMOUS CELL CARCINOMA, METASTA			5 (14%)	6 (17%)
*SEMINAL VESICLE	(19)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
#TESTIS	(19)	(20)	(45)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			8 (18%)	14 (30%)
*EPIDIDYMIS	(19)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			10 (20%)	10 (20%)
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
*EYE	(19)	(20)	(50)	(49)
MALIGNANT MELANOMA	1 (5%)			
MUSCOLOSKELETAL SYSTEM				
*RIB	(19)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)	
*MUSCLE OF BACK	(19)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1 (CONTINUED)

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M062	HIGH DOSE 02-M063
*ABDOMINAL MUSCLE	(19)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA			7 (14%)	2 (4%)
BODY CAVITIES				
*MESENTERY	(19)	(20)	(50)	(49)
SQUAMOUS CELL CARCINOMA, METASTA				4 (8%)
ALL OTHER SYSTEMS				
DIAPHRAGM				
SQUAMOUS CELL CARCINOMA, METASTA			4	1
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	16	2	46	49
MORIBUND SACRIFICE			2	
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	4	18	2	
ANIMAL MISSING				1

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1 (CONCLUDED)

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M062	HIGH DOSE 02-M063
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	5	2	45	33
TOTAL PRIMARY TUMORS	5	2	51	45
TOTAL ANIMALS WITH BENIGN TUMORS			4	13
TOTAL BENIGN TUMORS			4	13
TOTAL ANIMALS WITH MALIGNANT TUMORS	5	1	45	30
TOTAL MALIGNANT TUMORS	5	1	47	32
TOTAL ANIMALS WITH SECONDARY TUMORS#			29	26
TOTAL SECONDARY TUMORS			165	158
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1		
TOTAL UNCERTAIN TUMORS		1		
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2
SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE TREATED WITH 1,2-DIBROMOETHANE (EDB)

	CONTROL (UNTR) 02-F061	CONTROL (VEH) 02-F051	LOW DOSE 02-F064	HIGH DOSE 02-F065
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING			1	
ANIMALS NECROPSIED	20	20	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	48	50
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(48)	(50)
SQUAMOUS CELL CARCINOMA, METASTA				1 (2%)
*SUBCUT TISSUE	(20)	(20)	(48)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
FIBROSARCOMA			1 (2%)	1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(43)	(46)
CARCINOMA, NOS, METASTATIC	1 (5%)			
SQUAMOUS CELL CARCINOMA, METASTA			3 (7%)	
ALVEOLAR/BRONCHIOLAR ADENOMA			10 (23%)	6 (13%)
ALVEOLAR/BRONCHIOLAR CARCINOMA			1 (2%)	
HEMATOPOIETIC SYSTEM				
*MULTIPLE ORGANS	(20)	(20)	(48)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	4 (20%)		1 (2%)	
MALIGNANT LYMPHOMA, MIXED TYPE	1 (5%)			
#SPLEEN	(20)	(20)	(42)	(42)
SQUAMOUS CELL CARCINOMA, METASTA			24 (57%)	11 (26%)
#BRONCHIAL LYMPH NODE	(20)	(19)	(43)	(29)
SQUAMOUS CELL CARCINOMA, METASTA			8 (19%)	2 (7%)
#MESENTERIC L. NODE	(20)	(19)	(43)	(29)
SQUAMOUS CELL CARCINOMA, METASTA			18 (42%)	8 (28%)
#THYMUS	(20)	(20)	(38)	(19)
SQUAMOUS CELL CARCINOMA, METASTA			2 (5%)	
CIRCULATORY SYSTEM				
NONE				

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 02-F061	CONTROL (VEH) 02-F051	LOW DOSE 02-F064	HIGH DOSE 02-F065
DIGESTIVE SYSTEM				
#SALIVARY GLAND	(19)		(31)	(34)
FIBROSARCOMA, METASTATIC			1 (3%)	
#LIVER	(20)	(20)	(44)	(47)
SQUAMOUS CELL CARCINOMA, METASTA			26 (59%)	12 (26%)
HEPATOCELLULAR CARCINOMA			1 (2%)	
*GALLBLADDER	(20)	(20)	(48)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			7 (15%)	2 (4%)
#PANCREAS	(19)	(20)	(43)	(39)
CARCINOMA, NOS, METASTATIC	1 (5%)			
SQUAMOUS CELL CARCINOMA, METASTA			31 (72%)	13 (33%)
#ESOPHAGUS	(20)		(42)	(44)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	
#STOMACH	(20)	(20)	(49)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)	
SQUAMOUS CELL CARCINOMA			46 (94%)	28 (56%)
#SMALL INTESTINE	(20)	(20)	(41)	(42)
SQUAMOUS CELL CARCINOMA, METASTA			2 (5%)	
#DUODENUM	(20)	(20)	(41)	(42)
SQUAMOUS CELL CARCINOMA, METASTA			6 (15%)	5 (12%)
#LARGE INTESTINE	(19)	(20)	(40)	(42)
SQUAMOUS CELL CARCINOMA, METASTA			2 (5%)	2 (5%)
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(43)	(46)
SQUAMOUS CELL CARCINOMA, METASTA			7 (16%)	1 (2%)
TUBULAR-CELL ADENOMA				1 (2%)
#URINARY BLADDER	(18)	(19)	(37)	(41)
SQUAMOUS CELL CARCINOMA, METASTA			3 (8%)	
ENDOCRINE SYSTEM				
#ADRENAL	(19)	(19)	(41)	(45)
SQUAMOUS CELL CARCINOMA, METASTA			12 (29%)	4 (9%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2 (CONTINUED)

	CONTROL (UNTR) 02-F061	CONTROL (VEH) 02-F051	LOW DOSE 02-F064	HIGH DOSE 02-F065
#THYROID	(20)	(20)	(39)	(38)
FOLLICULAR-CELL CARCINOMA	1 (5%)			
#PANCREATIC ISLETS	(19)	(20)	(43)	(39)
ISLET-CELL ADENOMA			1 (2%)	
REPRODUCTIVE SYSTEM				
*MAMMARY GLAND	(20)	(20)	(48)	(50)
ADENOCARCINOMA, NOS			3 (6%)	1 (2%)
#UTERUS	(20)	(20)	(38)	(44)
SQUAMOUS CELL CARCINOMA, METASTA			8 (21%)	1 (2%)
ENDOMETRIAL STROMAL POLYP	1 (5%)		1 (3%)	3 (7%)
#OVARY/OVIDUCT	(20)	(20)	(38)	(44)
SQUAMOUS CELL CARCINOMA, METASTA			3 (8%)	
#OVARY	(20)	(20)	(37)	(41)
CARCINOMA,NOS	1 (5%)			
SQUAMOUS CELL CARCINOMA, METASTA			10 (27%)	2 (5%)
GRANULOSA-CELL TUMOR			1 (3%)	
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*ABDOMINAL MUSCLE	(20)	(20)	(48)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			2 (4%)	1 (2%)
BODY CAVITIES				
*ABDOMINAL WALL	(20)	(20)	(48)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2 (CONCLUDED)

	CONTROL (UNTR) 02-F061	CONTROL (VEH) 02-F051	LOW DOSE 02-F064	HIGH DOSE 02-F065
*MESENTERY	(20)	(20)	(48)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			8 (17%)	1 (2%)
ALL OTHER SYSTEMS				
NONE				
ANIMAL DISPOSITION SUMMARY				
ANIMALS INITIALLY IN STUDY	20	20	50	50
NATURAL DEATH@	1	2	40	47
MORIBUND SACRIFICE			2	
SCHEDULED SACRIFICE				
ACCIDENTALLY KILLED				
TERMINAL SACRIFICE	19	18	7	3
ANIMAL MISSING			1	
@ INCLUDES AUTOLYZED ANIMALS				
TUMOR SUMMARY				
TOTAL ANIMALS WITH PRIMARY TUMORS*	6		47	31
TOTAL PRIMARY TUMORS	8		67	40
TOTAL ANIMALS WITH BENIGN TUMORS	1		12	8
TOTAL BENIGN TUMORS	1		13	10
TOTAL ANIMALS WITH MALIGNANT TUMORS	6		47	29
TOTAL MALIGNANT TUMORS	7		53	30
TOTAL ANIMALS WITH SECONDARY TUMORS#	1		34	16
TOTAL SECONDARY TUMORS	2		186	66
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			1	
TOTAL UNCERTAIN TUMORS			1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC				
TOTAL UNCERTAIN TUMORS				

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS TREATED WITH 1,2-DIBROMOETHANE

TABLE C1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS
TREATED WITH 1,2-DIBROMOETHANE (EDB)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-061M	LOW DOSE 01-062M	HIGH DOSE 01-063M
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
RESPIRATORY SYSTEM				
#TRACHEA	(15)	(17)	(50)	(44)
INFLAMMATION, NOS			1 (2%)	
#LUNG	(20)	(20)	(50)	(50)
PNEUMONIA, CHRONIC MURINE	16 (80%)	4 (20%)	16 (32%)	8 (16%)
CALCIUM DEPOSIT	1 (5%)			
HEMATOPOIETIC SYSTEM				
#SPLEEN	(20)	(20)	(50)	(49)
HEMORRHAGIC CYST			1 (2%)	2 (4%)
INFLAMMATION, NOS			1 (2%)	1 (2%)
FIBROSIS, FOCAL				1 (2%)
HEMATOPOIESIS	1 (5%)		1 (2%)	
#CERVICAL LYMPH NODE	(19)	(20)	(47)	(46)
INFLAMMATION, NOS	1 (5%)			
#PULMONARY LYMPH NODE	(19)	(20)	(47)	(46)
HEMORRHAGE				1 (2%)
#THYMUS	(13)	(6)	(32)	(20)
CYST, NOS			1 (3%)	
HEMORRHAGE				1 (5%)
INFLAMMATION, NOS				1 (5%)
ANGIECTASIS				1 (5%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-061M	LOW DOSE 01-062M	HIGH DOSE 01-063M
CIRCULATORY SYSTEM				
#HEART	(20)	(20)	(50)	(50)
FIBROSIS		1 (5%)		
ARTERIOSCLEROSIS, NOS				1 (2%)
CALCIUM DEPOSIT	1 (5%)			1 (2%)
CALCIFICATION, NOS			1 (2%)	
#MYOCARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	2 (10%)			1 (2%)
DEGENERATION, NOS	1 (5%)	1 (5%)	1 (2%)	1 (2%)
CALCIUM DEPOSIT				1 (2%)
#ENDOCARDIUM	(20)	(20)	(50)	(50)
HYPERPLASIA, NOS	1 (5%)			
*AORTA	(20)	(20)	(50)	(50)
ANEURYSM			1 (2%)	
PERIARTERITIS				1 (2%)
MEDIAL CALCIFICATION	2 (10%)			1 (2%)
*AORTIC TUNICA MEDIA	(20)	(20)	(50)	(50)
CALCIFICATION, NOS			1 (2%)	1 (2%)
*PULMONARY ARTERY	(20)	(20)	(50)	(50)
HYPERTROPHY, NOS				1 (2%)
*MESENTERIC ARTERY	(20)	(20)	(50)	(50)
MEDIAL CALCIFICATION	1 (5%)			1 (2%)
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(50)	(50)
CYST, NOS				1 (2%)
THROMBUS, ORGANIZED				1 (2%)
HEMORRHAGE				2 (4%)
HEMORRHAGIC CYST			1 (2%)	
INFLAMMATION, NOS	1 (5%)		4 (8%)	5 (10%)
NECROSIS, FOCAL			10 (20%)	9 (18%)
METAMORPHOSIS FATTY	2 (10%)		1 (2%)	3 (6%)
FOCAL CELLULAR CHANGE			1 (2%)	1 (2%)
HEPATOCYTOMEGALY				1 (2%)
HYPERPLASIA, NOS			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-061M	LOW DOSE 01-062M	HIGH DOSE 01-063M
ANGIECTASIS	3 (15%)		1 (2%)	
#BILE DUCT	(20)	(20)	(50)	(50)
INFLAMMATION, NOS				1 (2%)
HYPERPLASIA, NOS	4 (20%)			
#PANCREAS	(20)	(20)	(49)	(46)
INFLAMMATION, NOS				2 (4%)
PERIARTERITIS	4 (20%)			
#ESOPHAGUS	(15)	(16)	(46)	(41)
INFLAMMATION, NOS				1 (2%)
#STOMACH	(20)	(20)	(50)	(50)
ULCER, NOS				1 (2%)
CALCIUM DEPOSIT	2 (10%)			
HYPERKERATOSIS				12 (24%)
ACANTHOSIS				12 (24%)
#COLON	(19)	(20)	(48)	(48)
NEMATODIASIS	1 (5%)			
PARASITISM				1 (2%)
#CECUM	(19)	(20)	(48)	(48)
INFLAMMATION, ACUTE				1 (2%)
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(49)	(50)
PYELONEPERITIS, NOS	1 (5%)		1 (2%)	
INFLAMMATION, NOS			1 (2%)	1 (2%)
ABSCESS, NOS				1 (2%)
INFLAMMATION, CHRONIC	15 (75%)	11 (55%)	8 (16%)	10 (20%)
CALCIUM DEPOSIT	1 (5%)		5 (10%)	8 (16%)
HYPERPLASIA, NOS			1 (2%)	
#KIDNEY/PELVIS	(20)	(20)	(49)	(50)
INFLAMMATION, NOS				1 (2%)
CALCIUM DEPOSIT			1 (2%)	
#URINARY BLADDER	(19)	(20)	(49)	(44)
INFLAMMATION, NOS	1 (5%)			
CALCIUM DEPOSIT				1 (2%)
HYPERPLASIA, EPITHELIAL				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONTINUED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-061M	LOW DOSE 01-062M	HIGH DOSE 01-063M
ENDOCRINE SYSTEM				
#PITUITARY	(20)	(20)	(50)	(46)
CYST, NOS			2 (4%)	
ANGIECTASIS	1 (5%)			
#ADRENAL	(20)	(20)	(48)	(47)
DEGENERATION, NOS				1 (2%)
NECROSIS, NOS				1 (2%)
ANGIECTASIS				1 (2%)
#ADRENAL CORTEX	(20)	(20)	(48)	(47)
DEGENERATION, NOS			13 (27%)	9 (19%)
NECROSIS, NOS				1 (2%)
ANGIECTASIS	1 (5%)			
#THYROID	(19)	(20)	(50)	(49)
ULTIMOBRANCHIAL CYST	2 (11%)			
HYPERPLASIA, C-CELL	1 (5%)			
HYPERPLASIA, FOLLICULAR-CELL	1 (5%)			
#PARATHYROID	(3)	(11)	(26)	(25)
HYPERPLASIA, NOS	2 (67%)			
REPRODUCTIVE SYSTEM				
#PROSTATE	(20)	(14)	(30)	(20)
INFLAMMATION, NOS	5 (25%)		3 (10%)	
*SEMINAL VESICLE	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		1 (2%)	2 (4%)
DEGENERATION, NOS				1 (2%)
ATROPHY, NOS				1 (2%)
#TESTIS	(20)	(20)	(49)	(50)
GRANULOMA, SPERMATIC	1 (5%)			
DEGENERATION, NOS				1 (2%)
CALCIFICATION, NOS				1 (2%)
ATROPHY, NOS	11 (55%)		14 (29%)	18 (36%)
*EPIDIDYMIS	(20)	(20)	(50)	(50)
GRANULOMA, SPERMATIC			2 (4%)	3 (6%)
NECROSIS, FAT	1 (5%)			
ATROPHY, NOS	3 (15%)			
NERVOUS SYSTEM				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1 (CONCLUDED)

	CONTROL (UNTR) 01-031M	CONTROL (VEH) 01-061M	LOW DOSE 01-062M	HIGH DOSE 01-063M
SPECIAL SENSE ORGANS				
*EYE/LACRIMAL GLAND	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
*HARDERIAN GLAND	(20)	(20)	(50)	(50)
INFLAMMATION, NOS		1 (5%)		
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)		1 (2%)	1 (2%)
*PERICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	2 (10%)			1 (2%)
*MESENTERY	(20)	(20)	(50)	(50)
PERIARTERITIS	4 (20%)			
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		8	1	1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS
TREATED WITH 1,2-DIBROMOETHANE (EDB)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-061F	LOW DOSE 01-064F	HIGH DOSE 01-065F
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS NECROPSIED	20	20	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	50	50
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(20)	(20)	(50)	(50)
ABSCESS, NOS		1 (5%)		
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(50)	(48)
PNEUMONIA, ASPIRATION				1 (2%)
PNEUMONIA, CHRONIC MURINE	18 (90%)	10 (50%)	11 (22%)	9 (19%)
HEMATOPOIETIC SYSTEM				
*SPLEEN	(20)	(20)	(49)	(48)
CYST, NOS		1 (5%)		
HEMORRHAGIC CYST			1 (2%)	
INFLAMMATION, NOS			3 (6%)	1 (2%)
LEUKEMOID REACTION			1 (2%)	
HEMATOPOIESIS				1 (2%)
*CERVICAL LYMPH NODE	(20)	(20)	(39)	(39)
INFLAMMATION, NOS				1 (3%)
*BRONCHIAL LYMPH NODE	(20)	(20)	(39)	(39)
HYPERPLASIA, NOS			1 (3%)	
CIRCULATORY SYSTEM				
#HEART	(20)	(20)	(50)	(47)
CALCIUM DEPOSIT			2 (4%)	
#MYOCARDIUM	(20)	(20)	(50)	(47)
INFLAMMATION, NOS			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-061F	LOW DOSE 01-064F	HIGH DOSE 01-065F
INFLAMMATION, CHRONIC			1 (2%)	
FIBROSIS	1 (5%)			
DEGENERATION, NOS			1 (2%)	
#ENDOCARDIUM	(20)	(20)	(50)	(47)
HYPERPLASIA, NOS		1 (5%)		
*AORTA	(20)	(20)	(50)	(50)
MEDIAL CALCIFICATION	1 (5%)			
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(47)	(48)
CYST, NOS			1 (2%)	2 (4%)
HEMORRHAGE				2 (4%)
HEMATOMA, NOS				1 (2%)
INFLAMMATION, NOS			4 (9%)	2 (4%)
PELIOSIS HEPATIS			1 (2%)	5 (10%)
NECROSIS, FOCAL				4 (8%)
METAMORPHOSIS FATTY	1 (5%)	1 (5%)		4 (8%)
CYTOPLASMIC VACUOLIZATION			1 (2%)	
FOCAL CELLULAR CHANGE				4 (8%)
HEPATOCYTOMEGALY				1 (2%)
#LIVER/CENTRILOBULAR	(20)	(20)	(47)	(48)
NECROSIS, NOS	1 (5%)			1 (2%)
*BILE DUCT	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
HYPERPLASIA, NOS			1 (2%)	1 (2%)
#PANCREAS	(20)	(20)	(45)	(47)
INFLAMMATION, NOS			1 (2%)	
#STOMACH	(20)	(20)	(50)	(50)
INFLAMMATION, NOS	1 (5%)			
ULCER, NOS			2 (4%)	1 (2%)
ULCER, FOCAL			1 (2%)	1 (2%)
HYPERKERATOSIS	1 (5%)		4 (8%)	18 (36%)
ACANTHOSIS	1 (5%)		4 (8%)	18 (36%)
#COLON	(19)	(20)	(45)	(47)
PARASITISM		1 (5%)		1 (2%)
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(47)	(48)
HYDRONEPHROSIS				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONTINUED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-061F	LOW DOSE 01-064F	HIGH DOSE 01-065F
PYELONEPHRITIS, NOS				1 (2%)
INFLAMMATION, CHRONIC	9 (45%)	7 (35%)	3 (6%)	7 (15%)
NEPHROPATHY			1 (2%)	
CALCIUM DEPOSIT	1 (5%)		4 (9%)	1 (2%)
HYPERPLASIA, NOS			1 (2%)	
ENDOCRINE SYSTEM				
#ADRENAL	(20)	(20)	(44)	(45)
ANGIECTASIS				4 (9%)
#ADRENAL CORTEX	(20)	(20)	(44)	(45)
THROMBOSIS, NOS			1 (2%)	
DEGENERATION, NOS		1 (5%)	3 (7%)	8 (18%)
ANGIECTASIS	3 (15%)			
#THYROID	(20)	(20)	(43)	(43)
HYPERPLASIA, C-CELL	4 (20%)			
HYPERPLASIA, FOLLICULAR-CELL				2 (5%)
#PARATHYROID	(1)	(12)	(33)	(26)
HYPERPLASIA, NOS	1 (100%)			
REPRODUCTIVE SYSTEM				
*VAGINA	(20)	(20)	(50)	(50)
INFLAMMATION, NOS		1 (5%)		
#UTERUS	(20)	(20)	(45)	(45)
HYDROMETRA	4 (20%)	6 (30%)	1 (2%)	4 (9%)
INFLAMMATION, NOS		1 (5%)		
#UTERUS/ENDOMETRIUM	(20)	(20)	(45)	(45)
INFLAMMATION, NOS	1 (5%)			
HYPERPLASIA, CYSTIC	1 (5%)	1 (5%)		
#OVARY	(20)	(20)	(47)	(48)
CYST, NOS		1 (5%)		
NERVOUS SYSTEM				
NONE				
SPECIAL SENSE ORGANS				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2 (CONCLUDED)

	CONTROL (UNTR) 01-031F	CONTROL (VEH) 01-061F	LOW DOSE 01-064F	HIGH DOSE 01-065F
MUSCULOSKELETAL SYSTEM				
NONE				
BODY CAVITIES				
*PERITONEUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			5 (10%)	3 (6%)
*PERICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			2 (4%)	
*EPICARDIUM	(20)	(20)	(50)	(50)
INFLAMMATION, NOS			1 (2%)	
INFLAMMATION WITH FIBROSIS			1 (2%)	
ALL OTHER SYSTEMS				
THORAX				
ABSCESS, NOS			1	
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		4		1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE TREATED WITH 1,2-DIBROMOETHANE

TABLE D1
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE
TREATED WITH 1,2-DIBROMOETHANE (EDB)

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M062	HIGH DOSE 02-M063
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING				1
ANIMALS NECROPSIED	19	20	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	19	20	50	49
INTEGUMENTARY SYSTEM				
*SUBCUT TISSUE	(19)	(20)	(50)	(49)
ABSCESS, NOS	2 (11%)		1 (2%)	
RESPIRATORY SYSTEM				
#TRACHEA	(19)		(39)	(43)
INFLAMMATION, NOS				1 (2%)
#LUNG/BRONCHUS	(18)	(20)	(45)	(47)
INFLAMMATION, NOS			1 (2%)	
EMPYEMA				1 (2%)
#LUNG	(18)	(20)	(45)	(47)
CONGESTION, NOS				1 (2%)
EDEMA, NOS	1 (6%)		1 (2%)	
HEMORRHAGE			1 (2%)	
INFLAMMATION, NOS	1 (6%)			
INFLAMMATION, SUPPURATIVE	1 (6%)		1 (2%)	14 (30%)
PNEUMONIA, CHRONIC MURINE	1 (6%)		15 (33%)	4 (9%)
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(17)	(2)	(42)	(46)
NECROSIS, NOS	1 (6%)			
#SPLEEN	(19)	(20)	(45)	(33)
CONTRACTURE			1 (2%)	5 (15%)
AMYLOIDOSIS	12 (63%)		21 (47%)	2 (6%)
HEMOSIDEROSIS				1 (3%)
ATROPHY, NOS	2 (11%)			1 (3%)
LEUKEMOID REACTION				6 (18%)
HYPERPLASIA, LYMPHOID				3 (9%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M062	HIGH DOSE 02-M063
HEMATOPOIESIS			5 (11%)	1 (3%)
#CERVICAL LYMPH NODE	(18)	(18)	(41)	(32)
INFLAMMATION, NOS			1 (2%)	
#BRONCHIAL LYMPH NODE	(18)	(18)	(41)	(32)
INFLAMMATION, NOS			4 (10%)	3 (9%)
#MESENTERIC L. NODE	(18)	(18)	(41)	(32)
INFLAMMATION, NOS			1 (2%)	
HYPERPLASIA, LYMPHOID				3 (9%)
#THYMUS	(12)	(19)	(37)	(31)
AMYLOIDOSIS			1 (3%)	
CIRCULATORY SYSTEM				
#HEART	(19)	(20)	(45)	(47)
MINERALIZATION			1 (2%)	
EMBOLUS, SEPTIC				1 (2%)
ABSCESS, NOS	1 (5%)			
CALCIFICATION, NOS	3 (16%)		1 (2%)	1 (2%)
CALCIFICATION, DYSTROPHIC				1 (2%)
#MYOCARDIUM	(19)	(20)	(45)	(47)
INFLAMMATION, NOS			4 (9%)	1 (2%)
INFLAMMATION, FOCAL				3 (6%)
INFLAMMATION, SUPPURATIVE	1 (5%)			
DEGENERATION, NOS	1 (5%)		6 (13%)	3 (6%)
#MESENTERIC ARTERY	(19)	(20)	(50)	(49)
PERIARTERITIS			1 (2%)	
DIGESTIVE SYSTEM				
#LIVER	(19)	(20)	(45)	(48)
THROMBUS, ORGANIZED	1 (5%)			
INFLAMMATION, NOS			7 (16%)	4 (8%)
INFLAMMATION, SUPPURATIVE				1 (2%)
INFLAMMATION, ACUTE SUPPURATIVE				1 (2%)
ABSCESS, NOS				2 (4%)
NECROSIS, FOCAL	1 (5%)			
INFARCT, NOS				1 (2%)
AMYLOIDOSIS	12 (63%)		17 (38%)	10 (21%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M062	HIGH DOSE 02-M063
CALCIFICATION, NOS	1 (5%)			
#LIVER/CENTRILOBULAR	(19)	(20)	(45)	(48)
DEGENERATION, NOS	3 (16%)		4 (9%)	7 (15%)
NECROSIS, NOS	1 (5%)			1 (2%)
#PANCREAS	(19)	(19)	(44)	(36)
INFLAMMATION, NOS				1 (3%)
INFLAMMATION, CHRONIC				1 (3%)
AMYLOIDOSIS	6 (32%)		1 (2%)	
ATROPHY, NOS			1 (2%)	1 (3%)
#STOMACH	(20)	(20)	(50)	(49)
INFLAMMATION, NOS			2 (4%)	1 (2%)
INFLAMMATION, FOCAL	1 (5%)			
INFLAMMATION, SUPPURATIVE				2 (4%)
CALCIFICATION, NOS	3 (15%)		1 (2%)	
HYPERKERATOSIS				13 (27%)
ACANTHOSIS			1 (2%)	5 (10%)
#GASTRIC SEROSA	(20)	(20)	(50)	(49)
MINERALIZATION			1 (2%)	
#SMALL INTESTINE	(18)	(19)	(42)	(42)
NEMATODIASIS	1 (6%)			
#LARGE INTESTINE	(19)	(19)	(42)	(40)
NEMATODIASIS	1 (5%)			
PARASITISM			3 (7%)	
URINARY SYSTEM				
#KIDNEY	(19)	(20)	(45)	(47)
CONGESTION, NOS			1 (2%)	1 (2%)
PYELONEPHRITIS, NOS			4 (9%)	
INFLAMMATION, SUPPURATIVE				3 (6%)
PYELONEPHRITIS SUPPURATIVE	1 (5%)			
ABSCESS, NOS			1 (2%)	
INFLAMMATION, CHRONIC	15 (79%)	2 (10%)	12 (27%)	14 (30%)
AMYLOIDOSIS	6 (32%)		4 (9%)	2 (4%)
CALCIFICATION, NOS	1 (5%)		2 (4%)	
#KIDNEY/TUBULE	(19)	(20)	(45)	(47)
CALCIFICATION, NOS				1 (2%)
#URINARY BLADDER	(17)	(19)	(40)	(45)
INFLAMMATION, NOS			3 (8%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1 (CONTINUED)

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M062	HIGH DOSE 02-M063
INFLAMMATION, FOCAL	1 (6%)			1 (2%)
CALCIFICATION, NOS			1 (3%)	1 (2%)
ENDOCRINE SYSTEM				
#PITUITARY	(12)	(18)	(27)	(24)
CYST, NOS			1 (4%)	
#ADRENAL	(19)	(20)	(43)	(46)
INFLAMMATION, NOS			2 (5%)	1 (2%)
INFLAMMATION, SUPPURATIVE				1 (2%)
AMYLOIDOSIS	2 (11%)			
ANGIECTASIS	1 (5%)			
REPRODUCTIVE SYSTEM				
*PREPUTIAL GLAND	(19)	(20)	(50)	(49)
ABSCESS, NOS		1 (5%)		
#PROSTATE	(18)	(20)	(37)	(35)
INFLAMMATION, NOS			2 (5%)	1 (3%)
#TESTIS	(19)	(20)	(45)	(47)
INFLAMMATION, NOS			1 (2%)	
INFLAMMATION, SUPPURATIVE				1 (2%)
GRANULOMA, SPERMATIC	1 (5%)			
CALCIFICATION, DYSTROPHIC				4 (9%)
ATROPHY, NOS				10 (21%)
NERVOUS SYSTEM				
*NEURON	(19)	(20)	(50)	(49)
INFLAMMATION, NOS			1 (2%)	
#BRAIN/MENINGES	(18)	(20)	(45)	(46)
INFLAMMATION, NOS			1 (2%)	
#BRAIN	(18)	(20)	(45)	(46)
INFLAMMATION, NOS				1 (2%)
CALCIFICATION, NOS	1 (6%)			
SPECIAL SENSE ORGANS				
NONE				

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1 (CONCLUDED)

	CONTROL (UNTR) 02-M061	CONTROL (VEH) 02-M051	LOW DOSE 02-M062	HIGH DOSE 02-M063
MUSCULOSKELETAL SYSTEM				
*SKELETAL MUSCLE	(19)	(20)	(50)	(49)
INFLAMMATION, NOS			1 (2%)	
*MUSCLE HIP/THIGH	(19)	(20)	(50)	(49)
INFLAMMATION, NOS				1 (2%)
DEGENERATION, NOS				1 (2%)
CALCIFICATION, NOS			1 (2%)	
CALCIFICATION, DYSTROPHIC				2 (4%)
BODY CAVITIES				
*PERITONEUM	(19)	(20)	(50)	(49)
INFLAMMATION, NOS			2 (4%)	4 (8%)
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		14	2	5
ANIMAL MISSING/NO NECROPSY				1
AUTO/NECROPSY/HISTO PERF		1		1
AUTOLYSIS/NO NECROPSY	1			

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2
SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE
TREATED WITH 1,2-DIBROMOETHANE (EDB)

	CONTROL (UNTR) 02-F061	CONTROL (VEH) 02-F051	LOW DOSE 02-F064	HIGH DOSE 02-F065
ANIMALS INITIALLY IN STUDY	20	20	50	50
ANIMALS MISSING			1	
ANIMALS NECROPSIED	20	20	48	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY**	20	20	48	50
INTEGUMENTARY SYSTEM				
*SKIN	(20)	(20)	(48)	(50)
INFLAMMATION, CHRONIC	1 (5%)			
PARASITISM			1 (2%)	
*SUBCUT TISSUE	(20)	(20)	(48)	(50)
ABSCESS, NOS				1 (2%)
RESPIRATORY SYSTEM				
#LUNG	(20)	(20)	(43)	(46)
CONGESTION, NOS			1 (2%)	4 (9%)
HEMORRHAGE			2 (5%)	1 (2%)
INFLAMMATION, FOCAL				1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)	2 (4%)
PNEUMONIA, CHRONIC MURINE	11 (55%)		21 (49%)	12 (26%)
HYPERPLASIA, LYMPHOID	1 (5%)		2 (5%)	
HEMATOPOIETIC SYSTEM				
#BONE MARROW	(19)	(20)	(43)	(46)
FIBROUS OSTEODYSTROPHY			7 (16%)	4 (9%)
#SPLEEN	(20)	(20)	(42)	(42)
CONTRACTURE			2 (5%)	
INFLAMMATION, NOS			2 (5%)	
AMYLOIDOSIS			3 (7%)	
ATROPHY, NOS				6 (14%)
LEUKEMOID REACTION			7 (17%)	2 (5%)
HYPERPLASIA, LYMPHOID			1 (2%)	1 (2%)
HEMATOPOIESIS			17 (40%)	3 (7%)
#CERVICAL LYMPH NODE	(20)	(19)	(43)	(29)
INFLAMMATION, NOS			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED
**EXCLUDES PARTIALLY AUTOLYZED ANIMALS

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 02-P061	CONTROL (VEH) 02-P051	LOW DOSE 02-P064	HIGH DOSE 02-P065
#BRONCHIAL LYMPH NODE	(20)	(19)	(43)	(29)
INFLAMMATION, NOS			1 (2%)	
HYPERPLASIA, LYMPHOID				1 (3%)
#MESENTERIC L. NODE	(20)	(19)	(43)	(29)
INFLAMMATION, NOS			3 (7%)	1 (3%)
PERIARTERITIS			1 (2%)	
ANGIECTASIS	1 (5%)			
HYPERPLASIA, LYMPHOID			3 (7%)	3 (10%)
#THYMUS	(20)	(20)	(38)	(19)
CYST, NOS			1 (3%)	
INFLAMMATION, NOS			1 (3%)	
INFLAMMATION, SUPPURATIVE				1 (5%)
HYPERPLASIA, LYMPHOID	1 (5%)		4 (11%)	1 (5%)
CIRCULATORY SYSTEM				
#HEART	(20)	(20)	(43)	(46)
THROMBUS, ORGANIZED				1 (2%)
CALCIFICATION, NOS			2 (5%)	
CALCIFICATION, DYSTROPHIC				1 (2%)
#MYOCARDIUM	(20)	(20)	(43)	(46)
INFLAMMATION, NOS	1 (5%)		1 (2%)	
INFLAMMATION, FOCAL			2 (5%)	
DEGENERATION, NOS			2 (5%)	3 (7%)
#ENDOCARDIUM	(20)	(20)	(43)	(46)
INFLAMMATION, NOS				1 (2%)
*FEMORAL ARTERY	(20)	(20)	(48)	(50)
INFLAMMATION, NOS				1 (2%)
DIGESTIVE SYSTEM				
#LIVER	(20)	(20)	(44)	(47)
CONGESTION, NOS			1 (2%)	
INFLAMMATION, NOS			5 (11%)	2 (4%)
INFLAMMATION, FOCAL				1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)	
ABSCESS, NOS			1 (2%)	
NECROSIS, NOS				1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 02-F061	CONTROL (VEH) 02-F051	LOW DOSE 02-F064	HIGH DOSE 02-F065
AMYLOIDOSIS			5 (11%)	2 (4%)
METAMORPHOSIS FATTY				1 (2%)
CYTOPLASMIC VACUOLIZATION			3 (7%)	4 (9%)
#LIVER/CENTRILOBULAR	(20)	(20)	(44)	(47)
DEGENERATION, NOS	2 (10%)		5 (11%)	7 (15%)
NECROSIS, NOS	1 (5%)		2 (5%)	1 (2%)
*MUCOSA OF GALLBLADDE	(20)	(20)	(48)	(50)
EDEMA, NOS			1 (2%)	
*BILE DUCT	(20)	(20)	(48)	(50)
DILATATION, NOS				1 (2%)
INFLAMMATION, NOS	1 (5%)		3 (6%)	
INFLAMMATION, FOCAL	1 (5%)			1 (2%)
#PANCREAS	(19)	(20)	(43)	(39)
INFLAMMATION, NOS				1 (3%)
INFLAMMATION, FOCAL			1 (2%)	
PERIARTERITIS			1 (2%)	
#STOMACH	(20)	(20)	(49)	(50)
INFLAMMATION, NOS				1 (2%)
INFLAMMATION, SUPPURATIVE			1 (2%)	2 (4%)
ABSCESS, NOS				1 (2%)
CALCIFICATION, NOS			1 (2%)	
HYPERKERATOSIS			1 (2%)	12 (24%)
ACANTHOSIS				9 (18%)
#LARGE INTESTINE	(19)	(20)	(40)	(42)
PARASITISM			4 (10%)	2 (5%)
#COLON	(19)	(20)	(40)	(42)
PARASITISM			1 (3%)	
URINARY SYSTEM				
#KIDNEY	(20)	(20)	(43)	(46)
HYDRONEPHROSIS			2 (5%)	1 (2%)
PYELONEPHRITIS, NOS			1 (2%)	
INFLAMMATION, SUPPURATIVE			1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	13 (65%)		22 (51%)	6 (13%)
CALCIFICATION, DYSTROPHIC				1 (2%)
#KIDNEY/TUBULE	(20)	(20)	(43)	(46)
MINERALIZATION			1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 02-P061	CONTROL (VEH) 02-P051	LOW DOSE 02-P064	HIGH DOSE 02-P065
#URINARY BLADDER	(18)	(19)	(37)	(41)
INFLAMMATION, NOS			3 (8%)	
INFLAMMATION, FOCAL	4 (22%)		13 (35%)	2 (5%)
ENDOCRINE SYSTEM				
#PITUITARY	(18)	(19)	(28)	(27)
CYST, NOS			1 (4%)	
#ADRENAL	(19)	(19)	(41)	(45)
INFLAMMATION, NOS			3 (7%)	
INFLAMMATION, SUPPURATIVE			1 (2%)	
ANGIECTASIS			1 (2%)	
#ADRENAL CORTEX	(19)	(19)	(41)	(45)
HYPERPLASIA, NOS			1 (2%)	
REPRODUCTIVE SYSTEM				
#MAMMARY GLAND	(20)	(20)	(48)	(50)
METAPLASIA, SQUAMOUS			1 (2%)	1 (2%)
#UTERUS	(20)	(20)	(38)	(44)
HYDROMETRA		4 (20%)	1 (3%)	3 (7%)
CONGESTION, NOS			1 (3%)	
#UTERUS/ENDOMETRIUM	(20)	(20)	(38)	(44)
INFLAMMATION, NOS			2 (5%)	
HYPERPLASIA, CYSTIC	17 (85%)	3 (15%)	19 (50%)	7 (16%)
#OVARY	(20)	(20)	(37)	(41)
CYST, NOS		3 (15%)		2 (5%)
FOLLICULAR CYST, NOS			3 (8%)	1 (2%)
PAROVARIAN CYST	4 (20%)		1 (3%)	
INFLAMMATION, NOS	1 (5%)			
ANGIECTASIS	1 (5%)			
NERVOUS SYSTEM				
#BRAIN/MENINGES	(20)	(20)	(40)	(45)
INFLAMMATION, NOS			1 (3%)	2 (4%)
INFLAMMATION, FOCAL	1 (5%)			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2 (CONTINUED)

	CONTROL (UNTR) 02-P061	CONTROL (VEH) 02-P051	LOW DOSE 02-P064	HIGH DOSE 02-P065
*SPINAL CORD	(20)	(20)	(48)	(50)
CYST, NOS	1 (5%)			
*ACCESSORY NERVE	(20)	(20)	(48)	(50)
INFLAMMATION, NOS				1 (2%)
SPECIAL SENSE ORGANS				
NONE				
MUSCULOSKELETAL SYSTEM				
*BONE	(20)	(20)	(48)	(50)
FIBROUS OSTEODYSTROPHY			1 (2%)	
*SKELETAL MUSCLE	(20)	(20)	(48)	(50)
INFLAMMATION, FOCAL	1 (5%)			
*MUSCLE HIP/THIGH	(20)	(20)	(48)	(50)
DEGENERATION, NOS			1 (2%)	
CALCIFICATION, NOS			1 (2%)	
BODY CAVITIES				
*PERITONEUM	(20)	(20)	(48)	(50)
INFLAMMATION, SUPPURATIVE			1 (2%)	
*PLEURA	(20)	(20)	(48)	(50)
INFLAMMATION, NOS			1 (2%)	
*PERICARDIUM	(20)	(20)	(48)	(50)
INFLAMMATION, NOS			1 (2%)	
ALL OTHER SYSTEMS				
NONE				
SPECIAL MORPHOLOGY SUMMARY				
NO LESION REPORTED		12		8

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2 (CONCLUDED)

	CONTROL (UNTR) 02-F061	CONTROL (VEH) 02-F051	LOW DOSE 02-F064	HIGH DOSE 02-F065
ANIMAL MISSING/NO NECROPSY			1	
AUTOLYSIS/NO NECROPSY			1	

* NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

Review of the Bioassay of 1,2-Dibromoethane* for Carcinogenicity by the Data Evaluation/Risk Assessment Subgroup of the Clearinghouse on Environmental Carcinogens

April 26, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/ Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of 1,2-Dibromoethane for carcinogenicity.

The primary reviewer said that the compound induced squamous-cell carcinomas of the forestomach in both sexes of rats and mice, hepatocellular carcinomas in female rats, and hemangiosarcomas in male rats. After a brief description of the experimental design, he noted the poor survival among control male rats and mice and that the data from the subchronic study was not very useful in establishing the chronic dose levels. Despite the experimental shortcomings, the primary reviewer said that the evidence for the carcinogenicity of 1,2-Dibromoethane was convincing enough that the results of the bioassay could be considered valid. He concluded that 1,2-Dibromoethane may pose a carcinogenic risk to man.

The secondary reviewer also agreed with the conclusion that 1,2-Dibromoethane was carcinogenic in both the treated rats and mice. She questioned, however, the appropriateness of the route of exposure since humans are exposed mainly by

inhalation. Another Subgroup member said that the oral exposure allowed the administration of a sufficiently high dose to produce cancer within the animals' lifespan. He added that particular routes of exposure should be considered in the risk assessment process.

It was moved that the report on the bioassay of 1,2-Dibromoethane be accepted as written. The motion was seconded and approved unanimously.

Members present were:

Michael Shimkin (Acting Chairman), University of California at San Diego
Joseph Highland, Environmental Defense Fund
George Roush, Jr., Monsanto Company
Louise Strong, University of Texas Health Sciences Center
John Weisburger, American Health Foundation

---

* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

U S GOVERNMENT PRINTING OFFICE 1978-260 899/3164

DHEW Publication No. (NIH) 78-1336