NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 316

TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIMETHYLVINYL CHLORIDE (1-CHLORO-2-METHYLPROPENE)

(CAS NO. 513-37-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

NATIONAL TOXICOLOGY PROGRAM

The National Toxicology Program (NTP), established in 1978, develops and evaluates scientific information about potentially toxic and hazardous chemicals. This knowledge can be used for protecting the health of the American people and for the primary prevention of disease. By bringing together the relevant programs, staff, and resources from the U.S. Public Health Service, DHHS, the National Toxicology Program has centralized and strengthened activities relating to toxicology research, testing and test development/validation efforts, and the dissemination of toxicological information to the public and scientific communities and to the research and regulatory agencies.

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

NTP TECHNICAL REPORT

ON THE

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

August 1986

NTP TR 316

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
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NOTE TO THE READER

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for testing in the NTP Carcinogenesis Program are chosen primarily on the bases of human exposure, level of production, and chemical structure. Selection per se is not an indicator of a chemical's carcinogenic potential. Negative results, in which the test animals do not have a greater incidence of cancer than control animals, do not necessarily mean that a test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a test chemical is carcinogenic for animals under the conditions of the test and indicate that exposure to the chemical has the potential for hazard to humans. The determination of the risk to humans from chemicals found to be carcinogenic in animals requires a wider analysis which extends beyond the purview of this study.

Five categories of interpretative conclusions were adopted for use in June 1983 in the Technical Reports series to specifically emphasize consistency and the concept of actual evidence of carcinogenicity. For each definitive study result (male rats, female rats, male mice, female mice), one of the following quintet will be selected to describe the findings. These categories refer to the strength of the experimental evidence and not to either potency or mechanism.

- **Clear Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of malignant neoplasms, studies that exhibit a substantially increased incidence of benign neoplasms, or studies that exhibit an increased incidence of a combination of malignant and benign neoplasms where each increases with dose.
- **Some Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of benign neoplasms, studies that exhibit marginal increases in neoplasms of several organs/tissues, or studies that exhibit a slight increase in uncommon malignant or benign neoplasms.
- **Equivocal Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing a chemically related marginal increase of neoplasms.
- **No Evidence of Carcinogenicity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.
- **Inadequate Study of Carcinogenicity** demonstrates that because of major qualitative or quantitative limitations, the studies cannot be interpreted as valid for showing either the presence or absence of a carcinogenic effect.

Additionally, the following concepts (as patterned from the International Agency for Research on Cancer Monographs) have been adopted by the NTP to give further clarification of these issues:

> The term *chemical carcinogenesis* generally means the induction by chemicals of neoplasms not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, or the induction by chemicals of more neoplasms than are generally found. Different mechanisms may be involved in these situations. Etymologically, the term *carcinogenesis* means induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign neoplasms. In the Technical Reports, the words *tumor* and *neoplasm* are used interchangeably.

This study was initiated by the National Cancer Institute's Carcinogenesis Bioassay Program, now part of the National Institute of Environmental Health Sciences, National Toxicology Program. The studies described in this Technical Report have been conducted in compliance with NTP chemical health and safety requirements and must meet or exceed all applicable Federal, state, and local health and safety regulations. Animal care and use were in accordance with the U.S. Public Health Service Policy on Humane Care and Use of Animals. All NTP toxicology and carcinogenesis studies are subjected to a data audit before being presented for peer review.

Although every effort is made to prepare the Technical Reports as accurately as possible, mistakes may occur. Readers are requested to identify any mistakes so that corrective action may be taken. Further, anyone who is aware of related ongoing or published studies not mentioned in this report is encouraged to make this information known to the NTP. Comments and questions about the National Toxicology Program Technical Reports on Toxicology and Carcinogenesis Studies should be directed to Dr. J.E. Huff, National Toxicology Program, P.O. Box 12233, Research Triangle Park, NC 27709 (919-541-3780).

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

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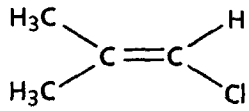

DIMETHYLVINYL CHLORIDE

CAS No. 513-37-1

(1-Chloro-2-methylpropene)

C_4H_7Cl Molecular weight 90.55

ABSTRACT

Toxicology and carcinogenesis studies of dimethylvinyl chloride (96%-98% pure), a structural analog of vinyl chloride monomer, a known human carcinogen, were conducted by administering dimethylvinyl chloride in corn oil by gavage to groups of 50 male and 50 female F344/N rats and B6C3F$_1$ mice at doses of 0, 100, or 200 mg/kg body weight 5 days per week for 102 or 103 weeks. The selection of these doses was based on results of 13-week studies, which included depression of body weight at doses of 500 mg/kg or above in rats as well as histopathologic changes in intestinal epithelium, bone marrow, hepatocytes, and the testes at doses of 250 mg/kg and above; doses in mice were selected on the basis of histopathologic changes in lymphopoietic cells, liver, pancreatic islets, ovary, testis, and spleen, with changes being most prominent at doses of 500 mg/kg and above.

In the 2-year studies, body weights of rats and mice given 100 mg/kg were comparable to those of the vehicle controls except for the last few weeks in mice when body weights were markedly lower than those for the vehicle controls. At 200 mg/kg, the mean body weights of rats and mice were progressively decreased relative to those of vehicle controls, with the significant departure from vehicle controls occurring somewhat earlier in males than in females. Survival of vehicle control rats and mice was comparable to historical values; however, survival of dosed male and female rats was significantly lower than that of vehicle controls, with the incidence of mortality being more severe at the high dose than at the low dose. There were no survivors in the high dose group of male rats after week 85 or in the high dose group of female rats after week 97. Survival was significantly lower among dosed male and female mice compared with vehicle controls. In the absence of toxicologic findings that would explain the early deaths, it is assumed that the high incidence of tumors and chemical-related toxicity contributed to the decreased survival of dosed rats and mice.

In rats, the severity and incidence of nonneoplastic lesions were minimal; these lesions included necrosis of the duodenum and epithelial hyperplasia at the sites of tumor formation--the nasal cavity, esophagus, and forestomach. In mice, the severity of nonneoplastic lesions was also minimal; the lesions included necrosis of the liver, bone marrow granulocytic hyperplasia, and inflammation of the nasal cavity (small number, females only).

Several types of neoplastic lesions occurred with significantly increased incidences in dosed animals as shown in the following table. Among rats, these lesions included malignant epithelial tumors of the nasal cavity and squamous cell tumors of the oral cavity, esophagus, and forestomach in males and females. The increased number of fibroadenomas of the mammary gland in female rats may have been related to dimethylvinyl chloride administration. The lack of a clear dose-response relationship for certain tumors in rats is considered to be related to the increased number of early deaths observed in the high dose groups.

INCIDENCES OF NEOPLASTIC LESIONS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

	Male			Female		
	Vehicle Control	Low Dose	High Dose	Vehicle Control	Low Dose	High Dose
RATS						
Nasal cavity						
Carcinoma, squamous cell carcinoma, or adenocarcinoma	0/47	23/46	28/32	0/50	16/49	35/41
Oral cavity						
Squamous cell carcinoma	0/50	5/50	2/50	0/50	2/50	1/50
Squamous cell papilloma	0/50	0/50	2/50	0/50	0/50	4/50
Esophagus						
Squamous cell carcinoma	0/50	4/50	1/49	0/49	3/50	1/49
Squamous cell papilloma	0/50	2/50	3/49	0/49	0/50	0/49
Forestomach						
Squamous cell carcinoma	0/49	7/50	0/50	0/50	5/50	1/49
Squamous cell papilloma	0/49	7/50	0/50	1/50	4/50	1/49
Mammary gland						
Fibroadenoma	2/50	2/50	0/50	10/50	18/50	5/50
MICE (a)						
Forestomach						
Squamous cell carcinoma	0/48	42/47	35/44	0/50	40/47	36/43
Squamous cell papilloma	1/48	3/47	8/44	0/50	1/47	3/43
Preputial gland						
Squamous cell carcinoma	1/48	3/47	16/44	--	--	--
Harderian gland						
Papillary adenoma	2/48	3/47	3/44	0/50	3/47	5/43
Lung						
Alveolar/bronchiolar adenoma or carcinoma	6/48	9/47	8/44	3/50	1/46	7/43

(a) Mice that died before week 3 are excluded.

Among dosed mice, there were significantly increased incidences of squamous cell carcinomas of the forestomach (both sexes), squamous cell papillomas of the forestomach (males), and squamous cell carcinomas of the preputial gland (males). The increased incidence of papillary adenomas of the harderian gland and alveolar/bronchiolar adenomas or carcinomas in female mice may have been related to administration of dimethylvinyl chloride.

Limited metabolism studies of ^{14}C-labeled dimethylvinyl chloride were conducted in male F344/N rats and $B6C3F_1$ mice. Single doses of 150 mg/kg were administered to rats for 1, 2, or 4 consecutive days. About 25% of the administered doses was exhaled as carbon dioxide; this amount was independent of the number of doses administered. Another 25%-35% of the administered dose was exhaled; 96% of this was parent material. Approximately 35% and 6% were excreted in the urine and feces, respectively. The elimination half-life of radioactive label was 3-4 days for the liver and kidney, the two organs containing the greatest amounts of the administered dose. In mice, a much smaller fraction of the dose was exhaled and a larger proportion was excreted in urine compared with rats.

Dimethylvinyl chloride was not mutagenic in four strains of *Salmonella typhimurium* with or without metabolic activation, but it was mutagenic in the mouse lymphoma L5178Y/TK$^{+/-}$ assay in the absence of metabolic activation. Sister-chromatid exchanges were induced in Chinese hamster ovary cells with and without metabolic activation, but there was no increase in chromosomal aberrations. When fed to Drosophila, dimethylvinyl chloride induced significant increases in the frequencies of both sex-linked recessive lethal mutations and reciprocal translocations.

Studies of the immunotoxicity of dimethylvinyl chloride were conducted in which female $B6C3F_1$ mice received 14 daily oral doses of 0, 50, 100, 200, or 400 mg dimethylvinyl chloride per kilogram body weight. Compound-related increases in susceptibility to bacterial infection and decreases in macrophage cytostasis were observed at all doses. At the highest dose, the decreased resistance to bacterial and viral challenge could be related to alterations in specific immune function. However, the increased mortality in rats and mice in the 2-year studies was not relatable to infectious processes.

An audit of the experimental data was conducted for these 2-year toxicology and carcinogenesis studies on dimethylvinyl chloride. No data discrepancies were found that influenced the final interpretations.

Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenicity** of dimethylvinyl chloride for both sexes of F344/N rats and $B6C3F_1$ mice. This was based on increased incidences of neoplasms of the nasal cavity, oral cavity, esophagus, and forestomach of male and female F344/N rats. $B6C3F_1$ mice showed increased incidences of squamous cell neoplasms of the forestomach in males and females and squamous cell carcinomas of the preputial gland in males.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2. The public discussion regarding the interpretative conclusions is summarized on page 16.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of Dimethylvinyl Chloride is based on the 13-week studies that began in August 1978 and ended in November 1978 and on the 2-year studies that began in June 1980 (rats) or March 1981 (mice) and ended in June 1982 (rats) or March 1983 (mice) at Litton Bionetics, Inc.

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The members of the Peer Review Panel who evaluated the draft Technical Report on dimethylvinyl chloride on December 9, 1985, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have five major responsibilities: (a) to ascertain that all relevant literature data have been adequately cited and interpreted, (b) to determine if the design and conditions of the NTP studies were appropriate, (c) to ensure that the Technical Report presents the experimental results and conclusions fully and clearly, (d) to judge the significance of the experimental results by scientific criteria, and (e) to assess the evaluation of the evidence of carcinogenicity and other observed toxic responses.

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SUMMARY OF PEER REVIEW COMMENTS ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF DIMETHYLVINYL CHLORIDE

On December 9, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of dimethylvinyl chloride received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held in the Conference Center, Building 101, South Campus, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. B. Schwetz, NTP Chemical Manager, introduced the toxicology and carcinogenesis studies of dimethylvinyl chloride by reviewing the experimental designs, results, and proposed conclusions (clear evidence of carcinogenicity for both sexes of rats and mice).

Dr. Crowley, a principal reviewer for the draft Technical Report, agreed with the conclusions as written. He asked for clarification or more definition of the relationship between tumors and early mortality in the dose groups vs. a relationship with compound-induced toxicity.

As a second principal reviewer, Dr. Perera agreed with the conclusions. Her principal criticisms had to do with presentation and discussion in the text of tumor incidence data displayed in the tables. She cited a number of examples and noted especially instances where there was little comment about increased tumor incidences in low dose groups. Dr. Schwetz responded that for some tumors, especially those with increases in the low dose groups, there was little or no mention in the text because of only marginally increased incidence, the lack of a high dose effect, or the primarily benign nature of the tumors. Dr. Perera noted that although harderian gland tumors were significantly increased in incidence and with a positive trend in female mice, this was considered to be an "uncertain relationship" to chemical administration. She questioned this interpretation.

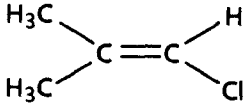
As a third principal reviewer, Dr. Purchase also agreed with the conclusions. He thought there was very good evidence that early mortality was due to malignant neoplasms, noting that virtually all animals dying after about 60-70 weeks had malignant neoplasms. Dr. Schwetz replied that most of the dosed rats dying without nasal tumors died earlier than those with such tumors, citing this as an example of why the causes of death were probably a combination of cancer and dimethylvinyl chloride toxicity. Dr. Purchase said the argument that dimethylvinyl chloride acts directly on the nasal mucosa was weaker than the one suggesting that the nasal lesions were a result of systemic absorption and gave reasons in support of an indirect effect. Dr. Scala said the lack of kidney or bladder tumors in mice also spoke to the tumorigenicity occurring through systemic rather than local effects.

In other discussion, Dr. Scala commented on the introduction of information on chemical metabolism and immunotoxicology studies for the first time in the discussion without prior presentation of data in the results section.

Dr. Crowley moved that the Technical Report on dimethylvinyl chloride with the conclusions as written for rats and mice of both sexes, clear evidence of carcinogenicity, be accepted. Dr. Hooper seconded the motion, and it was approved unanimously with 11 affirmative votes.

I. INTRODUCTION

I. INTRODUCTION



DIMETHYLVINYL CHLORIDE

CAS No. 513-37-1

(1-Chloro-2-methylpropene)

C_4H_7Cl Molecular weight 90.55

Dimethylvinyl chloride is a clear colorless liquid, which, because of its volatility and flammability at room temperature, is a significant fire hazard. It has a boiling point of 68.1° C (155° F) and a density at 20° C of 0.919 g/ml (Merck, 1976). Dimethylvinyl chloride is a byproduct in the production of 3-chloro-2-methylpropene by the chlorination of isobutene. It is not known to be produced intentionally in the United States for other than laboratory purposes. This chemical was nominated for toxicologic studies because of its reported presence in ambient air in the Baltimore area (personal communication from H. Kraybill to NCI Chemical Selection Working Group, 1976) and was selected for toxicologic characterization because of its structural similarity to the known animal and human carcinogen, vinyl chloride monomer.

No threshold limit value is identified for dimethylvinyl chloride, and no recently published toxicologic data have been found. Silverman and Abreu (1938) reported that dimethylvinyl chloride was mildly irritating to the eyes and mucous membranes of humans and mice and had anesthetic properties in mice. In "barbitalized" rabbits administered dimethylvinyl chloride by inhalation, these authors reported a moderate rise in blood pressure that rapidly returned to normal after exposure ceased. The increase in blood pressure was considered to be a reflex result of inhalation of a respiratory tract irritant.

Vinyl chloride monomer is a well-recognized human carcinogen and in laboratory animals is a carcinogen in multiple organs, producing a variety of tumors in all species in which it has been studied and in animals of both sexes and of different ages by different routes of administration (Maltoni et al., 1984). The potency of vinyl chloride monomer as a carcinogen and its close structural similarity to vinyl chloride monomer suggested that dimethylvinyl chloride might also be an animal carcinogen.

No information was found in the literature regarding the disposition of dimethylvinyl chloride in animals.

Dimethylvinyl chloride was not mutagenic in strains TA98, TA100, TA1535, or TA1537 of *Salmonella typhimurium* in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 when tested according to the preincubation protocol (Appendix G, Table G1). However, dimethylvinyl chloride was mutagenic in the mouse lymphoma L5178Y/TK$^{+/-}$ assay in the absence of S9 (Table G2); it was not tested in the presence of S9. The compound induced sister-chromatid exchanges in Chinese hamster ovary cells in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat liver S9 (Table G3); it did not induce chromosomal aberrations in these cells (Table G4). Dimethylvinyl chloride induced a significant increase in the frequency of both sex-linked recessive lethal mutations and reciprocal translocations in the germ cells of Drosophila when fed to males at a dose of 12,750 ppm in 5% sucrose. Dimethylvinyl chloride induced greater absolute and relative increases in the frequency of reciprocal translocations than in the frequency of sex-linked recessive lethal mutations (Table G5). No information was found in the literature on the genetic toxicology of dimethylvinyl chloride.

3-Chloro-2-methylpropene recently has been reported to be a carcinogen when given by gavage to rats and mice (NTP, 1986). The lots of this

chemical which were evaluated for carcinogenicity contained as much as 5% dimethylvinyl chloride. Dose-related increases in the incidences of forestomach basal cell hyperplasia were observed in rats and mice of each sex. Forestomach squamous cell carcinomas were observed in male rats dosed with 150 mg/kg per day and in male and female mice dosed with 75 or 150 mg/kg per day. The potential role of dimethylvinyl chloride in the observed carcinogenicity in the 3-chloro-2-methylpropene studies was not established.

Dimethylvinyl chloride was selected for study to characterize and evaluate its toxicologic potential, including carcinogenic activity, because of its structural similarity to the potent human and animal carcinogen, vinyl chloride monomer. Since available inhalation facilities were limited and because 3-chloro-2-methylpropene was studied by the oral route, dimethylvinyl chloride was administered orally by gavage.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF DIMETHYLVINYL CHLORIDE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

SINGLE-ADMINISTRATION STUDIES

FOURTEEN-DAY STUDIES

THIRTEEN-WEEK STUDIES

TWO-YEAR STUDIES

Study Design

Source and Specifications of Animals

Animal Maintenance

Clinical Examinations and Pathology

Statistical Methods

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF DIMETHYLVINYL CHLORIDE

Dimethylvinyl chloride (1-chloro-2-methylpropene) was obtained from the Aldrich Chemical Company in three lots (Table 1). Purity, identity, and stability analyses were conducted at Midwest Research Institute (Kansas City, Missouri) (Appendix H). All three lots were identified as dimethylvinyl chloride by spectroscopy. The infrared, ultraviolet/visible, and nuclear magnetic resonance spectra were consistent with the structure of dimethylvinyl chloride and with available literature references. The purity for all three lots ranged from 96% for lot nos. 062537 and KD090967 to 98% for lot no. 1103BH based on elemental analysis, water analysis, acid titration, and gas chromatography. No epichlorohydrin was detected in any of the lots. The identity and concentration of major impurities observed in these lots of dimethylvinyl chloride are presented in Table 2.

The bulk chemical was stable when stored for 2 weeks at temperatures ranging from $-20°$ to $25°$ C (Appendix H). Several portions of the chemical were stored at $-20°$ C as reference samples, and the remainder was stored at room temperature. Periodic reanalysis of the study and reference samples by infrared spectroscopy and gas chromatography indicated that a decrease in the purity (approximately 1.7%) of the study material and a corresponding increase in the concentration and/or number of impurities in the reference and bulk chemical occurred in lot no. 062537 after storage for 3 years at the study laboratory. This lot was immediately replaced with lot nos. KD090967 and 1103BH.

Periodic reanalysis of these lots indicated no decomposition of dimethylvinyl chloride for the remainder of the studies (Appendix H).

TABLE 1. IDENTITY AND SOURCE OF LOTS USED IN THE GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers			
062537	062537	062537	062537, KD090967, 1103BH
Date of Initial Use of Each Lot			
	Rats--5/10/78; mice--5/8/78	8/31/78	Rats--062537: 6/20/80-1/8/81; KD090967: 1/8/81-3/4/81; 1103BH: 3/4/81-6/11/82; mice--1103BH: 3/20/81-3/1/83
Supplier			
Aldrich Chemical Co. (Milwaukee, WI)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies

TABLE 2. IDENTITY AND CONCENTRATION OF MAJOR IMPURITIES IN DIMETHYLVINYL CHLORIDE

Impurity	Concentration (percent) in Lot No. 062537	Lot no. KD090967	Lot No. 1103BH
Acetone	(a) 0.12	(b) 0.20	(c) ND
Acrylonitrile	ND	ND	0.14
t-Butanol	0.16	ND	ND
t-Butyl chloride	0.91	ND	0.10
Chloroform	<0.1	ND	(d)
3-Chloro-2-methylpropene	0.68	2.48	1.18
1,2-Dichloro-2-methylpropane	1.04	ND	0.1
2,2,4-Trimethyl-3-hydroxypentanal	0.92	ND	ND

(a) An impurity, tentatively identified as methylpropene from a comparison of its mass spectrum with a literature reference, was observed to coelute with the acetone impurity. The combined concentration of these two impurities is estimated to be 0.12%.
(b) Percent of major peak area; not quantitated against a standard.
(c) Not detected at a level ≥0.1%
(d) The concentration of chloroform could not be determined because of its low concentration and coelution with *t*-butyl chloride. When quantitated against a *t*-butyl chloride standard, the combined concentration of these two impurities was estimated to be 0.1%.

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

Accurately measured amounts of dimethylvinyl chloride were mixed with corn oil to yield the desired concentrations (Table 3). Dose mixtures of dimethylvinyl chloride (6%, w/v) in corn oil were stable when stored at room temperature for 7 days (Appendix I). An additional stability study conducted at the study laboratory indicated that the dose formulations were stable for up to 21 days at 25° C. Dimethylvinyl chloride and corn oil mixtures were stored at 25° C for no longer than 21 days. The study laboratory experienced difficulty in preparing the dose mixtures of dimethylvinyl chloride. Periodic analysis for dimethylvinyl chloride in the corn oil vehicle was performed by the study laboratory and analytical chemistry laboratory to determine if the dose mixtures contained the correct concentrations of study material (Appendix J). Because 58/72 mixtures analyzed were within ± 10% of the target concentration, it is estimated that the dose mixtures were prepared within specifications 81% of the time (Table 4; Appendix K, Table K1). Of the 14 dose formulations determined to be out of specification, 9 were found to be within ± 20% of the target concentrations and the remaining 5 samples were greater than 20% above the target concentrations.

TABLE 3. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation			
The appropriate amount of dimethylvinyl chloride was added to a graduated cylinder, brought to volume with corn oil, and mixed by inversion	Same as the single-administration studies	Same as the single-administration studies	Same as the single-administration studies
Maximum Storage Time			
Not applicable	Dosing solution prepared daily except for 5/13/78, 5/14/78, 5/20/78, and 5/21/78 when solutions prepared the preceding Friday were used	Dosing solutions prepared daily	21 d
Storage Conditions			
Not applicable	Room temperature	Room temperature	Room temperature

TABLE 4. SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

	Target Concentration (mg/ml)			
	10	20	20	40
Mean (mg/ml)	10.5	21.2	21.1	41.1
Standard deviation	1.13	1.43	2.26	4.09
Coefficient of variation (percent)	10.8	6.7	10.7	10.0
Range (mg/ml)	8.8-13.2	19.0-23.9	18.6-28.7	34.5-54.1
Number of samples	16	14	21	21

SINGLE-ADMINISTRATION STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and observed for 2 weeks before the studies began. Groups of five male and five female unfasted rats were administered a single dose of 10, 31.6, 100, 316, 1,000, 3,160, or 10,000 mg/kg dimethylvinyl chloride in corn oil by gavage. Groups of five unfasted mice of each sex were administered 100, 316, 1,000, 3,160, or 10,000 mg/kg dimethylvinyl chloride. Groups of five mice of each sex were administered 31.6, 100, 316, 1,000, or 3,160 mg/kg; these mice were fasted 4 hours before dosing. All animals were observed 4 hours after dosing and then daily for 14 days; they were killed on day 15. A necropsy was performed on all animals that died before the end of the studies and on some animals that lived to the end of the studies. Details of animal maintenance are given in Table 5.

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and held for 3 weeks (rats) or 4 weeks (mice) before the studies began. (Although water was available during the quarantine period, quarantined mice appeared to be dehydrated. They recovered

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	50 males and 50 females of each species
Doses			
Rats--10, 31.6, 100, 316, 1,000, 3,160, or 10,000 mg/kg dimethylvinyl chloride in corn oil by gavage; mice (unfasted)--100, 316, 1,000, 3,100, or 10,000 mg/kg dimethylvinyl chloride in corn oil by gavage; mice (fasted)--31.6, 100, 316, 1,000, or 3,160 mg/kg dimethylvinyl chloride in corn oil by gavage	Rats--0, 500, 750, 1,250, 1,750, or 2,500 mg/kg dimethylvinyl chloride in corn oil by gavage; mice--0, 250, 500, 1,000, 1,500, or 2,000 mg/kg dimethylvinyl chloride in corn oil by gavage; dose vol--3.33 ml/kg	0, 63, 125, 250, 500, or 750 mg/kg dimethylvinyl chloride in corn oil by gavage; dose vol--3.33 ml/kg	Rats--0, 100, or 200 mg/kg dimethylvinyl chloride in corn oil by gavage; dose vol--5 ml/kg; mice--0, 100, or 200 mg/kg dimethylvinyl chloride in corn oil by gavage; dose vol--10 ml/kg
Date of First Dose			
	Rats--5/10/78; mice--5/8/78	8/31/78	Rats--6/20/80; mice--3/20/81
Date of Last Dose			
N/A	Rats--5/23/78; mice--5/21/78	Rats--11/28/78; mice--11/24/78	Rats--6/11/82; mice--3/1/83
Duration of Dosing			
One time only	14 consecutive d	5 d/wk for 13 wk	5 d/wk for 103 wk (rats) or 102 wk (mice)
Type and Frequency of Observation			
Observed immediately after dosing, at 1 and 4 h, and 1 × d thereafter for 14 d; weighed on the day of dosing	Observed 1 × d; weighed on d 1 and 15	Observed 2 × d; clinical observations 1 × wk; weighed 1 × wk	Observed 2 × d; palpated 1 × 4 wk; weighed 1 × wk for 13 wk, 1 × 4 wk thereafter
Necropsy and Histologic Examination			
Necropsy performed on all animals dying during the study and on some of the animals killed 14 d after dosing	Necropsy performed on all animals	Necropsy and histologic examination performed on all animals; the following tissues were examined: gross lesions and tissue masses, mandibular or mesenteric lymph node, salivary gland, sternebrae, femur, or vertebrae including marrow, thyroid gland, parathyroids, small intestine, colon, liver, prostate/testes or	Necropsy and histologic examination performed on all animals; the following tissues were examined: gross lesions and tissue masses, blood smear, mandibular and mesenteric lymph nodes, salivary gland, sternum including marrow, thyroid gland, parathyroids, colon, liver, urinary bladder, prostate/ testes/seminal vesicles or ovaries/uterus, lungs and

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE (Continued)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Necropsy and Histologic Examination (Continued)			
		ovaries/uterus, spinal cord (if neurologic signs present), lungs and mainstem bronchi, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, eyes (if grossly abnormal), mammary gland, skin, and gallbladder (mice)	mainstem bronchi, skin, gallbladder (mice), cecum, thigh muscle, costochondral junction (rib), larynx, nasal cavity, heart, esophagus, stomach, brain, thymus, trachea, pancreas, spleen, kidneys, adrenal glands, pituitary gland, spinal cord, eyes, mammary gland, duodenum, ileum, sciatic nerve, rectum, and jejunum
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species			
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source			
Harlan Industries (Indianapolis, IN)	Same as single-admistration studies	Charles River Breeding Laboratories (Portage, MI)	Charles River Breeding Laboratories (Kingston, NY)
Study Laboratory			
Litton Bionetics, Inc.	Litton Bionetics, Inc.	Litton Bionetics, Inc.	Litton Bionetics, Inc.
Method of Animal Identification			
	Ear punch	Ear notches	Rats--ear tag; mice--ear punch, toe clip
Time Held Before Study			
2 wk	Rats--3 wk; mice--4 wk	2 wk	Rats--2.5 wk; mice--2 wk
Age When Placed on Study			
			Rats--7 wk; mice--8 wk
Age When Killed			
			111 wk
Necropsy Dates			
	Rats--5/24/78; mice--5/22/78	Rats--11/29/78; mice--11/27/78	Rats--6/21/82-6/22/82; mice--3/9/83-3/10/83
Method of Animal Distribution			
		Animals assigned to cages and groups according to tables of random numbers	Assigned to groups according to tables of random number
Feed			
Purina Lab Chow® (Ralston Purina, St. Louis, MO); available ad libitum	Same as single-administration studies	Same as single-administration studies	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum
Bedding			
Ab-sorb-dri	Same as single-administration studies	Ab-sorb-dri hardwood chips	Ab-sorb-dri hardwood chips (Lab Products, Inc.) 3/20/81-9/23/81; Sani-chips hardwood chips (P.J. Murphy Forest Products, Corp., Rochelle Park, NJ) 9/23/81-end of studies

TABLE 5. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE (Continued)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Water			
Acidified water in bottles, available ad libitum	Same as single-administration studies	Tap water in bottles acidified to pH 2.5 with HCl for bacterial control; available ad libitum	Same as 13-wk studies
Cages			
Polycarbonate	Same as single-administration studies	Polycarbonate (Lab Products, Inc.)	Polycarbonate (Lab Products, Inc., Garfield, NJ, and Rochelle Park, NJ, and Hazleton Systems, Aberdeen, MD)
Cage Filters			
			Nonwoven polyester sheets (Snow Filtration Co., Cincinnati, OH)
Cage Rotation			
None	None		None
Animals per Cage			
5	5	5	5
Other Chemicals on Study in the Same Room			
	3-Chloro-2-methylpropene	None	None
Animal Room Environment			
		Temp--74° ± 2° F; hum--generally maintained between 30% and 70%; fluorescent light 12 h/d; 15 room air changes/h	Temp--generally 72°-76° F, range: 70°-81° F; hum--30%-70%; fluorescent light 12 h/d; 12-15 room air changes/h

before the studies began.) Groups of five male and five female rats were administered 0, 500, 750, 1,250, 1,750, or 2,500 mg/kg dimethylvinyl chloride in corn oil by gavage for 14 consecutive days. Groups of five male and five female mice were administered 0, 250, 500, 1,000, 1,500, or 2,000 mg/kg on the same schedule.

Animals were housed five per cage and received water (acidified to pH 2.5 with hydrochloric acid) and feed ad libitum. Further details of animal maintenance are presented in Table 5. The rats and mice were observed daily and were weighed on days 1 and 15. A necropsy was performed on all animals.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of dimethylvinyl chloride and to determine the doses to be used in the 2-year studies.

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories, observed for 14 days, and then assigned to cages according to a table of random numbers. The cages were then assigned to dosed and vehicle control groups according to a table of random numbers.

Groups of 10 rats and 10 mice of each sex were administered 0, 63, 125, 250, 500, or 750 mg/kg dimethylvinyl chloride in corn oil by gavage, 5 days per week for 13 weeks. Animals were checked twice per day; moribund animals were killed. Further experimental details are summarized in Table 5.

At the end of the 13-week studies, survivors were killed. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 5.

TWO-YEAR STUDIES

Study Design

Groups of 50 male and 50 female rats and groups of 50 male and 50 female mice were administered 0, 100, or 200 mg/kg dimethylvinyl chloride in corn oil by gavage, 5 days per week for 103 weeks (rats) or 102 weeks (mice).

Source and Specifications of Animals

The male and female F344/N rats and $B6C3F_1$ (C57BL/6N, female, × C3H/HeN MTV^-, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories under a contract to the Carcinogenesis Program. Breeding stock for the foundation colonies at the production facility originated at the National Institutes of Health Repository. Animals shipped for study were progeny of defined microflora-associated parents that were transferred from isolators to barrier-maintained rooms. Rats were shipped to the study laboratory at 4-5 weeks of age and mice, at 5-6 weeks of age. The animals were quarantined at the study laboratory for 2.5 weeks (rats) or 2 weeks (mice). Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. The rats were placed on study at 7 weeks of age and the mice, at 8 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the NTP Sentinel Animal Program (Appendix L).

A quality control skin grafting program has been in effect since early 1978 to monitor the genetic integrity of the inbred mice used to produce the hybrid $B6C3F_1$ study animal. In mid-1981, data were obtained that showed incompatibility between the NIH C3H reference colony and the C3H colony from a Program supplier. In August 1981, inbred parental lines of mice were further tested for genetic integrity via isozyme and protein electrophoresis profiles that demonstrate phenotype expressions of known genetic loci.

The C57BL/6 mice were homogeneous at all loci tested. Eighty-five percent of the C3H mice monitored were variant at one to three loci, indicating some heterogeneity in the C3H line from this supplier. Nevertheless, the genome of this line is more homogeneous than that of randomly bred stocks.

Male mice from the C3H colony and female mice from the C57BL/6 colony were used as parents for the hybrid $B6C3F_1$ mice used in these studies. The influence of the potential genetic nonuniformity in the hybrid mice on these results is not known, but results of the studies are not affected because concurrent controls were included in each study.

Animal Maintenance

Animals were housed five per cage. Feed and water were available ad libitum. Further details of animal maintenance are given in Table 5.

Clinical Examinations and Pathology

All animals were observed twice daily, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 13 weeks of the studies and once per month thereafter. Mean body weights were calculated for each group. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead, unless they were excessively autolyzed or cannibalized, missexed, or found missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined microscopically are listed in Table 5.

When the pathology evaluation was completed, the slides, paraffin blocks, and residual wet tissues were sent to the NTP Archives for inventory, slide/block match, and wet tissue audit.

The slides, individual animal data records, and pathology tables were sent to an independent quality assessment laboratory. The individual animal records and tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tumor diagnoses, all target tissues, and all tissues from a randomly selected 10% of the animals were evaluated by a quality assessment pathologist. The quality assessment report and slides were submitted to the Pathology Working Group (PWG) Chairperson, who reviewed all target tissues and those about which there was a disagreement between the laboratory and quality assessment pathologists.

Representative slides selected by the Chairperson were reviewed by the PWG, which includes the laboratory pathologist, without knowledge of previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the laboratory pathologist was asked to reconsider the original diagnosis. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final diagnoses represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Slides/tissues are generally not evaluated in a blind fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle or unless there is an inconsistent diagnosis of lesions by the laboratory pathologist. Nonneoplastic lesions are not examined routinely by the quality assessment pathologist or PWG unless they are considered part of the toxic effect of the chemical.

Statistical Methods

Data Recording: Data on this experiment were recorded in the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, survival, body weight, and individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969).

Survival Analyses: The probability of survival was estimated by the product-limit procedure of Kaplan and Meier (1958) and is presented in the form of graphs. Animals were censored from the survival analyses at the time they were found dead of other than natural causes or were found to be missing; animals dying from natural causes were not censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) life table test for a dose-related trend. When significant survival differences were detected, additional analyses utilizing these procedures were carried out to determine the week at which significant differences in the survival curves were first observed. All reported P values for the survival analysis are two-sided.

Calculation of Incidence: The incidence of neoplastic or nonneoplastic lesions is given as the ratio of the number of animals bearing such lesions at a specific anatomic site to the number of animals in which that site was examined. In most instances, the denominators include only those animals for which the site was examined histologically. However, when macroscopic examination was required to detect lesions (e.g., skin or mammary tumors) prior to histologic sampling, or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the number of animals on which a necropsy was performed.

Analysis of Tumor Incidence: Three statistical methods were used to analyze tumor incidence data. The two that adjust for intercurrent mortality employ the classical method for combining contingency tables developed by Mantel and Haenszel (1959). Tests of significance included pairwise comparisons of high dose and low dose groups with vehicle controls and tests for overall dose-response trends.

For studies in which compound administration has little effect on survival, the results of the three alternative analyses will generally be similar. When differing results are obtained by the three methods, the final interpretation of the data will depend on the extent to which the tumor under consideration is regarded as being the cause of death. Continuity-corrected tests are

used in the analysis of tumor incidence, and reported P values are one-sided. Twenty-one mice that died before the 3rd week of the studies (two vehicle control, three low dose, and six high dose males; three low dose and seven high dose females) have been excluded from the statistical analyses of tumor incidence.

Life Table Analyses--The first method of analysis assumed that all tumors of a given type observed in animals dying before the end of the study were "fatal"; i.e., they either directly or indirectly caused the death of the animal. According to this approach, the proportions of tumor-bearing animals in the dosed and vehicle control groups were compared at each point in time at which an animal died with a tumor of interest. The denominators of these proportions were the total number of animals at risk in each group. These results, including the data from animals killed at the end of the study, were then combined by the Mantel-Haenszel method to obtain an overall P value. This method of adjusting for intercurrent mortality is the life table method of Cox (1972) and of Tarone (1975). The underlying variable considered by this analysis is time to death due to tumor. If the tumor is rapidly lethal, then time to death due to tumor closely approximates time to tumor onset. In this case, the life table test also provides a comparison of the time-specific tumor incidences.

Incidental Tumor Analyses--The second method of analysis assumed that all tumors of a given type observed in animals that died before the end of the studies were "incidental"; i.e., they were merely observed at necropsy in animals dying of an unrelated cause. According to this approach, the proportions of tumor-bearing animals in dosed and vehicle control groups were compared in each of five time intervals: weeks 0-52, weeks 53-78, weeks 79-92, week 93 to the week before the terminal-kill period, and the terminal-kill period. The denominators of these proportions were the number of animals on which a necropsy was actually performed during the time interval. The individual time interval comparisons were then combined by the previously described method to obtain a single overall result. (See Haseman, 1984, for the computational details of both methods.)

Unadjusted Analyses--Primarily, survival-adjusted methods are used to evaluate tumor incidence. In addition, the results of the Fisher exact test for pairwise comparisons and the Cochran-Armitage linear trend test (Armitage, 1971; Gart et al., 1979) are given in the appendix containing the analyses of primary tumor incidence. These two tests are based on the overall proportion of tumor-bearing animals and do not adjust for survival differences.

Historical Control Data: Although the concurrent control group is always the first and most appropriate control group used for evaluation, there are certain instances in which historical control data can be helpful in the overall assessment of tumor incidence. Consequently, control tumor incidences from the NTP historical control data base (Haseman et al., 1984) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

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Body Weights and Clinical Signs

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MICE

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III. RESULTS: RATS

SINGLE-ADMINISTRATION STUDIES

All rats that received 10,000 mg/kg dimethylvinyl chloride and 1/5 female rats that received 3,160 mg/kg died before the end of the studies (Table 6). Compound-related clinical signs included weakness, discharge from the eyes, disorientation, staggering gait, inactivity, emaciation, hunched back, urine stains, and difficulty in breathing.

FOURTEEN-DAY STUDIES

All rats that received 1,250, 1,750, or 2,500 mg/kg dimethylvinyl chloride died before the end of the studies (Table 7). Two of the five deaths in the group of males administered 1,750 mg/kg were not compound related. The final mean body weight of males that received 750 mg/kg was 79% that of the vehicle controls, and the final mean body weight of females that received 750 mg/kg was 70% that of the vehicle controls. Compound-related signs included emaciation, urine stains, weakness, inactivity, hunched back, rough fur coat, discharge from eyes and nose, and stains around the anus.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Dose (mg/kg)	Survival (a)	Initial Mean Body Weight (b) (grams)
MALE		
10	5/5	127
31.6	5/5	126
100	5/5	126
316	5/5	125
1,000	5/5	127
(c) 3,160	5/5	134
(c) 10,000	(d) 0/5	132
FEMALE (e)		
10	5/5	99
31.6	5/5	98
100	5/5	97
316	5/5	98
1,000	5/5	97
(c) 3,160	(f) 4/5	113
(c) 10,000	(g) 0/5	114

(a) Number surviving/number initially in group
(b) Final body weights not recorded
(c) Groups administered 3,160 or 10,000 mg/kg were started 4 days after the other groups.
(d) Day of death: 1, 3, 3, 4, 4
(e) LD_{50} value estimated at 4,465 mg/kg (95% confidence interval 2,843-7,012 mg/kg) by the Spearman-Karber method.
(f) Day of death: 8
(g) Day of death: 1, 1, 1, 1, 3

TABLE 7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial	Final	Change (b)	
MALE					
0	5/5	124	167	+ 43	--
500	(c) 4/5	125	158	+ 33	94.6
750	5/5	123	132	+ 9	79.0
1,250	(d) 0/5	124	(e)	(e)	(e)
1,750	(f) 0/5	127	(e)	(e)	(e)
2,500	(g) 0/5	124	(e)	(e)	(e)
FEMALE					
0	5/5	100	122	+ 22	--
500	5/5	99	117	+ 18	95.9
750	(h) 2/5	99	85	- 14	69.7
1,250	(i) 0/5	100	(e)	(e)	(e)
1,750	(j) 0/5	99	(e)	(e)	(e)
2,500	(k) 0/5	99	(e)	(e)	(e)

(a) Number surviving/number initially in group
(b) Mean body weight change of the survivors
(c) Day of death: 2 (judged accidental)
(d) Day of death: 8, 8, 9, 9, 10
(e) No data are reported due to the 100% mortality in this group.
(f) Day of death: 1 (accidental), 6, 8 (not compound related), 8, 8
(g) Day of death: 3, 4, 4, 5, 5
(h) Day of death: 10, 10, 13
(i) Day of death: 5, 5, 7, 8, 8
(j) Day of death: 6, 6, 7, 7, 7
(k) Day of death: 2, 3, 4, 4, 5

THIRTEEN-WEEK STUDIES

Two of 10 male rats that received 750 mg/kg dimethylvinyl chloride died before the end of the study (Table 8). The deaths of two female rats were not considered to be compound related. The final mean body weights were 25% and 37% lower than that of the vehicle controls for males and 9% and 23% lower for females that received 500 or 750 mg/kg.

Compound-related clinical signs in the 500 and 750 mg/kg groups included rough hair, inactivity, and perianal wetness. Compound-related histopathologic changes were observed in the liver, intestine, bone marrow, and testis (Table 9). The necrosis in the intestine involved mainly the crypts of either the duodenum or jejunum; the observed incidence at each location depended on the portion of the upper small intestine present on the slide. The changes were distributed focally and included minimal to mild involvement of cells at the base of the crypts. The crypts showed varying stages of degeneration with pyknosis and karyorrhexis, and the surrounding crypt cells often appeared swollen. Similar changes occurred in the colonic mucosa but at a lower incidence. Bone marrow hypoplasia was characterized by a minimal to moderate decrease in marrow cellular elements, and the erythropoietic cells appeared to be most affected. The vacuolization of hepatocytes was generally mild and had a periportal distribution.

TABLE 8. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change (b)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	108	244	+ 136	--
63	10/10	111	253	+ 142	103.7
125	10/10	114	261	+ 147	107.0
250	10/10	110	244	+ 134	100.0
500	10/10	109	184	+ 75	75.4
750	(c) 8/10	100	153	+ 53	62.7
FEMALE					
0	10/10	91	158	+ 67	--
63	(d) 9/10	90	160	+ 70	101.3
125	10/10	90	165	+ 75	104.4
250	10/10	95	165	+ 70	104.4
500	(d) 9/10	88	144	+ 56	91.1
750	10/10	87	122	+ 35	77.2

(a) Number surviving/number initially in group
(b) Mean body weight change of the survivors
(c) Week of death: 3, 10
(d) Death judged accidental

TABLE 9. INCIDENCES OF COMPOUND-RELATED LESIONS IN RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Site/Lesion	Dose (mg/kg) 0	63	125	250	500	750
MALE						
Liver						
Periportal vacuolar change	0/10	0/10	0/10	2/10	7/10	4/10
Necrosis, centrilobular or focal	0/10	0/10	0/10	0/10	0/10	3/10
Jejunum/duodenum						
Focal necrosis, crypts	0/6	0/10	0/9	2/10	7/10	3/5
Colon						
Focal necrosis	0/10	0/10	0/10	0/10	1/10	2/10
Bone marrow						
Hypoplasia	0/10	0/10	0/10	0/10	4/10	3/10
Testis						
Hypoplasia of seminiferous tubules and reduction of spermatozoa in testicle and epididymis	0/10	(a) --	--	--	--	7/10
FEMALE						
Liver						
Periportal vacuolar change	0/10	0/9	0/10	2/10	7/9	7/10
Necrosis, centrilobular or focal	0/10	0/9	0/10	0/10	0/9	0/10
Jejunum/duodenum						
Focal necrosis, crypts	0/7	0/9	0/10	1/10	4/9	7/7
Colon						
Focal necrosis	0/9	0/9	0/10	0/10	0/9	2/10
Bone marrow						
Hypoplasia	0/10	0/8	0/10	2/9	2/9	7/10

(a) No data available

Dose Selection Rationale: Based on histopathologic changes at doses of 250 mg/kg or more and significant effects on body weight at 500 mg/kg or more, doses selected for rats for the 2-year studies were 100 and 200 mg/kg dimethylvinyl chloride administered in corn oil by gavage, 5 days per week.

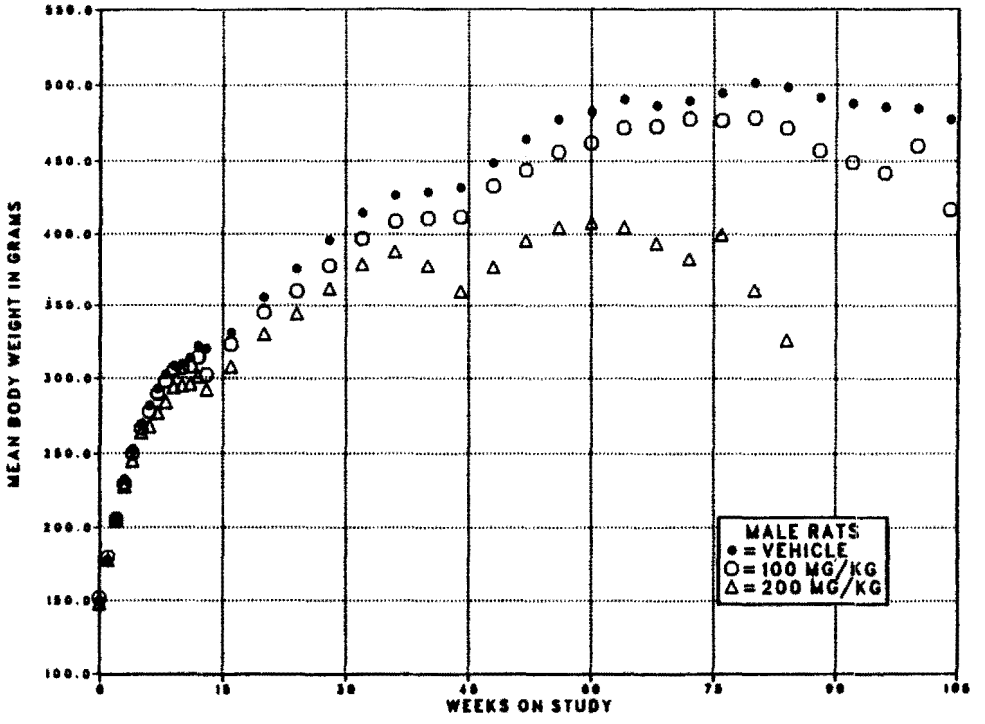
TWO-YEAR STUDIES

Body Weights and Clinical Signs

Throughout most of the study, mean body weights of dosed male rats were notably lower than those of the vehicle controls (Table 10 and Figure 1). After week 40, the mean body weights of the high dose male rats were over 10% lower than those of the vehicle controls. Mean body weights of high dose female rats were lower than those of the vehicle controls throughout most of the study. After week 56, mean body weights of low dose female rats were greater than those of the vehicle controls. During the second year of the studies, many dosed animals, particularly in the high dose group, had crusts around the nose and mouth. Some dosed animals had swelling of the nose and, occasionally, tilted heads.

TABLE 10. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	100 mg/kg Av. Wt. (grams)	100 mg/kg Wt. (percent of veh. controls)	100 mg/kg No. of Survivors	200 mg/kg Av. Wt. (grams)	200 mg/kg Wt. (percent of veh. controls)	200 mg/kg No. of Survivors
MALE								
0	150	50	152	101	50	148	99	50
1	178	50	180	101	50	178	100	50
2	207	50	206	100	50	206	100	50
3	233	50	230	99	50	228	98	50
4	253	50	250	99	50	245	97	50
5	270	50	267	99	50	264	98	50
6	282	50	278	99	50	268	95	50
7	293	50	290	99	50	277	95	50
8	303	50	298	98	50	284	94	50
9	309	50	306	99	50	294	95	50
10	310	50	307	99	50	295	95	50
11	314	50	308	98	50	296	94	50
12	322	50	314	98	50	301	93	50
13	320	50	302	94	50	292	91	50
20	356	50	345	97	50	330	93	50
24	376	50	360	96	50	344	91	50
28	396	50	378	95	50	362	91	50
32	415	50	397	96	50	379	91	50
36	427	50	409	96	49	388	91	50
40	429	50	411	96	49	378	88	50
44	432	49	412	95	49	360	83	48
48	449	48	433	96	49	377	84	46
52	465	47	444	95	48	396	85	42
56	478	47	456	95	48	405	85	37
60	483	46	462	96	47	408	84	32
64	491	46	472	96	47	405	82	25
68	487	45	473	97	47	394	81	14
72	490	45	478	98	45	383	78	9
76	495	45	477	96	45	400	81	4
80	502	45	479	95	40	361	72	2
84	499	45	472	95	39	326	65	1
88	492	45	457	93	35			
92	488	45	449	92	27			
96	486	43	442	91	20			
100	485	41	460	95	13			
104	478	38	417	87	8			
FEMALE								
0	117	50	119	102	50	117	100	50
1	131	50	132	101	50	130	99	50
2	145	50	143	99	50	142	98	50
3	155	50	154	99	50	152	98	50
4	165	50	162	98	50	160	97	50
5	172	50	171	99	50	169	98	50
6	176	50	175	99	50	172	98	50
7	181	50	181	100	50	177	98	50
8	186	50	187	101	50	183	98	50
9	188	50	188	100	50	185	98	50
10	190	50	189	99	50	185	97	50
11	191	50	188	98	50	186	97	50
12	196	50	193	98	50	189	96	50
13	196	50	195	99	50	191	97	50
16	205	50	204	100	50	195	95	50
20	210	50	207	99	50	201	96	48
24	216	50	212	98	50	206	95	48
28	223	50	216	97	50	211	95	48
32	230	50	225	98	50	217	94	48
36	236	50	230	97	50	223	94	48
40	243	50	241	99	50	224	92	48
44	249	50	246	99	50	225	90	47
48	252	50	251	100	50	229	91	47
52	253	50	254	100	50	232	92	46
56	260	50	264	102	50	235	90	44
60	263	50	271	103	50	240	91	39
64	272	49	281	103	49	242	89	37
68	271	49	285	105	48	243	90	33
72	279	49	293	105	48	242	87	21
76	286	48	299	105	47	243	85	10
80	296	47	308	104	45	252	85	7
84	295	46	312	106	39	239	81	4
88	294	46	306	104	36	234	80	2
92	296	45	309	104	33	246	83	1
96	300	45	310	103	28	227	76	1
100	303	43	320	106	14			
104	303	41	317	105	11			



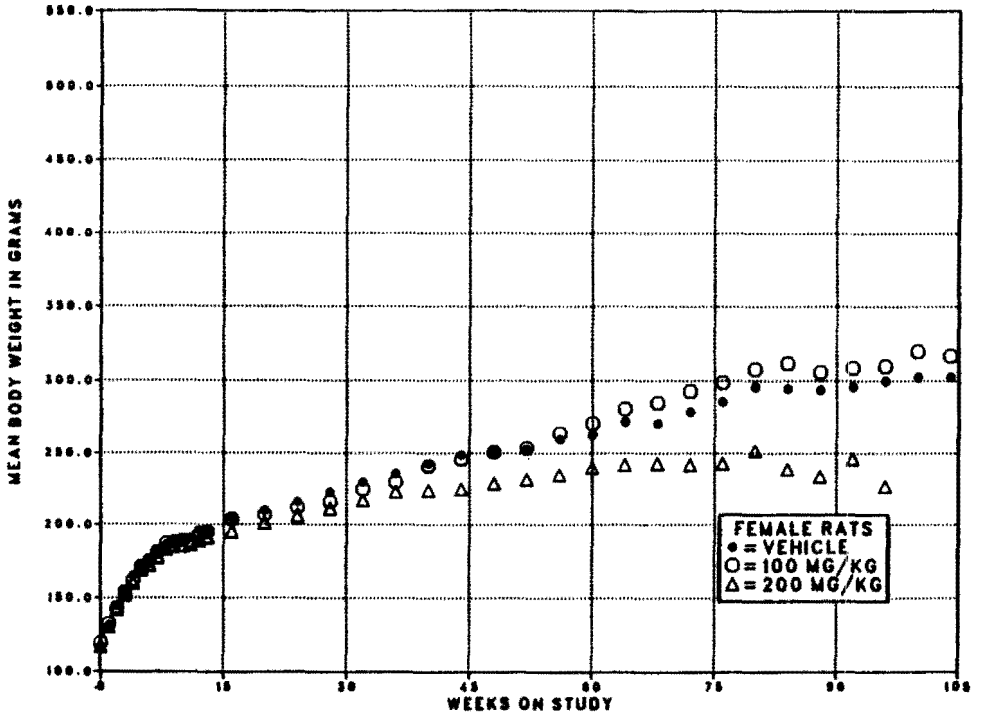


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED DIMETHYLVINYL CHLORIDE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered dimethylvinyl chloride at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 2. The survival of the dosed groups of males (low dose after week 88, high dose after week 55) and females (low dose after week 85, high dose after week 55) was significantly lower than that of the vehicle controls based on life table comparisons (Table 11). The survival of both the male and female high dose groups was significantly lower than that of the low dose groups ($P<0.001$).

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the nasal cavity, brain, oral cavity, esophagus, forestomach, thyroid gland, duodenum, and mammary gland. Histopathologic findings on neoplasms in rats are summarized in Appendix A (Tables A1 and A2); Appendix A (Tables A3 and A4) also gives the survival and tumor status for individual male and female rats. Findings on nonneoplastic lesions are summarized in Appendix C (Tables C1 and C2). Appendix E (Tables E1 and E2) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). The statistical analyses and interpretation of tumor incidence data for rats were complicated by the marked reduction in survival in dosed male and female rats when compared with that of the vehicle controls. No vehicle control animals were killed when dosed animals were dying. Consequently, the incidental tumor test has reduced sensitivity, since there is little overlapping of survival in the dosed and vehicle control groups. Hence, the incidental tumor test was not given primary emphasis, although for completeness the results of this test are given in Appendix E. Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 11. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	12	41	48
Accidentally killed	0	0	2
Killed at termination	38	7	0
Died during termination period	0	2	0
Survival P values (c)	<0.001	<0.001	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	6	39	50
Accidentally killed	1	0	0
Killed at termination	41	11	0
Died during termination period	2	0	0
Survival P values (c)	<0.001	<0.001	<0.001

(a) Terminal-kill period: week 104
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

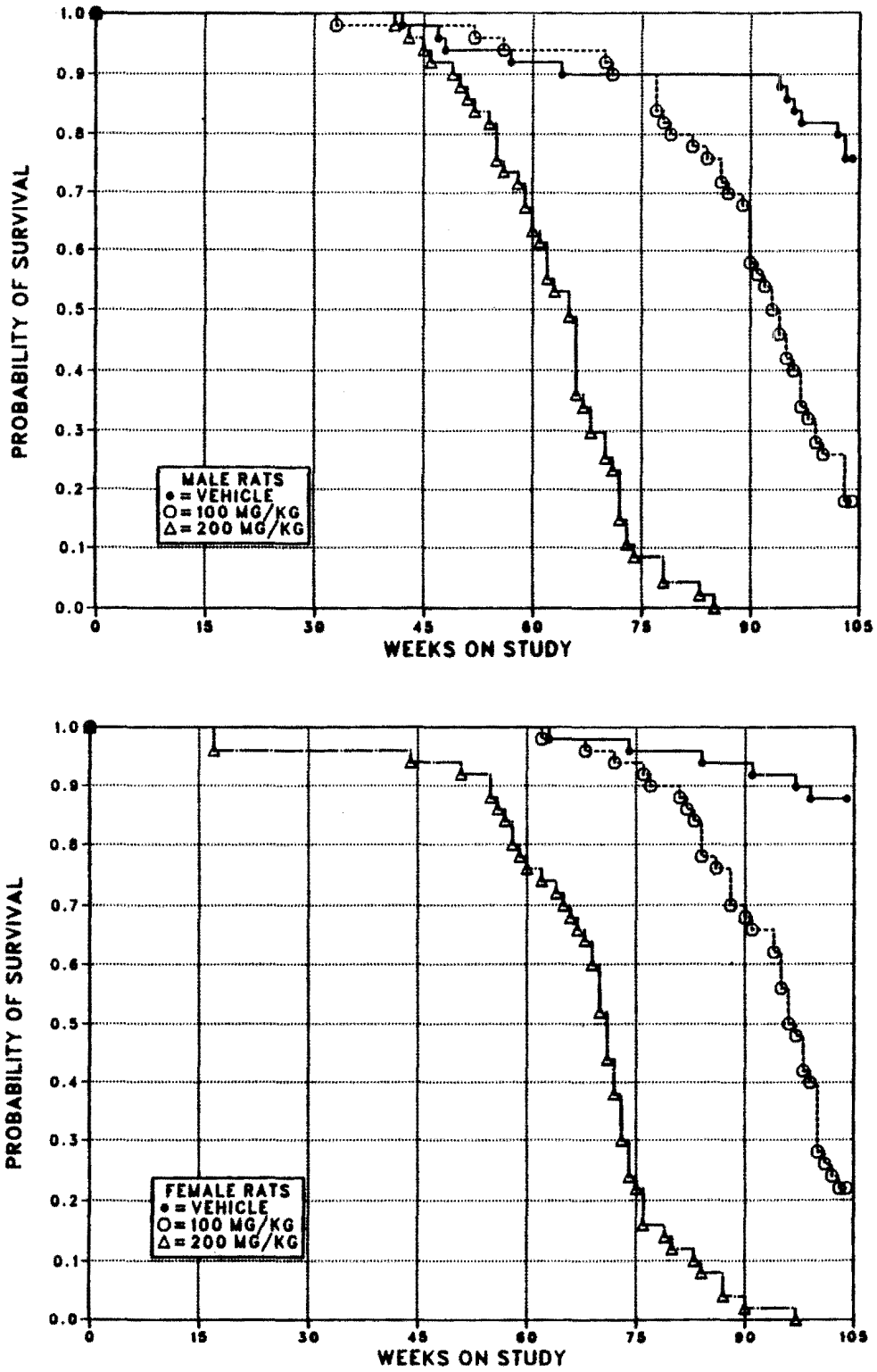


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED DIMETHYLVINYL CHLORIDE IN CORN OIL BY GAVAGE FOR TWO YEARS

Nasal Cavity: Epithelial hyperplasia and squamous metaplasia were seen at low incidences in dosed male and female rats, but the incidences were greater than those of the vehicle controls (Table 12).

Malignant epithelial neoplasms of the nasal cavity occurred with significantly increased incidences in dosed male and female rats; nasal cavity neoplasms were not observed in vehicle control rats (Table 13). Malignant epithelial neoplasms were combined on the premise that they all originated from the epithelial linings of the nasal cavity/adnexal structures and because of the difficulty in defining the exact epithelium of origin due to the expansile nature of the neoplasms. These tumors included carcinomas, not otherwise specified (NOS), squamous cell carcinomas, and adenocarcinomas, NOS. These neoplasms originated most often from the respiratory epithelium of the nasal septum and turbinates, epithelium of the submucosal glands, or the stratified squamous epithelium of the nasolacrimal duct. Most were poorly differentiated and contained morphologic components that included interconnecting cords of keratinized and nonkeratinized stratified squamous epithelium, cuboidal or columnar cells arranged in poorly defined tubulo-alveolar patterns, and solid clusters or sheets of pleomorphic cells. Other malignant tumors observed were two carcinosarcomas and a rhabdomyosarcoma. The malignant neoplasms were highly aggressive and often invaded or metastasized to surrounding structures including the maxillary and cranial bones, brain, and regional lymph nodes.

Carcinomas invasive to the brain from the nasal cavity were observed in at least 52% of the high dose male rats and 50% of the high dose female rats (Table 14). According to the protocols of the studies, the nasal cavity was not one of the tissues requiring examination, and it was not saved for animals that died before week 80. The nasal cavity was recognized as an affected site after invasive carcinomas to the brain were found in some animals that died early in the studies. Several rats without diagnoses of primary carcinoma of the nasal cavity had invasive carcinomas to the brain. Of these, five male and three female rats did not have nasal sections taken. A carcinoma invasive to the brain was observed in one male and one female rat from the high dose groups, but nasal sections taken from these animals did not contain tumors. These invasive carcinomas, however, were histologically similar to those nasal carcinomas that invaded the brains of other rats in these studies and were considered to have originated in the nasal cavity. The only primary brain tumors in these studies were astrocytomas observed in 1/50 vehicle control male rat and 2/50 low dose female rats.

TABLE 12. NUMBER OF RATS WITH LESIONS OF THE NASAL CAVITY IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

	Male			Female		
	Dose (mg/kg)			Dose (mg/kg)		
Lesion	0	100	200	0	100	200
Number of rats examined grossly	50	50	50	50	50	50
Number of nasal cavities examined microscopically	47	46	32	50	49	41
Hyperplasia, epithelial or atypical	0	4	0	0	3	2
Squamous metaplasia	0	2	2	1	2	4
Adenoma, NOS	0	1	0	0	1	0
Squamous cell papilloma	0	0	1	0	0	0
Squamous cell carcinoma	0	3	0	0	2	2
Adenocarcinoma, NOS	0	8	4	0	3	6
Carcinoma, NOS	0	12	24	0	11	28
Carcinosarcoma	0	1	0	0	0	1
Rhabdomyosarcoma	0	0	0	0	0	1

TABLE 13. ANALYSIS OF NASAL CAVITY TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE (a)

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Adenoma			
Overall Rates	0/47 (0%)	(b) 1/46 (2%)	0/32 (0%)
Squamous Cell Papilloma			
Overall Rates	0/47 (0%)	0/46 (0%)	(c) 1/32 (3%)
Squamous Cell Carcinoma			
Overall Rates	0/47 (0%)	3/46 (7%)	0/32 (0%)
Adenocarcinoma			
Overall Rates	0/47 (0%)	8/46 (17%)	4/32 (13%)
Adjusted Rates	0.0%	46.8%	100.0%
Terminal Rates	0/38 (0%)	3/9 (33%)	0/0
Week of First Observation		79	45
Life Table Tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P=0.028		
Fisher Exact Test		P=0.003	P=0.024
Carcinoma			
Overall Rates	0/47 (0%)	12/46 (26%)	24/32 (75%)
Adjusted Rates	0.0%	36.7%	93.5%
Terminal Rates	0/38 (0%)	0/9 (0%)	0/0
Week of First Observation		70	58
Life Table Tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Carcinosarcoma			
Overall Rates	0/47 (0%)	1/46 (2%)	0/32 (0%)
Malignant Epithelial Tumors (Carcinoma, Squamous Cell Carcinoma, or Adenocarcinoma) (d)			
Overall Rates	0/47 (0%)	23/46 (50%)	28/32 (88%)
Adjusted Rates	0.0%	71.8%	100%
Terminal Rates	0/38 (0%)	3/9 (33%)	0/0
Week of First Observation		70	45
Life Table Tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
FEMALE			
Adenoma			
Overall Rates	0/50 (0%)	1/49 (2%)	0/41 (0%)
Squamous Cell Carcinoma			
Overall Rates	0/50 (0%)	2/49 (4%)	2/41 (5%)
Carcinoma			
Overall Rates	0/50 (0%)	11/49 (22%)	28/41 (68%)
Adjusted Rates	0.0%	44.3%	100.0%
Terminal Rates	0/43 (0%)	3/11 (27%)	0/0
Week of First Observation		72	55
Life Table Tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001

TABLE 13. ANALYSIS OF NASAL CAVITY TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
FEMALE (Continued)			
Adenocarcinoma			
Overall Rates	0/50 (0%)	3/49 (6%)	6/41 (15%)
Adjusted Rates	0.0%	20.1%	40.0%
Terminal Rates	0/43 (0%)	1/11 (9%)	0/0
Week of First Observation		98	67
Life Table Tests	P<0.001	P=0.011	P<0.001
Cochran-Armitage Trend Test	P=0.005		
Fisher Exact Test		P=0.117	P=0.007
Carcinosarcoma			
Overall Rates	0/50 (0%)	0/49 (0%)	1/41 (2%)
Rhabdomyosarcoma			
Overall Rates	0/50 (0%)	0/49 (0%)	1/41 (2%)
Malignant Epithelial Tumors (Carcinoma, Squamous Cell Carcinoma, or Adenocarcinoma) (e)			
Overall Rates	0/50 (0%)	16/49 (33%)	35/41 (85%)
Adjusted Rates	0.0%	61.6%	100.0%
Terminal Rates	0/43 (0%)	4/11 (36%)	0/0
Week of First Observation		72	55
Life Table Tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) The animal with the adenoma also had an adenocarcinoma.
(c) The animal with the squamous cell papilloma also had a carcinoma.
(d) No nasal cavity tumors have been observed in 350 corn oil vehicle control male rats at the study laboratory; historical incidence in NTP studies (mean): 1/1,100 (0.1%).
(e) No nasal cavity tumors have been observed in 350 corn oil vehicle control female rats at the study laboratory; historical incidence in NTP studies: 0/1,100.

TABLE 14. INCIDENCE OF RATS WITH TUMOR INVASION TO THE BRAIN FROM THE NASAL CAVITY IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Carcinoma, NOS, invasive	0/50	8/50 (16%)	26/50 (52%)
Adenocarcinoma, invasive	0/50	3/50 (6%)	3/50 (6%)
FEMALE			
Carcinoma, NOS, invasive	0/50	7/50 (14%)	25/50 (50%)
Adenocarcinoma, invasive	0/50	2/50 (4%)	5/50 (10%)
Rhabdomyosarcoma, invasive	0/50	0/50	1/50 (2%)
Carcinosarcoma, invasive	0/50	0/50	1/50 (2%)

Oral Cavity (Mouth, Palate, Lip, Tongue, Oral Mucosa, or Gum): Squamous cell papillomas and squamous cell papillomas or carcinomas (combined) in female rats occurred with significant positive trends (Table 15). The incidences of squamous cell carcinomas in low dose male rats and squamous cell papillomas or carcinomas (combined) in high dose female rats were significantly greater than those in the vehicle controls.

TABLE 15. ANALYSIS OF ORAL CAVITY TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Squamous Cell Carcinoma			
Overall Rates	0/50 (0%)	5/50 (10%)	2/50 (4%)
Adjusted Rates	0.0%	21.9%	100.0%
Terminal Rates	0/38 (0%)	1/9 (11%)	0/0
Week of First Observation		71	41
Life Table Tests	P<0.001	P=0.007	P=0.030
Cochran-Armitage Trend Test	P=0.238		
Fisher Exact Test		P=0 028	P=0.247
Squamous Cell Papilloma			
Overall Rates	0/50 (0%)	0/50 (0%)	2/50 (4%)
Squamous Cell Papilloma or Carcinoma (a)			
Overall Rates	0/50 (0%)	5/50 (10%)	4/50 (8%)
Adjusted Rates	0.0%	21.9%	100.0%
Terminal Rates	0/38 (0%)	1/9 (11%)	0/0
Week of First Observation		71	41
Life Table Tests	P<0.001	P=0.007	P=0.001
Cochran-Armitage Trend Test	P=0.070		
Fisher Exact Test		P=0.028	P=0.059
FEMALE			
Squamous Cell Papilloma			
Overall Rates	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates	0.0%	0.0%	21.9%
Terminal Rates	0/43 (0%)	0/11 (0%)	0/0
Week of First Observation			65
Life Table Tests	P<0.001	(b)	P=0.004
Cochran-Armitage Trend Test	P=0.015		
Fisher Exact Test		(b)	P=0.059
Squamous Cell Carcinoma			
Overall Rates	0/50 (0%)	2/50 (4%)	1/50 (2%)
Squamous Cell Papilloma or Carcinoma (c)			
Overall Rates	0/50 (0%)	2/50 (4%)	5/50 (10%)
Adjusted Rates	0.0%	8.1%	41.4%
Terminal Rates	0/43 (0%)	0/11 (0%)	0/0
Week of First Observation		95	65
Life Table Tests	P<0 001	P=0.126	P<0.001
Cochran-Armitage Trend Test	P=0.016		
Fisher Exact Test		P=0 247	P=0.028

(a) No oral cavity tumors have been observed in 350 corn oil vehicle control male rats at the study laboratory; historical incidence in NTP studies (mean): 2/1,110 (0.2%).
(b) No P value is reported because no tumors were observed in the 100 mg/kg and vehicle control groups.
(c) No oral cavity tumors have been observed in 350 corn oil vehicle control female rats at the study laboratory; historical incidence in NTP studies (mean): 3/1,100 (0.3%).

Esophagus: The incidences of epithelial hyperplasia were increased in dosed rats (Table 16). The incidence of squamous cell papillomas or carcinomas (combined) in low dose male rats was significantly greater than that in the vehicle control group.

TABLE 16. ANALYSIS OF ESOPHAGEAL LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Epithelial Hyperplasia			
Overall Rates	0/50 (0%)	6/50 (12%)	4/49 (8%)
Squamous Cell Papilloma			
Overall Rates	0/50 (0%)	2/50 (4%)	3/49 (6%)
Adjusted Rates	0.0%	16.7%	20.8%
Terminal Rates	0/38 (0%)	1/9 (11%)	0/0
Week of First Observation		99	61
Life Table Tests	P<0.001	P=0.043	P=0.011
Cochran-Armitage Trend Test	P=0.079		
Fisher Exact Test		P=0.247	P=0.117
Squamous Cell Carcinoma			
Overall Rates	0/50 (0%)	4/50 (8%)	1/49 (2%)
Adjusted Rates	0.0%	28.1%	4.3%
Terminal Rates	0/38 (0%)	2/9 (22%)	0/0
Week of First Observation		90	66
Life Table Tests	P=0.001	P=0.004	P=0.366
Cochran-Armitage Trend Test	P=0.383		
Fisher Exact Test		P=0.059	P=0.495
Squamous Cell Papilloma or Carcinoma (a)			
Overall Rates	0/50 (0%)	6/50 (12%)	4/49 (8%)
Adjusted Rates	0.0%	42.2%	24.3%
Terminal Rates	0/38 (0%)	3/9 (33%)	0/0
Week of First Observation		90	61
Life Table Tests	P<0.001	P<0.001	P=0.004
Cochran-Armitage Trend Test	P=0.076		
Fisher Exact Test		P=0.013	P=0.056
FEMALE			
Epithelial Hyperplasia			
Overall Rates	0/49 (0%)	7/50 (14%)	4/49 (8%)
Squamous Cell Carcinoma (b)			
Overall Rates	0/49 (0%)	3/50 (6%)	1/49 (2%)
Adjusted Rates	0.0%	16.4%	12.5%
Terminal Rates	0/42 (0%)	1/11 (9%)	0/0
Week of First Observation		95	79
Life Table Tests	P=0.002	P=0.024	P=0.157
Cochran-Armitage Trend Test	P=0.378		
Fisher Exact Test		P=0.125	P=0.500

(a) One squamous cell carcinoma has been observed in 1,037 (0.1%) male corn oil vehicle control rats in NTP studies.
(b) No esophageal tumors have been observed in 1,036 female corn oil vehicle controls in NTP studies.

Forestomach: Epithelial hyperplasia was observed at increased incidences in dosed rats (Table 17). This lesion was considered to be preneoplastic and was characterized by a thickening of the epithelium, down-growth of basal cells, and cellular atypia consisting of a loss of cell polarity, increased basophilic staining of the cytoplasm, and pleomorphism.

The incidences of squamous cell papillomas and squamous cell carcinomas in low dose male rats, squamous cell carcinomas in low dose female rats, and squamous cell papillomas or carcinomas (combined) in low dose male and low dose female rats were significantly greater than those in the vehicle controls (Table 17). The squamous cell papillomas were exophytic papilliferous growths consisting of keratinized, stratified squamous epithelium overlaying thin connective tissue cords. The carcinomas consisted of cords and nests of stratified squamous epithelium which invaded adjacent tissues.

TABLE 17. ANALYSIS OF FORESTOMACH LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Epithelial Hyperplasia			
Overall Rates	0/49 (0%)	24/50 (48%)	19/50 (38%)
Squamous Cell Papilloma (a)			
Overall Rates	0/49 (0%)	7/50 (14%)	0/50 (0%)
Adjusted Rates	0.0%	52.2%	0.0%
Terminal Rates	0/38 (0%)	4/9 (44%)	0/0
Week of First Observation		90	
Life Table Tests	P<0.001	P<0.001	(b)
Cochran-Armitage Trend Test	P=0.585N		
Fisher Exact Test		P=0.007	(b)
Squamous Cell Carcinoma (c)			
Overall Rates	0/49 (0%)	7/50 (14%)	0/50 (0%)
Adjusted Rates	0.0%	30.4%	0.0%
Terminal Rates	0/38 (0%)	1/9 (11%)	0/0
Week of First Observation		82	
Life Table Tests	P<0.001	P<0.001	(b)
Cochran-Armitage Trend Test	P=0.585N		
Fisher Exact Test		P=0.007	(b)
Squamous Cell Papilloma or Carcinoma			
Overall Rates	0/49 (0%)	14/50 (28%)	0/50 (0%)
Adjusted Rates	0.0%	70.1%	0.0%
Terminal Rates	0/38 (0%)	5/9 (56%)	0/0
Week of First Observation		82	
Life Table Tests	P<0.001	P<0.001	(b)
Cochran-Armitage Trend Test	P=0.556N		
Fisher Exact Test		P<0.001	(b)

TABLE 17. ANALYSIS OF FORESTOMACH LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
FEMALE			
Epithelial Hyperplasia			
Overall Rates	0/50 (0%)	29/50 (58%)	24/49 (49%)
Squamous Cell Papilloma (d)			
Overall Rates	1/50 (2%)	4/50 (8%)	1/49 (2%)
Adjusted Rates	2.0%	25.5%	25.0%
Terminal Rates	0/43 (0%)	2/11 (18%)	0/0
Week of First Observation	74	98	87
Life Table Tests	P=0.005	P=0.027	P=0.356
Cochran-Armitage Trend Test	P=0.593		
Fisher Exact Test		P=0.181	P=0.748
Squamous Cell Carcinoma (e)			
Overall Rates	0/50 (0%)	5/50 (10%)	1/49 (2%)
Adjusted Rates	0.0%	22.2%	2.7%
Terminal Rates	0/43 (0%)	1/11 (9%)	0/0
Week of First Observation		90	64
Life Table Tests	P=0.002	P=0.004	P=0.444
Cochran-Armitage Trend Test	P=0.391		
Fisher Exact Test		P=0.028	P=0.495
Squamous Cell Papilloma or Carcinoma			
Overall Rates	1/50 (2%)	9/50 (18%)	2/49 (4%)
Adjusted Rates	2.0%	43.6%	27.0%
Terminal Rates	0/43 (0%)	3/11 (27%)	0/0
Week of First Observation	74	90	64
Life Table Tests	P<0.001	P<0.001	P=0.142
Cochran-Armitage Trend Test	P=0.415		
Fisher Exact Test		P=0.008	P=0.492

(a) Historical incidence at study laboratory (mean): 0/350; historical incidence of squamous cell papillomas of the stomach in NTP studies: 4/1,091 (0.4%)
(b) No P values are reported because no tumors were observed in the 200 mg/kg and vehicle control groups.
(c) Historical incidence at study laboratory: 0/350; historical incidence of squamous cell carcinomas of the stomach in NTP studies: 0/1,091
(d) Historical incidence at study laboratory (mean): 1/349 (0.3%); historical incidence of squamous cell papillomas of the stomach in NTP studies: 4/1,096 (0.4%)
(e) Historical incidence at study laboratory: 0/349; historical incidence in NTP studies: 0/1,096

Thyroid Gland: The incidences of follicular cell hyperplasia in dosed and vehicle control rats of each sex were similar (male: vehicle control, 1/50, 2%; low dose, 1/48, 2%; high dose, 0/47; female: vehicle control, 0/49; low dose, 1/49, 2%; high dose, 1/47, 2%). The incidences of follicular cell carcinomas and follicular cell adenomas or carcinomas (combined) in low dose female rats were significantly greater than those in the vehicle controls by life table analysis but not by the Fisher exact test (Table 18). In male rats, the incidences of follicular cell adenomas were as follows: vehicle control, 1/50 (2%); low dose, 2/48 (4%); high dose, 0/47.

Duodenal Mucosa: Necrosis was observed at increased incidences in dosed male and female rats (male: vehicle control, 0/45; low dose, 2/49, 4%; high dose, 6/48, 13%; female: vehicle control, 0/47; low dose, 1/50, 2%; high dose, 8/47, 17%).

Mammary Gland: The incidence of fibroadenomas in low dose female rats was significantly greater than that in the vehicle controls by the life table test but not by the Fisher exact test (Table 19). Early deaths among female rats in the high dose group may account for the lower incidence of these tumors for this group when compared with the low dose and vehicle control groups.

TABLE 18. ANALYSIS OF THYROID GLAND TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
Follicular Cell Carcinoma (a)			
Overall Rates	1/49 (2%)	5/49 (10%)	0/47 (0%)
Adjusted Rates	2.4%	34.7%	0.0%
Terminal Rates	1/42 (2%)	3/10 (30%)	0/0
Week of First Observation	104	95	
Life Table Tests	P=0.003	P=0.002	(b)
Cochran-Armitage Trend Test	P=0.415N		
Fisher Exact Test		P=0.102	P=0.510N
Follicular Cell Adenoma or Carcinoma			
Overall Rates	1/49 (2%)	5/49 (10%)	1/47 (2%)
Adjusted Rates	2.4%	34.7%	2.9%
Terminal Rates	1/42 (2%)	3/10 (30%)	0/0
Week of First Observation	104	95	67
Life Table Tests	P=0.001	P=0.002	P=0.427
Cochran-Armitage Trend Test	P=0.576		
Fisher Exact Test		P=0.102	P=0.742

(a) Historical incidence at study laboratory (mean ± SD): 3/342 (0.9% ± 1%); historical incidence in NTP studies: 5/1,076 (0.5% ± 0.9%)
(b) No P value could be determined because all 200 mg/kg animals died before the first tumor was observed in the vehicle control group.

TABLE 19. ANALYSIS OF MAMMARY GLAND TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
Fibroadenoma (a)			
Overall Rates	10/50 (20%)	18/50 (36%)	5/50 (10%)
Adjusted Rates	23.3%	71.6%	100.0%
Terminal Rates	10/43 (23%)	6/11 (55%)	0/0
Week of First Observation	104	84	74
Life Table Tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P=0.139N		
Fisher Exact Test		P=0.059	P=0.131N
Adenocarcinoma (b)			
Overall Rates	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted Rates	2.0%	19.2%	0.0%
Terminal Rates	0/43 (0%)	1/11 (9%)	0/0
Week of First Observation	74	94	
Life Table Tests	P=0.112	P=0.055	P=0.735N
Cochran-Armitage Trend Test	P=0.390N		
Fisher Exact Test		P=0.181	P=0.500N

(a) Historical incidence of all benign mammary gland tumors at study laboratory (mean ± SD): 86/350 (25% ± 9%); historical incidence in NTP studies: 280/1,100 (26% ± 8%)
(b) Historical incidence of all malignant mammary gland tumors at study laboratory (mean ± SD): 4/350 (1% ± 2%); historical incidence in NTP studies: 17/1,100 (2% ± 2%)

SINGLE-ADMINISTRATION STUDIES

Unfasted: All mice that received 3,160 or 10,000 mg/kg dimethylvinyl chloride died by day 5 (Table 20). Compound-related clinical signs included weakness, staggering gait, prostration, shallow breathing, diarrhea, and distended stomach.

Fasted: All mice that received 3,160 mg/kg dimethylvinyl chloride died by day 2 (Table 20). Compound-related clinical signs included distended stomach, inactivity, prostration, and incoordination.

FOURTEEN-DAY STUDIES

All mice that received 1,500 or 2,000 mg/kg dimethylvinyl chloride and 4/5 males and 5/5 females that received 1,000 mg/kg died before the end of the studies (Table 21). Compound-related signs included inactivity, staggering gait, rough fur coat, labored/shallow breathing, weakness, hunched back, prostration, and opaque eyes.

TABLE 20. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Male			Female		
Dose (mg/kg)	Survival (a)	Initial Mean Body Weights (b) (grams)	Dose (mg/kg)	Survival (a)	Initial Mean Body Weights (b) (grams)
Unfasted					
100	5/5	20	100	5/5	19
316	5/5	22	316	5/5	19
1,000	5/5	21	1,000	5/5	19
3,160	(c) 0/5	21	3,160	(c) 0/5	19
10,000	(d) 0/5	22	10,000	(d) 0/5	19
Fasted (e)					
31.6	5/5	21	31.6	5/5	19
100	5/5	21	100	5/5	19
316	5/5	20	316	5/5	18
1,000	5/5	21	1,000	5/5	18
3,160	(f) 0/5	21	3,160	(f) 0/5	18

(a) Number surviving/number initially in group
(b) Final body weights not recorded
(c) Day of death: all 5
(d) Day of death: 1, 1, 2, 2, 2
(e) Mice were denied food 4 hours before gavage.
(f) Day of death: all 2

TABLE 21. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial	Final	Change (b)	
MALE					
0	5/5	22	23	+1	--
250	(c) 4/5	22	25	+3	108.7
500	5/5	23	24	+1	104.3
1,000	(d) 1/5	22	16	−6	69.6
1,500	(e) 0/5	22	(f)	(f)	(f)
2,000	(g) 0/5	23	(f)	(f)	(f)
FEMALE					
0	5/5	18	19	+1	--
250	5/5	18	18	0	94.7
500	5/5	19	20	+1	105.3
1,000	(h) 0/5	18	(f)	(f)	(f)
1,500	(g) 0/5	18	(f)	(f)	(f)
2,000	(g) 0/5	18	(f)	(f)	(f)

(a) Number surviving/number initially in group
(b) Mean body weight change of the survivors
(c) Death not compound related
(d) Day of death: 3, 4, 4, 5
(e) Day of death: 2, 2, 2, 2, 3
(f) No data are reported due to the 100% mortality in this group.
(g) Day of death: all 2
(h) Day of death: 4, 4, 4, 4, 12

THIRTEEN-WEEK STUDIES

The vehicle control male mice received 750 mg/kg dimethylvinyl chloride once during week 10; as a result, four died (Table 22). All male and 9/10 female mice that received 750 mg/kg also died before the end of the studies. Clinical signs observed in the 750 mg/kg groups included decreased activity and prostration. At week 12, mean body weights relative to those of the vehicle controls were 7% lower for male mice that received 500 mg/kg dimethylvinyl chloride and 4.5% lower for female mice that received 750 mg/kg.

Necrosis of lymphopoietic cells (leading to atrophy of lymphoid tissue) was observed in the thymus, lymph nodes, and spleen (Table 23). Compound-related necrotic and/or degenerative changes also occurred in the pancreatic islets, liver, ovary, and testis. The severity of the lesions was greater in males than in females.

Dose Selection Rationale: Based on the pattern of histopathologic, necrotic, and degenerative changes at all doses (but most prominent at doses of 500 mg/kg and above), the doses originally selected for mice for the 2-year studies were 200 and 400 mg/kg dimethylvinyl chloride, administered in corn oil by gavage, 5 days per week. Because of the large number of deaths in the 400 mg/kg groups, the studies were restarted at doses of 100 and 200 mg/kg dimethylvinyl chloride.

TABLE 22. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial	Final	Change (b)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	(c) 5/10	27	29	+2	--
63	10/10	25	29	+4	100.0
125	10/10	26	30	+4	103.4
250	10/10	26	30	+4	103.4
500	10/10	26	27	+1	93.1
750	(d) 0/10	26	(e)	(e)	(e)
FEMALE					
0	10/10	17	22	+5	--
63	10/10	19	24	+5	109.1
125	10/10	20	23	+3	104.5
250	10/10	19	24	+5	109.1
500	10/10	20	23	+3	104.5
750	(f) 1/10	20	21	+1	95.5

(a) Number surviving/number initially in group
(b) Mean body weight change of the survivors
(c) Four deaths resulted from an accidental dosing with 750 mg/kg dimethylvinyl chloride of all vehicle control mice during week 10.
(d) Week of death: 1, 1, 1, 1, 2, 3, 3, 4, 7, 11
(e) No data reported due to the 100% mortality in this group.
(f) Week of death: 1, 3, 3, 3, 5, 8, 9, 9, 12

TABLE 23. INCIDENCES OF LESIONS IN MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Site/Lesion	Dose (mg/kg)						
	0 (a)	0 (b)	63	125	250	500	750
MALE							
Liver							
Necrosis	0/10	1/10	0/10	0/10	0/10	0/10	4/10
Vacuolization	0/10	0/10	0/10	0/10	0/10	2/10	1/10
Pancreatic islets							
Necrosis	0/10	5/10	1/10	0/10	0/10	3/10	8/10
Atrophy	0/10	0/10	0/10	0/10	0/10	0/10	6/10
Testis							
Spermatogenic hypoplasia	0/10	1/9	0/10	1/10	0/10	3/10	2/10
Bone marrow							
Hypoplasia	0/8	3/10	0/10	0/9	0/10	0/10	10/10
Mandibular lymph node							
Necrosis of lymphocytes	0/7	7/7	1/5	3/7	1/10	2/7	5/7
Lymphoid atrophy	0/7	0/7	0/5	0/7	0/10	0/7	5/7
Mesenteric lymph node							
Necrosis of lymphocytes	0/1	0/0	0/10	1/8	0/10	5/6	1/1
Thymus							
Necrosis	0/4	8/8	0/10	0/10	0/10	7/7	4/5
Lymphoid atrophy	0/4	3/8	0/10	0/10	0/10	0/7	2/5
Spleen							
Necrosis of lymphocytes	0/9	8/9	0/10	0/10	0/10	8/10	5/9
FEMALE							
Liver							
Necrosis	0/10	0/10	0/10	0/10	0/10	0/10	1/10
Vacuolization	0/10	0/10	0/10	0/10	0/10	1/10	7/10
Pancreatic islets							
Necrosis	0/10	0/10	0/10	0/10	0/10	1/10	4/10
Atrophy	0/10	0/10	0/10	0/10	0/10	0/10	3/10
Ovary							
Atrophy	0/9	0/10	0/10	0/10	0/9	0/10	5/8
Necrosis of granulosa cells	0/9	9/10	5/10	7/10	6/9	8/10	5/8
Bone marrow							
Hypoplasia	0/10	0/9	0/10	0/10	0/10	0/10	6/10
Mandibular lymph node							
Necrosis of lymphocytes	0/10	6/9	1/5	1/5	1/8	5/8	2/6
Lymphoid atrophy	0/10	0/9	0/5	0/5	0/8	0/8	1/6
Mesenteric lymph node							
Necrosis of lymphocytes	0/0	0/2	0/1	0/0	0/0	1/3	2/6
Thymus							
Necrosis	0/5	9/10	0/10	0/9	0/10	10/10	4/5
Lymphoid atrophy	0/5	0/10	0/10	0/9	0/10	0/10	1/5
Spleen							
Necrosis of lymphocytes	0/9	9/10	0/10	4/10	3/10	8/9	8/10

(a) Controls from another study at the same laboratory (for comparison only)
(b) Male controls from present study (received dimethylvinyl chloride, 750 mg/kg, once during week 10)

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice were 6%-24% lower than those of the vehicle controls after week 4 (Table 24 and Figure 3). The mean body weights of the low dose male mice were 2%-8% lower than those of the vehicle controls between weeks 2 and 76 and 9%-16% lower thereafter. Mean body weights of high dose female mice were at least 5% lower than those of the vehicle controls after week 44. Mean body weights of low dose female mice were 4%-11% lower than those of the vehicle controls after week 88.

TABLE 24. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Weeks on Study	Vehicle Control Av. Wt. (grams)	Vehicle Control No. of Survivors	100 mg/kg Av. Wt. (grams)	100 mg/kg Wt. (percent of veh. controls)	100 mg/kg No. of Survivors	200 mg/kg Av. Wt. (grams)	200 mg/kg Wt. (percent of veh. controls)	200 mg/kg No. of Survivors
MALE								
0	23 5	50	23 0	98	50	23 1	98	50
1	24 3	50	24 4	100	50	24 5	101	49
2	26 1	48	25 1	96	50	25 4	97	49
3	26 9	48	25 9	96	47	26 0	97	44
4	29 3	48	27 1	92	47	27 3	93	44
5	29 3	48	28 0	96	47	27 5	94	44
6	29 8	48	28 7	96	47	28 0	94	44
7	30 0	48	28 9	96	47	28 1	94	44
8	31 3	48	29 9	96	47	28 9	92	44
9	32 1	48	30 4	95	47	29 5	92	44
10	32 4	48	30 9	95	47	29 9	92	44
11	33 2	48	31 3	94	47	30 2	91	44
12	33 6	48	32 5	97	47	31 1	93	44
13	33 5	48	32 2	96	47	30 9	92	44
16	34 9	48	34 2	98	47	32 8	94	44
20	36 6	48	35 2	96	47	33 5	92	44
24	37 2	48	35 8	96	47	33 7	91	44
28	38 1	48	37 3	98	47	35 0	92	44
32	37 8	48	36 9	98	47	35 0	93	44
36	39 0	48	37 2	95	47	35 7	92	44
40	38 7	48	36 7	95	47	35 3	91	44
44	39 4	46	37 1	94	47	35 8	91	44
48	40 0	46	38 0	95	47	36 0	90	44
52	40 4	46	38 6	96	46	36 3	90	44
56	40 4	46	38 7	96	46	36 5	90	40
60	40 7	45	39 5	97	46	37 2	91	39
64	41 8	45	39 9	95	45	37 8	90	37
68	43 1	45	40 8	95	45	37 9	88	34
72	43 1	45	40 6	94	44	38 5	89	31
76	43 5	44	39 7	91	42	37 3	86	28
80	44 3	44	40 2	91	37	36 8	83	20
84	42 8	44	39 3	92	32	37 0	86	11
88	43 9	43	38 4	87	28	35 6	81	10
92	44 1	42	37 1	84	20	33 7	76	6
96	42 9	41	37 1	86	15	37 0	86	2
100	41 6	38	36 5	88	10	35 5	85	2
FEMALE								
0	18 3	50	18 4	101	50	18 1	99	50
1	18 9	50	19 8	105	50	19 8	105	49
2	19 7	50	20 3	103	50	20 4	104	49
3	20 3	50	20 8	102	47	21 0	103	43
4	21 8	50	22 0	101	47	22 4	103	43
5	21 3	50	22 4	105	47	22 3	105	43
6	22 0	50	23 0	105	47	22 7	103	43
7	22 2	50	22 5	101	47	22 7	102	43
8	22 8	50	23 2	102	46	23 0	101	43
9	22 7	50	23 5	104	46	23 3	103	43
10	22 9	50	23 7	103	46	23 6	103	43
11	23 8	50	24 1	101	46	24 3	102	43
12	23 9	50	24 7	103	46	24 4	102	43
13	24 3	50	24 5	101	46	24 0	99	43
16	24 6	50	25 5	104	46	25 1	102	43
20	25 8	50	26 1	101	46	25 3	98	43
24	25 9	50	26 6	103	46	25 3	98	43
28	27 5	50	27 7	101	46	26 4	96	43
32	27 5	50	27 3	99	46	26 0	95	43
36	28 1	50	27 8	99	45	26 9	96	43
40	27 5	50	27 5	100	45	26 6	97	42
44	28 3	50	28 1	99	45	26 8	95	42
48	28 7	50	28 8	100	43	27 3	95	42
52	29 4	49	29 2	99	43	27 4	93	42
56	29 8	49	29 2	98	41	27 7	93	40
60	30 3	49	29 9	99	39	28 3	93	37
64	31 3	49	30 6	98	38	29 3	94	37
68	32 4	49	30 9	95	38	30 1	93	36
72	33 1	48	32 2	97	34	30 6	92	34
76	32 9	48	32 0	97	33	30 4	92	28
80	33 5	47	31 9	95	28	31 3	93	23
84	32 9	47	31 8	97	24	31 0	94	20
88	33 7	46	30 8	91	22	29 9	89	17
92	34 3	45	31 6	92	13	31 0	90	10
96	34 0	42	32 6	96	9	29 7	87	7
100	33 6	41	29 9	89	7	28 5	85	4

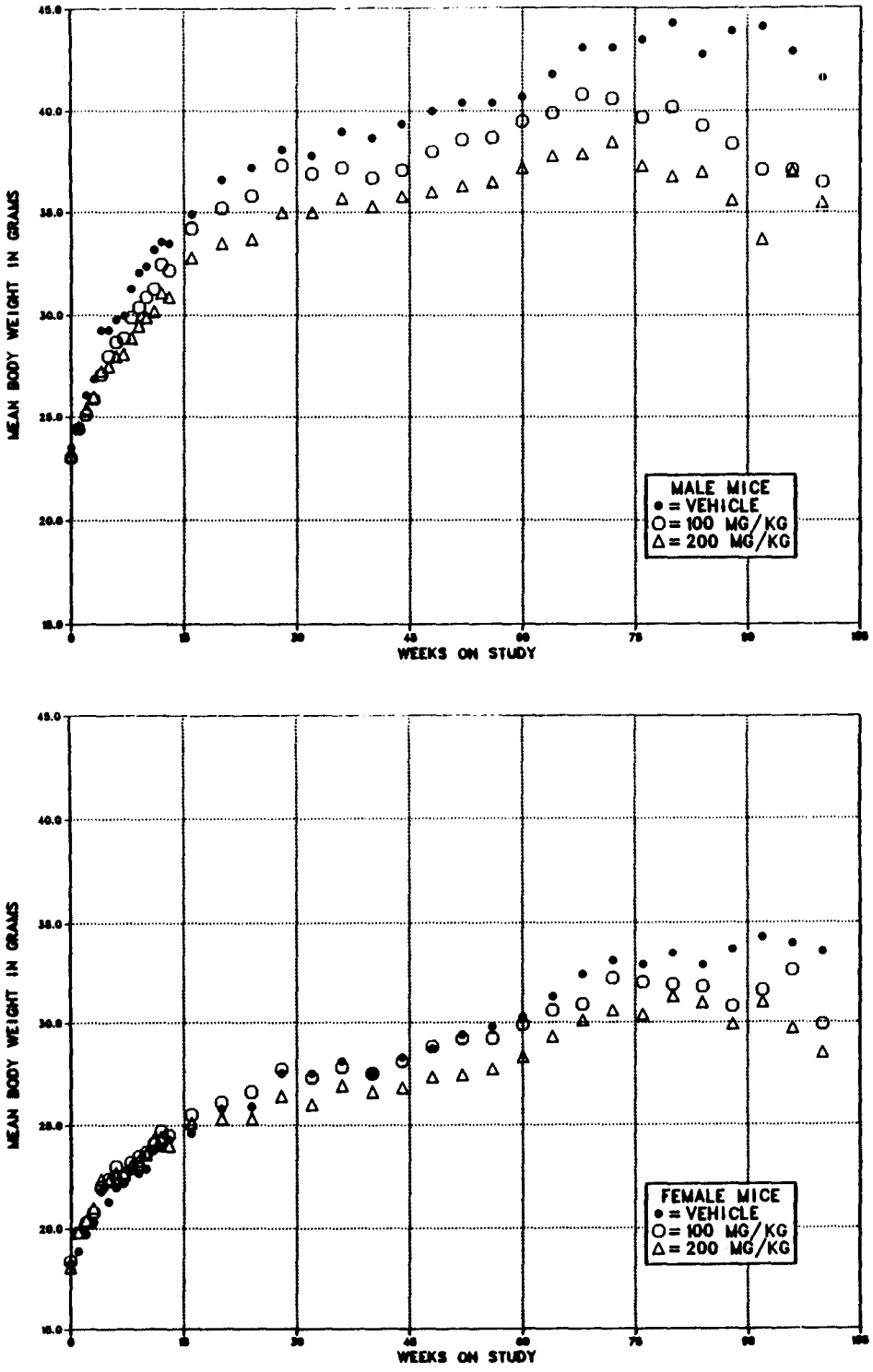


FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED DIMETHYLVINYL CHLORIDE IN CORN OIL BY GAVAGE FOR TWO YEARS

III. RESULTS: MICE

Survival

Estimates of the probabilities of survival for male and female mice administered dimethylvinyl chloride at the doses used in these studies and for vehicle controls are shown in the Kaplan and Meier curves in Figure 4. The survival of the dosed groups of both males (low dose after week 83, high dose after week 67) and females (low dose after week 58, high dose after week 54) was significantly lower than that of the vehicle control groups (Table 25).

Pathology and Statistical Analyses of Results

This section describes the significant or noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the forestomach, preputial gland, harderian gland, liver, bone marrow, spleen, thyroid gland, testis, nasal cavity, and lung. Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); Appendix B (Tables B3 and B4) also gives the survival and tumor status for individual male and female mice. Findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2). Appendix E (Tables E3 and E4) contains the statistical analyses of those primary tumors that occurred with an incidence of at least 5% in one of the three groups. The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes). The statistical analyses and interpretation of tumor incidence data for mice were complicated by the marked reduction in survival in dosed male and female mice when compared with that of the vehicle controls. No vehicle control animals were killed when dosed animals were dying. Consequently, the incidental tumor test has reduced sensitivity, since there is little overlapping of survival in dosed and vehicle control groups. Hence, the incidental tumor test was not given primary emphasis, although for completeness the results of this test are presented in Appendix E. Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 25. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	12	42	48
Killed at termination	38	8	1
Died during termination period	0	0	1
Survival P values (c)	<0.001	<0.001	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	9	43	46
Accidentally killed	0	1	1
Killed at termination	41	5	2
Died during termination period	0	1	1
Survival P values (c)	<0.001	<0.001	<0.001

(a) Terminal-kill period: week 103
(b) Includes animals killed in a moribund condition
(c) The result of the life table trend test is in the vehicle control column, and the results of the life table pairwise comparisons with the vehicle controls are in the dosed columns.

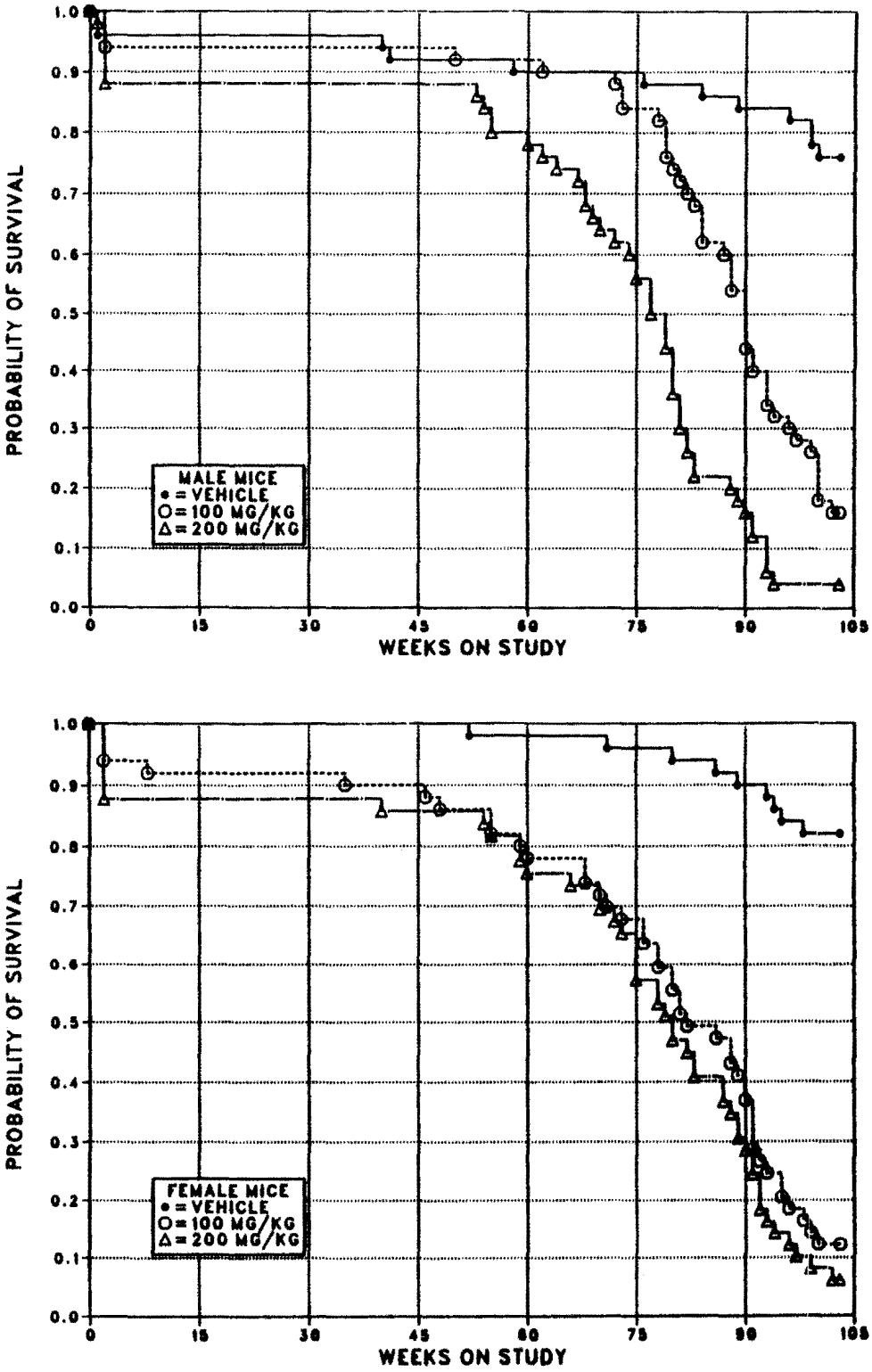


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED DIMETHYLVINYL CHLORIDE IN CORN OIL BY GAVAGE FOR TWO YEARS

Forestomach: Papillomas in males and carcinomas in males and females occurred with significant positive trends; the incidences of papillomas in high dose males and carcinomas in dosed males and females were significantly greater than those in the vehicle controls (Table 26).

TABLE 26. ANALYSIS OF FORESTOMACH TUMORS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE (a)

	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Squamous Cell Papilloma (b)			
Overall Rates	1/48 (2%)	3/47 (6%)	8/44 (18%)
Adjusted Rates	2.6%	19.6%	25.8%
Terminal Rates	1/38 (3%)	1/8 (13%)	0/2 (0%)
Week of First Observation	103	78	54
Life Table Tests	P<0.001	P=0.054	P=0.001
Cochran-Armitage Trend Test	P=0.005		
Fisher Exact Test		P=0.301	P=0.011
Squamous Cell Carcinoma (c)			
Overall Rates	0/48 (0%)	42/47 (89%)	35/44 (90%)
Adjusted Rates	0.0%	95.3%	100.0%
Terminal Rates	0/38 (0%)	6/8 (75%)	2/2 (100%)
Week of First Observation		50	53
Life Table Tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Squamous Cell Papilloma or Carcinoma			
Overall Rates	1/48 (2%)	43/47 (91%)	41/44 (93%)
Adjusted Rates	2.6%	97.7%	100.0%
Terminal Rates	1/38 (3%)	7/8 (88%)	2/2 (100%)
Week of First Observation	103	50	53
Life Table Tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
FEMALE			
Squamous Cell Papilloma			
Overall Rates	0/50 (0%)	1/47 (2%)	3/43 (7%)
Squamous Cell Carcinoma (d)			
Overall Rates	0/50 (0%)	40/47 (85%)	36/43 (84%)
Adjusted Rates	0.0%	97.5%	97.0%
Terminal Rates	0/41 (0%)	5/6 (83%)	2/3 (67%)
Week of First Observation		35	54
Life Table Tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001
Squamous Cell Papilloma or Carcinoma			
Overall Rates	0/50 (0%)	40/47 (85%)	38/43 (88%)
Adjusted Rates	0.0%	97.5%	100.0%
Terminal Rates	0/41 (0%)	5/6 (83%)	3/3 (100%)
Week of First Observation		35	54
Life Table Tests	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P<0.001	P<0.001

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Historical incidence of stomach papillomas or squamous cell papillomas at study laboratory (mean): 6/343 (2%); historical incidence in NTP studies: 9/1,070 (1%)
(c) Historical incidence of stomach squamous cell carcinomas at study laboratory (mean): 1/343 (0.3%); historical incidence in NTP studies: 5/1,070 (0.5%)
(d) No stomach tumors have been observed in 343 corn oil vehicle control female mice at the study laboratory; no stomach squamous cell carcinomas have been observed in corn oil vehicle controls in NTP studies.

Preputial Gland: Squamous cell carcinomas in male mice occurred with a significant positive trend, and the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 27).

Harderian Gland: Papillary adenomas in female mice occurred with a significant positive trend, and the incidence in the high dose group was significantly greater than that in the vehicle controls (Table 28).

Liver: Focal necrosis or necrosis, NOS, was observed at increased incidences in dosed male and dosed female mice. An increased number of hemangiomas and hemangiosarcomas was observed in low dose and high dose male mice compared with that in the vehicle controls (Table 29).

TABLE 27. ANALYSIS OF PREPUTIAL GLAND TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
Squamous Cell Carcinoma (a)			
Overall Rates	1/48 (2%)	3/47 (6%)	16/44 (36%)
Adjusted Rates	2.6%	21.4%	82.5%
Terminal Rates	1/38 (3%)	1/8 (13%)	1/2 (50%)
Week of First Observation	103	81	64
Life Table Tests	P<0.001	P=0.044	P<0.001
Cochran-Armitage Trend Test	P<0.001		
Fisher Exact Test		P=0.301	P<0.001

(a) No preputial gland tumors have been reported in 350 corn oil vehicle control male mice at the study laboratory; one adenoma was observed in 1,097 male corn oil vehicle control mice in NTP studies.

TABLE 28. ANALYSIS OF HARDERIAN GLAND TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
Papillary Adenoma (a)			
Overall Rates	0/50 (0%)	3/47 (6%)	5/43 (12%)
Adjusted Rates	0.0%	27.6%	49.4%
Terminal Rates	0/41 (0%)	1/6 (17%)	1/3 (33%)
Week of First Observation		80	82
Life Table Tests	P<0.001	P=0.005	P<0.001
Cochran-Armitage Trend Test	P=0.014		
Fisher Exact Test		P=0.110	P=0.019

(a) Historical incidence at study laboratory (mean ± SD): 4/349 (1% ± 2%); historical incidence in NTP studies: 20/1,096 (2% ± 2%)

TABLE 29. NUMBER OF MICE WITH LESIONS OF THE LIVER IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Lesion	Vehicle Control	100 mg/kg	200 mg/kg
MALE			
Number of mice examined	50	50	50
Number of livers examined	49	50	49
Necrosis, NOS or focal	2	15	8
Angiectasis	0	2	1
Hemangioma	0	1	1
Hemangiosarcoma	0	1	3
FEMALE			
Number of mice examined	50	50	50
Number of livers examined	50	50	48
Necrosis, focal	1	4	7
Angiectasis	0	1	0
Hemangioma	0	0	0
Hemangiosarcoma	0	0	0

Bone Marrow: Granulocytic hyperplasia was observed at increased incidences in dosed male and dosed female mice (male: vehicle control, 1/48, 2%; low dose, 13/50, 26%; high dose, 9/49, 18%; female: vehicle control, 2/50, 4%; low dose, 12/50, 24%; high dose, 14/48, 29%).

Spleen: Hematopoiesis was observed at increased incidences in dosed male and dosed female mice (male: vehicle control, 1/49, 2%; low dose, 13/50, 26%; high dose, 16/49, 33%; female: vehicle control, 3/50, 6%; low dose, 12/49, 24%; high dose, 12/47, 26%).

Thyroid Gland: Follicular cysts were observed at an increased incidence in low dose male mice (vehicle control, 1/49, 2%; low dose, 10/48, 21%; high dose, 2/45, 4%). A follicular cell adenoma was observed in one high dose male mouse, and a follicular cell carcinoma was observed in one vehicle control male mouse.

Testis: Atrophy was observed at an increased incidence in high dose male mice (vehicle control, 0/49; low dose, 1/50, 2%; high dose, 9/49, 18%).

Nasal Cavity: Suppurative inflammation was observed at an increased incidence in high dose female mice (vehicle control, 1/50, 2%; low dose, 3/50, 6%; high dose, 5/50, 10%).

Lung: Acute bronchopneumonia was observed at an increased incidence in high dose female mice (vehicle control, 0/50; low dose, 2/49, 4%; high dose, 6/48, 13%). Alveolar/bronchiolar adenomas and adenomas or carcinomas (combined) in female mice occurred with significant positive trends; the incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in the high dose group was significantly greater than that in the vehicle controls by life table analysis (Table 30).

TABLE 30. ANALYSIS OF LUNG TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
Alveolar/Bronchiolar Adenoma (a)			
Overall Rates	2/50 (4%)	1/46 (2%)	6/43 (14%)
Adjusted Rates	4.9%	4.2%	46.3%
Terminal Rates	2/41 (5%)	0/6 (0%)	1/3 (33%)
Week of First Observation	103	86	59
Life Table Tests	P<0.001	P=0.556	P=0.001
Cochran-Armitage Trend Test	P=0.048		
Fisher Exact Test		P=0.532N	P=0.091
Alveolar/Bronchiolar Carcinoma			
Overall Rates	1/50 (2%)	0/46 (0%)	1/43 (2%)
Alveolar/Bronchiolar Adenoma or Carcinoma (b)			
Overall Rates	3/50 (6%)	1/46 (2%)	7/43 (16%)
Adjusted Rates	7.0%	4.2%	73.2%
Terminal Rates	2/41 (5%)	0/6 (0%)	2/3 (67%)
Week of First Observation	93	86	59
Life Table Tests	P<0.001	P=0.657	P<0.001
Cochran-Armitage Trend Test	P=0.059		
Fisher Exact Test		P=0.341N	P=0.104

(a) Historical incidence at study laboratory (mean ± SD): 15/347 (4% ± 3%); historical incidence in NTP studies: 45/1,087 (4% ± 3%)
(b) Historical incidence at study laboratory (mean ± SD): 20/347 (6% ± 4%); historical incidence in NTP studies: 57/1,087 (5% ± 3%)

IV. DISCUSSION AND CONCLUSIONS

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Dimethylvinyl chloride was studied for toxicity, including carcinogenicity, in male and female F344/N rats and B6C3F$_1$ mice by administering the chemical in corn oil by gavage at doses of 0, 63, 125, 250, 500, or 750 mg/kg body weight, 5 days per week, for 13 weeks and at doses of 0, 100, or 200 mg/kg per day, 5 days per week, for 102 or 103 weeks.

The 13-week studies accurately identified the sites that were affected in the 2-year studies, except for the nasal cavity of rats. The histopathologic examination revealed noteworthy pathologic alterations in the intestinal epithelium, hepatocytes, and bone marrow. Changes observed in the testis were probably secondary effects of toxicity. Mortality at 750 mg/kg per day was substantially greater in mice than in rats, but the effect on body weight was less in mice than in rats.

Compared with the histopathologic alterations in rats, those in mice in the 13-week studies presented a more diffuse pattern of toxicity; these alterations included necrosis of the lymphopoietic cells, liver, pancreatic islets, ovary, and spleen. The effects on the ovary in female mice were observed at all doses in the 13-week study, and the effect on the spleen was seen in female mice at doses of 125 mg/kg and above. The testis of mice, like that of rats, may have been a secondary site of toxicity.

Because most of the adverse effects in mice occurred at 500 mg/kg and above in the 13-week studies, doses for the 2-year studies in mice were initially set at 200 and 400 mg/kg per day. After 5 months, however, the studies in mice were terminated because of the large number of deaths in the 400 mg/kg group; the studies were restarted with doses of 100 and 200 mg/kg per day. Thus, the 13-week studies identified the sites that would be affected in the 2-year studies, but the high dose initially set for the 2-year studies in mice exceeded the maximum tolerated dose. In fact, dose levels of 100 and 200 mg/kg per day caused significant decreases in body weight gain and survival in rats and mice of each sex. However, clinical observations as well as the gross and microscopic pathologic examination did not clearly identify causes of early mortality. In the absence of toxicologic findings that would explain the early mortality, it is assumed that the high incidence of tumors and other chemical-related toxicity contributed to the decreased survival of dosed rats and mice.

In the 2-year studies, malignant epithelial tumors of the nasal cavity and squamous cell carcinomas of the oral cavity, esophagus, and forestomach occurred at significantly dose-related increased incidences in male and female rats, and the incidence of fibroadenomas of the mammary gland was significantly increased in low dose female rats. The marginal increase in the incidence of mammary gland lesions and the lack of a high-dose effect make their relationship to dimethylvinyl chloride administration uncertain. Squamous cell carcinomas of the forestomach were observed at significantly increased incidences in dosed male and female mice, and the incidence of squamous cell carcinomas of the preputial gland was significantly increased in high dose males. Because of the nature and incidence of the tumors of the harderian gland and lung in female mice, their relationship to administration of dimethylvinyl chloride was considered uncertain.

Invasion and metastasis from primary tumor sites were observed in both rats and mice. For example, the malignant neoplasms of the nasal cavity of rats spread to surrounding structures including the maxillary and cranial bones, brain, and regional lymph nodes. In mice, tumors of the lymph nodes were found secondary to the high incidence of forestomach tumors.

Although both dimethylvinyl chloride and vinyl chloride are carcinogenic in laboratory animals, the types of tumors produced by vinyl chloride administration, particularly in rats, are more varied than those observed in the current studies of dimethylvinyl chloride. The following tumors have been related to exposure of rats to vinyl chloride at various concentrations: angiosarcomas of the liver, carcinomas of the Zymbal gland, nephroblastomas, adenocarcinomas of the mammary gland, papillomas and acanthomas of the forestomach, extrahepatic angiosarcomas, and hepatomas. These lesions have been generally found in rodents exposed by inhalation at concentrations greater than 10 ppm and by ingestion at 0.3 mg/kg for 2 years or more (Maltoni

et al., 1984). Although the spectrum of tumors observed has been broad even at low concentrations of vinyl chloride, the lesions observed in the present dimethylvinyl chloride studies are confined more to the squamous cells of tissues directly exposed. Although dimethylvinyl chloride was carcinogenic at both doses, the doses of vinyl chloride reported to be carcinogenic are considerably lower than those in the current studies. However, the available data are insufficient for comparison of relative carcinogenicity at lower dose levels.

Vinyl chloride is metabolized primarily in the liver by microsomal enzymes. Evidence suggests that the toxicity of vinyl chloride is due to its enzymatic oxidation to reactive polar metabolites. Bartsch and Montesano (1975) report two possible schemes, one involving alcohol dehydrogenase and the other mixed function oxidase. Chloroethylene oxide, which is thought to be formed by the mixed function oxidase system, may be the primary microsomal metabolite capable of alkylating cellular macromolecules (Laib and Bolt, 1977). The data of Hathaway (1977) suggest that vinyl chloride metabolites (chloroacetaldehyde, formed in either metabolic system) may interact with some purine and pyrimidine residues of DNA; this may explain the carcinogenicity of vinyl chloride. The predominant pathway for vinyl chloride metabolism probably depends on dose level (Hefner et al., 1975).

Knowledge of the metabolism of dimethylvinyl chloride is sparse compared with the considerable amount of data on the metabolism of vinyl chloride. However, some information on distribution, elimination, and metabolism has been provided by limited NTP studies in male F344/N rats and $B6C3F_1$ mice (Appendix N). Single doses of 150 mg/kg ^{14}C-labeled dimethylvinyl chloride in corn oil were administered by gavage to rats for 1, 2, or 4 consecutive days. The exhalation of labeled carbon dioxide and volatiles and the distribution of radioactivity in tissues were measured at various intervals after the last dose. Animals were killed 24 hours after the last dose was administered to that group. Twenty-six percent of the total dose to rats was exhaled as carbon dioxide and 35% as volatile material (96% of which was the parent material) (Table N1). Although mice eliminated 26% of the dose as expired carbon dioxide, only 5% was exhaled as dimethylvinyl chloride. Most of the retained radioactivity from dimethylvinyl chloride, like that from vinyl chloride (Watanabe et al., 1976a,b; Bolt et al., 1976), was found in the liver and kidney (Table N2). The profile of metabolites of dimethylvinyl chloride was independent of the number of days the chemical was administered. It is not possible with the available data to determine if vinyl chloride and dimethylvinyl chloride share common metabolic pathways; however, the data available from NTP indicate that metabolism occurs in large part at the methyl groups. It was determined from nuclear magnetic resonance and mass spectral data (Table N3) that the major urinary metabolite in both rats and mice was 2-amino-6-methyl-4-thia-5-heptene-1,7-dioic acid. This metabolite probably arises by oxidation of one of the methyl groups of dimethylvinyl chloride to a carboxylic acid followed by formal displacement of the chloride by glutathione and subsequent degradation of the glutathione moiety. Thus, the metabolism of dimethylvinyl chloride involves the formation of metabolites not available from vinyl chloride.

The apparent correspondence between tumor type and the route of elimination of dimethylvinyl chloride is noteworthy. The very high incidence of nasal cavity tumors in these gavage studies suggests that some "active" agent is exhaled. According to the metabolism data, dimethylvinyl chloride accounted for nearly all of the exhaled radioactivity; thus, dimethylvinyl chloride may be metabolized to an active toxin and remain localized in the nasal cavity. Studies in mice indicate considerably less exhalation of non-carbon-dioxide radioactivity than was observed in the rat and a corresponding increase in the amount of radioactivity excreted in the urine. This finding was consistent with the lack of nasal cavity tumors in mice versus the significantly increased incidence in rats.

The role of dimethylvinyl chloride (as a 5% contaminant) in the carcinogenicity of 3-chloro-2-methylpropene (NTP, 1986) cannot be established from the present studies of dimethylvinyl chloride. As a 5% contaminant, the oral dose of dimethylvinyl chloride received by rats and mice in the studies of 3-chloro-2-methylpropene was

3-10 mg/kg per day. These doses are considerably lower than the doses used in the present studies of dimethylvinyl chloride. However, no apparent no-observed-effect level was found in the current 2-year studies of dimethylvinyl chloride, so this chemical might be carcinogenic at doses lower than those administered.

The profile of toxicity and carcinogenicity in the 3-chloro-2-methylpropene studies (NTP, 1986) is somewhat different from that in the current studies of dimethylvinyl chloride. Although stomach tumors were observed in both studies, rats and mice in the 3-chloro-2-methylpropene studies had a very high incidence of basal cell hyperplasia, a high incidence of squamous cell papillomas, and a relatively low incidence of squamous cell carcinomas. In the dimethylvinyl chloride studies, the incidences of hyperplasia or squamous cell papillomas were considerably lower compared with the greatly increased incidence of carcinomas; in rats, there were slightly more carcinomas than papillomas in the oral cavity, esophagus, and stomach. Carcinomas of the nasal cavity were not reported in the studies of 3-chloro-2-methylpropene, but there was a high incidence of these tumors in rats administered dimethylvinyl chloride. Although the kidney may have been an affected organ in the studies of 3-chloro-2-methylpropene, it was not affected in the study of dimethylvinyl chloride. Thus, the toxic effects of these two chemicals do not overlap sufficiently to allow the toxicity of 3-chloro-2-methylpropene to be attributed solely to the presence of dimethylvinyl chloride as a 5% contaminant. Any contribution of the dimethylvinyl chloride contaminant to the toxicity of 3-chloro-2-methylpropene is uncertain.

A contaminant in one of the lots of dimethylvinyl chloride used in the 2-year studies, acrylonitrile, is also a potent animal carcinogen (IARC, 1979). However, the dose of acrylonitrile given unintentionally in these studies was very low, and the profile of tumors seen in the present studies is not consistent with that for acrylonitrile. Thus, it is unlikely that acrylonitrile played a significant role in the carcinogenicity of dimethylvinyl chloride observed in these studies.

The effects of dimethylvinyl chloride on the immune system have been studied (Appendix O). In a preliminary study, $B6C3F_1$ mice demonstrated altered immune competence without evidence of gross toxicity (Litton, 1981). The altered immunologic parameters consisted of thymic atrophy, leukopenia, diminished responsiveness of splenic T-cells to mitogens, and decreased resistance to challenge with syngeneic PYB6 tumor cells. A more comprehensive study of immune function and host resistance was thus conducted with the NTP Comprehensive Screening Panel (Luster et al., 1982; Luster et al., in preparation). Female $B6C3F_1$ mice received daily doses of 0, 50, 100, 200, or 400 mg/kg of dimethylvinyl chloride for 14 days. The specific cell-mediated immune function and the resistance to viral and bacterial challenge were significantly reduced at the highest dose; this dose did not alter body weight but did produce hepatomegaly, splenic and thymic atrophy, and leukopenia. The immune functions suppressed by 400 mg/kg per day consisted of lymphocyte responsiveness to T-cell mitogens, lymphocyte responsiveness to allogeneic lymphocytes (mixed lymphocyte culture), and delayed hypersensitivity response. There was also a slight suppression of natural killer cell activity. Antibody responses were not consistently altered. Host resistance to A2/Taiwan influenza virus challenge, *Listeria monocytogenes*, and both type 1 and type 2 herpes was decreased. Resistance to B16 tumor cell challenge and Streptococcus was not affected.

The responses of mice to dimethylvinyl chloride were biphasic in that many of the parameters suppressed at the high dose were slightly enhanced at one or more of the three lower dose levels. These parameters included lymphocyte response to mitogens, delayed hypersensitivity response, several measures of macrophage activity, thymic weight, and peripheral leukocyte counts. Biphasic patterns of immunologic responses are not uncommon and probably reflect secondary effects or additional toxicologic mechanisms coming into play as the dose level of an immunotoxin is increased. In the present immunotoxicity study, for example, some effects at the high dose might be attributed to hepatotoxicity,

since hepatomegaly was seen only at the higher doses. In the NTP 13-week studies in mice, liver necrosis was observed at 750 mg/kg but not at doses of 500 mg/kg or below.

Thus, dimethylvinyl chloride affected the immune system of mice administered doses that bracketed those used in the 2-year studies, including increased susceptibility to bacterial infection. At the highest dose, 400 mg/kg per day, decreased resistance to bacterial and viral challenge could be related to alterations in specific immune functions. However, early deaths in the 2-year studies were not relatable to infectious processes.

The relationship between the genetic toxicity of dimethylvinyl chloride and its carcinogenicity is unclear. Studies regarding genetic toxicity have been performed (Appendix G). In tests with four strains of *Salmonella typhimurium,* there was no evidence of a mutagenic effect in the presence or absence of metabolic activation. Similarly, no chromosomal aberrations were found in Chinese hamster ovary (CHO) cells in the presence or absence or metabolic activation. However, the volatility of the compound may be responsible for the negative results. Positive effects were observed in other systems: Dimethylvinyl chloride was mutagenic in the mouse lymphoma assay in the absence of S9, induced sister-chromatid exchanges in CHO cells in both the presence and absence of metabolic activation, and exhibited highly significant effects in the tests for reciprocal translocations as well as sex-linked recessive lethal mutations in Drosophila. In the tests with Drosophila, dimethylvinyl chloride was found to be toxic even when physical contact was prevented. This suggests that the vapors per se may have been responsible for some of the exposure that produced the positive responses. Bartsch and Montesano (1975) reported induction of mutations in Salmonella after gaseous exposure to vinyl chloride both in the presence and absence of metabolic activation. Gaseous exposure to dimethylvinyl chloride might prove mutagenic to Salmonella and perhaps to CHO cells as well.

Induction of tumors in directly exposed tissues and the chemical structure of dimethylvinyl chloride are features consistent with direct mutagenic and carcinogenic activity. However, studies by Eder et al. (1980), using S9 supernatants from livers of animals induced with a variety of different agents, demonstrated that the mutagenic activity of allyl chloride in Salmonella is reduced, rather than enhanced, by metabolic activation; Neudecker et al. (1980) found that mono-methylation of an allyl chloride enhanced mutagenic activity in Salmonella in the absence of S9. These results suggest that direct mutagenic activity by these compounds is accomplished through reactions other than an enzymatic epoxidation mechanism, as has been proposed for the structural analog and potent carcinogen vinyl chloride monomer.

The experimental and tabulated data in the NTP Technical Report on dimethylvinyl chloride were examined to determine the study laboratory's compliance with Good Laboratory Practice requirements. As summarized in Appendix P, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Conclusions: Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenicity** of dimethylvinyl chloride for both sexes of F344/N rats and $B6C3F_1$ mice. This was based on increased incidences of neoplasms of the nasal cavity, oral cavity, esophagus, and forestomach of male and female F344/N rats. $B6C3F_1$ mice showed increased incidences of squamous cell neoplasms of the forestomach in males and females and squamous cell carcinomas of the preputial gland in males.

*Categories of evidence of carcinogenicity are defined in the Note to the Reader on page 2. The public discussion regarding the interpretative conclusions is summarized on page 16.

V. REFERENCES

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma	4 (8%)	2 (4%)	
Squamous cell carcinoma, metastatic		1 (2%)	
Basal cell tumor	1 (2%)	1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS			1 (2%)
Fibroma	4 (8%)	2 (4%)	
Lipoma	1 (2%)		
Neurofibroma	2 (4%)	2 (4%)	
RESPIRATORY SYSTEM			
#Nasal cavity	(47)	(46)	(32)
Carcinoma, NOS		12 (26%)	24 (75%)
Squamous cell papilloma			1 (2%)
Squamous cell carcinoma		3 (7%)	
Adenoma, NOS		1 (2%)	
Adenocarcinoma, NOS		8 (17%)	4 (13%)
Carcinosarcoma		1 (2%)	
#Lung	(50)	(50)	(50)
Squamous cell carcinoma, metastatic		2 (4%)	
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	1 (2%)
Adenocarcinoma/squamous metaplasia		1 (2%)	
Pheochromocytoma, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	3 (6%)	6 (12%)	1 (2%)
#Spleen	(50)	(50)	(50)
Fibroma		1 (2%)	
#Mandibular lymph node	(50)	(46)	(45)
Carcinoma, NOS, metastatic			1 (2%)
Adenocarcinoma, NOS, metastatic			1 (2%)
#Mediastinal lymph node	(50)	(46)	(45)
Alveolar/bronchiolar carcinoma, metastatic	1 (2%)		
#Mesenteric lymph node	(50)	(46)	(45)
Squamous cell carcinoma, metastatic		1 (2%)	
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Palate	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)
Squamous cell carcinoma		1 (2%)	
*Lip	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
*Tongue	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)
Squamous cell carcinoma		3 (6%)	2 (4%)
#Liver	(50)	(50)	(50)
Squamous cell carcinoma, invasive		1 (2%)	
Neoplastic nodule	1 (2%)		1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Pancreas	(50)	(50)	(50)
Acinar cell adenoma	8 (16%)	7 (14%)	
Mixed tumor, benign	1 (2%)		
#Esophagus	(50)	(50)	(49)
Squamous cell papilloma		2 (4%)	3 (6%)
Squamous cell carcinoma		4 (8%)	1 (2%)
#Forestomach	(49)	(50)	(50)
Squamous cell papilloma		7 (14%)	
Squamous cell carcinoma		7 (14%)	
#Ileum	(45)	(49)	(48)
Adenomatous polyp, NOS	1 (2%)		
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma	1 (2%)		
Tubular cell adenocarcinoma		1 (2%)	
#Kidney/pelvis	(50)	(50)	(50)
Transitional cell carcinoma		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(47)
Chromophobe adenoma	17 (34%)	8 (16%)	1 (2%)
Chromophobe carcinoma		1 (2%)	
#Adrenal	(50)	(50)	(50)
Cortical adenoma	1 (2%)		
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	11 (22%)	6 (12%)	3 (6%)
Pheochromocytoma, malignant	2 (4%)	1 (2%)	
Ganglioneuroma			1 (2%)
#Thyroid	(50)	(48)	(47)
Follicular cell adenoma	1 (2%)	2 (4%)	
C-cell adenoma	3 (6%)	1 (2%)	
C-cell carcinoma	2 (4%)	2 (4%)	
#Pancreatic islets	(50)	(50)	(50)
Islet cell adenoma	5 (10%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenoma, NOS	1 (2%)		
Fibroadenoma	2 (4%)	2 (4%)	
*Penis	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
*Prepuce	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
Keratoacanthoma			1 (2%)
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	
Squamous cell carcinoma	1 (2%)		
Adenoma, NOS	2 (4%)		
#Prostate	(50)	(50)	(50)
Adenoma, NOS	2 (4%)		
#Testis	(49)	(50)	(50)
Interstitial cell tumor	40 (82%)	41 (82%)	6 (12%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Carcinoma, NOS, invasive		8 (16%)	26 (52%)
Adenocarcinoma, NOS, invasive		3 (6%)	3 (6%)
Astrocytoma	1 (2%)		
SPECIAL SENSE ORGANS			
*Eye/conjunctiva	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS	2 (4%)	1 (2%)	
Squamous cell carcinoma		1 (2%)	
Adenoma, NOS		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Adenocarcinoma, NOS, invasive		1 (2%)	
*Maxilla	(50)	(50)	(50)
Carcinoma, NOS, invasive		1 (2%)	
*Mandible	(50)	(50)	(50)
Squamous cell carcinoma, invasive		1 (2%)	
*Muscle of head	(50)	(50)	(50)
Carcinoma, NOS, invasive	1 (2%)		
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive	1 (2%)		
*Epicardium	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive	1 (2%)		
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mesothelioma, NOS	2 (4%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	7	12	18
Moribund sacrifice	5	31	30
Terminal sacrifice	38	7	
Dosing accident			1
Accidentally killed, NOS			1

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	45	48	31
Total primary tumors	124	147	54
Total animals with benign tumors	44	45	15
Total benign tumors	108	87	18
Total animals with malignant tumors	12	38	30
Total malignant tumors	13	59	35
Total animals with secondary tumors##	3	16	29
Total secondary tumors	5	19	31
Total animals with tumors uncertain--benign or malignant	3	1	1
Total uncertain tumors	3	1	1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Keratoacanthoma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS	2 (4%)		
Fibroma	1 (2%)		
Neurilemoma, malignant		1 (2%)	
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(49)	(41)
Carcinoma, NOS		11 (22%)	28 (68%)
Squamous cell carcinoma		2 (4%)	2 (5%)
Adenoma, NOS		1 (2%)	
Adenocarcinoma, NOS		3 (6%)	6 (15%)
Rhabdomyosarcoma			1 (2%)
Carcinosarcoma			1 (2%)
#Trachea	(48)	(49)	(47)
Squamous cell carcinoma, invasive		1 (2%)	
#Lung	(50)	(50)	(49)
Adenocarcinoma, NOS, metastatic	1 (2%)		
Alveolar/bronchiolar adenoma		2 (4%)	1 (2%)
Alveolar/bronchiolar carcinoma		2 (4%)	
Sarcoma, NOS, metastatic	1 (2%)		
Sarcoma, NOS, unclear primary or metastatic	1 (2%)		
Endometrial stromal sarcoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, mixed type		1 (2%)	
Lymphocytic leukemia		1 (2%)	
Leukemia, mononuclear cell	5 (10%)	7 (14%)	1 (2%)
#Mandibular lymph node	(45)	(46)	(49)
Carcinoma, NOS, metastatic		2 (4%)	4 (8%)
Squamous cell carcinoma, metastatic		1 (2%)	
CIRCULATORY SYSTEM			
None			

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*Oral mucosa	(50)	(50)	(50)
Squamous cell papilloma			3 (6%)
*Palate	(50)	(50)	(50)
Squamous cell papilloma			1 (2%)
Squamous cell carcinoma		1 (2%)	
*Tongue	(50)	(50)	(50)
Squamous cell carcinoma		1 (2%)	
*Gum	(50)	(50)	(50)
Squamous cell carcinoma			1 (2%)
#Esophagus	(49)	(50)	(49)
Squamous cell carcinoma		3 (6%)	1 (2%)
#Forestomach	(50)	(50)	(49)
Squamous cell papilloma	1 (2%)	4 (8%)	1 (2%)
Squamous cell carcinoma		5 (10%)	1 (2%)
Sarcoma, NOS		1 (2%)	
Carcinosarcoma		1 (2%)	
#Cecum	(49)	(49)	(48)
Adenomatous polyp, NOS		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Squamous cell carcinoma, metastatic	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(48)	(49)
Adenoma, NOS		1 (2%)	
Chromophobe adenoma	16 (32%)	12 (25%)	2 (4%)
Chromophobe carcinoma	1 (2%)	4 (8%)	
#Adrenal	(50)	(50)	(49)
Cortical adenoma	2 (4%)		
Cortical carcinoma	1 (2%)		
#Adrenal medulla	(50)	(50)	(49)
Pheochromocytoma	1 (2%)	2 (4%)	
#Thyroid	(49)	(49)	(47)
Follicular cell adenoma			1 (2%)
Follicular cell carcinoma	1 (2%)	5 (10%)	
C-cell adenoma	3 (6%)	4 (8%)	1 (2%)
C-cell carcinoma	4 (8%)		
#Pancreatic islets	(50)	(50)	(48)
Islet cell adenoma		1 (2%)	

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)	4 (8%)	
Fibroadenoma	10 (20%)	18 (36%)	5 (10%)
*Clitoral gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)		
Adenoma, NOS	2 (4%)		
#Uterus	(50)	(50)	(49)
Endometrial stromal polyp	8 (16%)	11 (22%)	2 (4%)
Endometrial stromal sarcoma		1 (2%)	
#Uterus/endometrium	(50)	(50)	(49)
Adenoma, NOS		1 (2%)	
#Ovary	(50)	(50)	(49)
Granulosa cell tumor		1 (2%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Chromophobe carcinoma, invasive		1 (2%)	
#Brain	(50)	(50)	(50)
Carcinoma, NOS, invasive		7 (14%)	25 (50%)
Adenocarcinoma, NOS, invasive		2 (4%)	5 (10%)
Rhabdomyosarcoma, invasive			1 (2%)
Carcinosarcoma, invasive			1 (2%)
Astrocytoma		2 (4%)	
*Optic nerve	(50)	(50)	(50)
Carcinoma, NOS, invasive		1 (2%)	2 (4%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Squamous cell carcinoma, invasive		1 (2%)	
*Eyelid	(50)	(50)	(50)
Basal cell tumor		1 (2%)	
*External ear	(50)	(50)	(50)
Neurilemoma	1 (2%)		
*Zymbal gland	(50)	(50)	(50)
Carcinoma, NOS		1 (2%)	2 (4%)
MUSCULOSKELETAL SYSTEM			
*Mandible	(50)	(50)	(50)
Squamous cell carcinoma, invasive		1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma, invasive		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Carcinoma, NOS, metastatic		1 (2%)	
Carcinoma, NOS, unclear primary or metastatic	1 (2%)		
Sarcoma, NOS, metastatic	1 (2%)		

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	7	11
Moribund sacrifice	3	32	39
Terminal sacrifice	41	11	
Dosing accident	1		
TUMOR SUMMARY			
Total animals with primary tumors**	33	47	38
Total primary tumors	63	117	62
Total animals with benign tumors	29	35	13
Total benign tumors	45	59	18
Total animals with malignant tumors	14	40	38
Total malignant tumors	16	57	44
Total animals with secondary tumors##	4	16	33
Total secondary tumors	4	20	38
Total animals with tumors uncertain--benign or malignant		1	
Total uncertain tumors		1	
Total animals with tumors uncertain--primary or metastatic	2		
Total uncertain tumors	2		

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE: VEHICLE CONTROL

ANIMAL NUMBER	0 2 9	0 3 5	0 0 6	0 1 1	0 2 5	0 3 2	0 0 5	0 2 8	0 2 1	0 2 2	0 4 4	0 4 9	0 0 1	0 0 2	0 0 3	0 0 4	0 0 7	0 0 8	0 0 9	0 1 0	0 1 2	0 1 3	0 1 4	0 1 5	0 1 6
WEEKS ON STUDY	0 4 2	0 4 7	0 4 8	0 5 7	0 6 4	0 9 4	0 9 5	0 9 6	0 9 7	1 0 2	1 0 3	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4
INTEGUMENTARY SYSTEM																									
Skin	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma													X				X					X			
Basal cell tumor																									
Subcutaneous tissue	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma						X							X										X		
Lipoma																									
Neurofibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma							X																		
Pheochromocytoma, metastatic																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal Cavity	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic							X																		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma									X																
Mixed tumor, benign																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	−	−	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																				X					
Large intestine	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma							X	X		X	X				X									X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																			X						
Pheochromocytoma									X		X												X		
Pheochromocytoma, malignant													X												
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma										X															
C-cell adenoma							X												X		X				
C-cell carcinoma											X														
Parathyroid	−	+	−	−	−	+	+	+	−	−	−	+	+	+	+	−	+	+	+	+	−	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma										X			X											X	
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	N	+	+	+	+	+	+	+	+
Adenoma, NOS																								X	
Fibroadenoma																									
Testis	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor						X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma												X													
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Astrocytoma																								X	
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	+	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS			X						X																
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS, invasive			X																						
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, invasive							X																		
Pericardium	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, invasive							X																		
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Mesothelioma, NOS												X													
Leukemia, mononuclear cell										X															

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	017	018	019	020	023	024	026	027	030	031	033	034	036	037	038	039	040	041	042	043	045	046	047	048	050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma		X																								4
Basal cell tumor																								X		1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma										X																4
Lipoma						X																				1
Neurofibroma								X												X						2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma									X																	2
Pheochromocytoma, metastatic					X																					1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Nasal Cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcin, metast																										1
Thymus	+	+	+	+	+	–	+	+	+	+	–	–	+	+	–	+	+	+	+	+	+	–	+	–	+	40
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule														X												1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma	X				X				X	X				X	X									X		8
Mixed tumor, benign					X																					1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+		45
Adenomatous polyp, NOS																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma														X												1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chromophobe adenoma	X	X		X				X	X				X			X		X		X		X				17
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Pheochromocytoma				X					X					X		X	X	X	X						X	11
Pheochromocytoma, malignant					X																					2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
C-cell adenoma																										3
C-cell carcinoma									X																	2
Parathyroid	+	+	–	+	+	–	+	–	+	–	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	35
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma										X								X								5
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	N	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenoma, NOS																X										1
Fibroadenoma																									X	2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		X	X	40
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS													X	X												2
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																										1
Adenoma, NOS				X					X																	2
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Astrocytoma																										1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	*50
Carcinoma, NOS																										2
MUSCULOSKELETAL SYSTEM																										
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS, invasive																										1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcin, invasive																										1
Pericardium	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcin, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Mesothelioma, NOS			X																							2
Leukemia, mononuclear cell							X															X				3

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE: LOW DOSE

ANIMAL NUMBER	049	027	038	019	012	006	022	028	029	014	023	041	015	044	030	013	005	008	026	035	040	046	039	037	050
WEEKS ON STUDY	033	052	056	070	071	077	077	077	078	079	082	084	086	086	087	089	090	090	090	090	090	091	092	093	093
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma, metastatic																									X
Basal cell tumor																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Neurofibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									X
Alveolar/bronchiolar carcinoma																									
Adenoca/squamous metaplasia																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	−	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+
Carcinoma, NOS				X		X		X			X	X						X						X	
Squamous cell carcinoma																									X
Adenoma, NOS																									
Adenocarcinoma, NOS										X				X							X				
Carcinosarcoma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																									
Lymph nodes	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic											X														
Thymus	−	+	+	−	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma					X									X					X						
Salivary gland	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive											X														
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Acinar cell adenoma																X			X	X	X				
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma																	X								
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																	X								
Squamous cell carcinoma											X		X								X				X
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenocarcinoma		X																							
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																									
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma							X					X						X					X	X	
Chromophobe carcinoma																									
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Pheochromocytoma, malignant																									
Thyroid	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									X
C-cell adenoma												X													
C-cell carcinoma																									
Parathyroid	−	+	−	+	−	+	+	−	−	+	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+
Fibroadenoma																			X						
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor						X		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																									
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive				X		X		X			X													X	
Adenocarcinoma, NOS, invasive														X							X				
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	N	N	N	N	N	N	+	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS										X															
Squamous cell carcinoma															X										
Adenoma, NOS																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																		X							
Squamous cell carcinoma, invasive																			X						
Adenocarcinoma, NOS, invasive														X											
BODY CAVITIES																									
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma, NOS																								X	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell									X													X			

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: LOW DOSE (Continued)

ANIMAL NUMBER	0 0 4	0 4 5	0 2 1	0 3 6	0 4 7	0 0 3	0 1 7	0 4 2	0 2 5	0 0 2	0 2 4	0 3 2	0 1 6	0 2 0	0 4 3	0 4 8	0 0 1	0 0 7	0 0 9	0 1 0	0 1 1	0 1 8	0 3 1	0 3 3	0 3 4	TOTAL TISSUES TUMORS
WEEKS ON STUDY	0 9 4	0 9 4	0 9 3	0 9 5	0 9 6	0 9 7	0 9 7	0 9 7	0 9 8	0 9 9	0 9 9	1 0 0	1 0 3	1 0 3	1 0 3	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma						X															X					2
Squamous cell carcinoma, metastatic																										1
Basal cell tumor																						X				1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma	X	X																								2
Neurofibroma						X	X																			2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic									X																	2
Alveolar/bronchiolar carcinoma											X															1
Adenoca/squamous metaplasia																								X		1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	49
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS		X	X			X		X								X										12
Squamous cell carcinoma									X		X															3
Adenoma, NOS																									X	1
Adenocarcinoma, NOS										X			X								X		X		X	8
Carcinosarcoma																	X									1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Fibroma											X															1
Lymph nodes	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Squamous cell carcinoma, metastatic																										1
Thymus	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma								X													X					5
Salivary gland	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, invasive																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Acinar cell adenoma				X												X			X							7
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma											X							X								2
Squamous cell carcinoma					X															X			X			4
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma		X											X					X				X	X	X		7
Squamous cell carcinoma									X		X									X						7
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenocarcinoma																										1
Kidney/pelvis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional cell carcinoma											X															1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chromophobe adenoma		X																		X			X			8
Chromophobe carcinoma								X																		1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma		X						X	X										X		X		X			6
Pheochromocytoma, malignant																								X		1
Thyroid	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Follicular cell adenoma																									X	2
C-cell adenoma																										1
C-cell carcinoma										X														X		2
Parathyroid	+	–	+	+	–	+	+	+	+	–	+	+	+	–	+	+	–	+	+	+	+	+	–	–	+	36
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma											X															1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma																	X									2
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	41
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																	X					X				2
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS	X																									1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive								X								X					X					8
Adenocarcinoma, NOS, invasive													X													3
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Squamous cell carcinoma																										1
Adenoma, NOS								X																		1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Carcinoma, NOS, invasive																										1
Squamous cell carcinoma, invasive																										1
Adenocarcinoma, NOS, invasive																										1
BODY CAVITIES																										
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell								X				X			X						X					6

* Animals necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE: HIGH DOSE

ANIMAL NUMBER	0036	0048	0042	0022	0017	0119	0040	0049	0029	0026	0110	0043	0045	0044	0550	0002	0059	0033	0014	0001	0013	0024	0034	0037	0038
WEEKS ON STUDY	041	043	045	046	049	049	050	051	052	054	055	055	055	056	058	059	059	060	060	061	062	062	062	062	063
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																									
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Nasal cavity	−	−	+	−	+	−	−	−	−	−	−	−	−	−	+	−	−	−	+	+	+	−	+	−	+
Carcinoma, NOS															X				X	X					X
Squamous cell papilloma																									
Adenocarcinoma, NOS			X																						
HEMATOPOIETIC SYSTEM																									
Bone marrow	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	−	+	+	+	+	+	+	+	−
Carcinoma, NOS, metastatic		X																							
Adenocarcinoma, NOS, metastatic																									
Thymus	+	+	−	+	+	−	+	+	−	−	+	−	−	−	+	−	−	+	+	+	−	+	+	−	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Squamous cell carcinoma	X																								
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																				X					
Squamous cell carcinoma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma																			X						
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma										X															
Ganglioneuroma										X															
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	+	−	+	−	+	+	+	+	−	−	+	−	+	+	+	−	+	+	+	+	+	−	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	+	N	N	N	+	N	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Keratoacanthoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive		X				X									X	X	X		X	X	X			X	X
Adenocarcinoma, NOS, invasive																									
SPECIAL SENSE ORGANS																									
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell																									

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	025	039	008	011	012	023	027	033	021	015	041	097	046	031	016	022	028	030	005	018	004	032	047	035	006	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	065	065	066	066	066	066	066	066	067	068	068	070	070	071	072	072	072	072	073	073	074	078	078	083	085	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS												X														1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																			X							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Nasal cavity	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	32
Carcinoma, NOS	X	X	X		X	X	X	X	X	X	X		X		X	X	X	X	X	X	X		X	X		24
Squamous cell papilloma	X																									1
Adenocarcinoma, NOS														X								X			X	4
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	45
Carcinoma, NOS, metastatic																										1
Adenocarcinoma, NOS, metastatic																									X	1
Thymus	–	–	+	–	–	+	+	–	–	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	31
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma									X				X													2
Squamous cell carcinoma																									X	2
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																									X	1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																X	X									3
Squamous cell carcinoma							X																			1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Chromophobe adenoma																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma										X															X	3
Ganglioneuroma																										1
Thyroid	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	47
Parathyroid	+	–	+	–	+	–	+	+	+	+	–	+	+	+	+	+	+	–	–	+	+	–	+	+	–	34
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell tumor					X		X									X	X					X			X	6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Penis	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Keratoacanthoma																			X							1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive	X	X	X		X	X		X	X	X	X		X		X	X	X			X	X			X		26
Adenocarcinoma, NOS, invasive														X								X			X	3
SPECIAL SENSE ORGANS																										
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma							X																			1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell																										1

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE: VEHICLE CONTROL

ANIMAL NUMBER	021	019	020	027	022	037	046	001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018
WEEKS ON STUDY	063	074	077	084	091	097	099	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																						X			
Fibroma				X																					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, metastatic		X																							
Sarcoma, NOS, metastatic																									
Sarcoma, NOS, unclear prim or metastatic		X																							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+
Nasal Cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+
Thymus	+	–	+	–	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma		X																							
Small intestine	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	–
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma		X					X	X			X				X				X				X		
Chromophobe carcinoma																									X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									X
Cortical carcinoma												X													
Pheochromocytoma		X																							
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																									
C-cell adenoma								X		X															
C-cell carcinoma		X								X											X				
Parathyroid	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS		X																							
Fibroadenoma								X				X					X								X
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS																						X			
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp											X				X				X		X				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Ear	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Neurilemoma																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS, unclear primary or metastatic							X																		
Sarcoma, NOS, metastatic					X	X																X			
Leukemia, mononuclear cell																				X					

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0023	0024	0025	0026	0028	0029	0030	0031	0032	0033	0034	0035	0036	0038	0039	0040	0041	0042	0043	0044	0045	0047	0048	0049	0050	TOTAL TISSUES TUMORS
WEEKS ON STUDY	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																		X								2
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, NOS, metastatic																										1
Sarcoma, NOS, metastatic																		X								1
Sarcoma, NOS, unc primary or metas																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Nasal Cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	45
Thymus	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic	X																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chromophobe adenoma			X		X	X				X	X				X	X		X	X							16
Chromophobe carcinoma																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma	X																									2
Cortical carcinoma																										1
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma																X										1
C-cell adenoma		X																								3
C cell carcinoma														X												4
Parathyroid	−	−	−	+	+	+	+	+	+	+	−	+	+	+	−	−	−	+	−	+	−	+	+	+	−	38
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	N	+	N	+	+	N	+	+	*50
Adenocarcinoma, NOS																										1
Fibroadenoma		X	X	X					X					X							X					10
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
Adenoma, NOS	X																			X						2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Endometrial stromal polyp		X	X		X																X					8
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Ear	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Neurilemoma			X																							1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS, unc primary or met																										1
Sarcoma, NOS, metastatic																										1
Leukemia, mononuclear cell				X	X																					5

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE: LOW DOSE

ANIMAL NUMBER	026	012	043	042	044	092	017	039	025	034	049	098	097	020	041	030	094	040	048	006	018	029	011	022	038
WEEKS ON STUDY	062	068	072	076	077	081	082	083	084	084	084	086	088	088	088	090	091	094	094	095	095	095	096	096	096
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant							X																		
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma												X													
Endometrial stromal sarcoma, metastatic																								X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																									
Nasal cavity	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS			X						X						X				X		X				
Squamous cell carcinoma																									
Adenoma, NOS																							X		
Adenocarcinoma, NOS																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+
Carcinoma, NOS, metastatic			X																						
Squamous cell carcinoma, metastatic				X																					
Thymus	–	+	+	+	+	+	+	–	–	+	–	+	+	+	+	–	+	+	+	+	–	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																			X						
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																			X						
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma															X							X			
Sarcoma, NOS																									
Carcinosarcoma																									
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenomatous polyp, NOS																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
Adenoma, NOS														X											
Chromophobe adenoma								X	X			X	X									X	X		
Chromophobe carcinoma																								X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																	X								
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma																			X					X	
C-cell adenoma														X											
Parathyroid	–	+	+	–	+	–	+	+	+	–	–	+	–	+	–	+	+	+	–	+	+	–	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																							X		
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																		X					X	X	
Fibroadenoma											X	X	X	X			X					X			
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Endometrial stromal polyp						X	X					X	X						X						X
Endometrial stromal sarcoma																								X	
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Nerves	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS, invasive																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive			X						X						X				X		X				
Adenocarcinoma, NOS, invasive																									
Chromophobe carcinoma, invasive																									
Astrocytoma					X									X											
SPECIAL SENSE ORGANS																									
Eye	+	+	+	N	+	+	N	+	+	N	N	N	+	N	+	N	+	N	+	+	+	+	+	N	+
Squamous cell carcinoma, invasive																									
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Basal cell tumor																									
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS												X													
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																									
BODY CAVITIES																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, invasive												X													
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS, metastatic												X													
Malignant lymphoma, mixed type																									
Lymphocytic leukemia										X															
Leukemia, mononuclear cell													X			X									X

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: LOW DOSE
(Continued)

ANIMAL NUMBER	0321	0110	0114	0311	0099	0115	0116	0221	0335	0336	0337	0033	0227	0233	0091	0054	0113	0194	0224	0288	0333	0445	0446	0477	0504	TOTAL
WEEKS ON STUDY	0997	0998	0998	0998	0999	1000	1000	1000	1000	1000	1000	1001	1002	1003	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Neurilemoma, malignant																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X			X																						2
Alveolar/bronchiolar carcinoma																	X									2
Endometrial stromal sarcoma, me																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+		49
Squamous cell carcinoma, invasive											X															1
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Carcinoma, NOS	X		X		X											X					X	X				11
Squamous cell carcinoma							X				X															2
Adenoma, NOS																										1
Adenocarcinoma, NOS		X												X				X								3
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+		48
Carcinoma, NOS, metastatic																						X				2
Squamous cell carcinoma, metastic																										1
Thymus	+	+	–	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Squamous cell carcinoma						X																				2
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Squamous cell carcinoma											X											X				3
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Squamous cell papilloma		X							X							X				X						4
Squamous cell carcinoma				X			X								X											5
Sarcoma, NOS									X																	1
Carcinosarcoma												X														1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Large intestine	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Adenomatous polyp, NOS					X																					1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+		48
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Adenoma, NOS																										1
Chromophobe adenoma		X				X	X	X	X											X						12
Chromophobe carcinoma				X	X																	X				4
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Pheochromocytoma		X																								2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+		49
Follicular cell carcinoma																	X			X				X		5
C-cell adenoma		X	X											X												4
Parathyroid	–	+	–	–	+	+	+	+	+	+	+	+	–	+	–	+	–	+	+	+	–	+	+	+		34
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Islet cell adenoma																										1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		*50
Adenocarcinoma, NOS								X								X										4
Fibroadeno ma		X		X	X			X					X		X	X	X			X	X			X		18
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																									X	1
Endometrial stromal polyp			X								X	X					X		X							11
Endometrial stromal sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Granulosa cell tumor										X																1
NERVOUS SYSTEM																										
Nerves	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Carcinoma, NOS, invasive			X																							1
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma, NOS, invasive			X		X																					7
Adenocarcinoma, NOS, invasive		X												X												2
Chromophobe carcinoma, invasive																						X				1
Astrocytoma																										2
SPECIAL SENSE ORGANS																										
Eye	+	+	+	+	+	N	N	+	+	+	+	N	+	N	+	+	+	+	+	N	+	+	+	+	N	*50
Squamous cell carcinoma, invasive											X															1
Eye appendages	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Basal cell tumor					X																					1
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		*50
Squamous cell carcinoma, invasive						X																				1
BODY CAVITIES																										
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Alveolar/bronchiolar ca, invasive																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N		*50
Carcinoma, NOS, metastatic																										1
Malignant lymphoma, mixed type								X																		1
Lymphocytic leukemia		X																								1
Leukemia, mononuclear cell	X					X								X												7

* Animals necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE: HIGH DOSE

ANIMAL NUMBER	0227	0448	0299	0440	0200	0355	0288	0117	0113	0441	0008	0334	0337	0226	0330	0443	0332	0455	0007	0912	0002	0211	0255	0336	0001
WEEKS ON STUDY	017	017	044	051	055	055	056	057	058	058	059	060	062	064	065	066	067	068	069	069	070	070	070	070	071
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Trachea	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Nasal cavity	−	−	−	−	+	−	−	−	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS					X				X		X		X	X	X	X		X	X	X	X		X	X	
Squamous cell carcinoma																									
Adenocarcinoma, NOS																	X								X
Rhabdomyosarcoma																									
Carcinosarcoma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, metastatic																		X							
Thymus	+	+	+	−	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma															X										
Squamous cell carcinoma																									
Salivary gland	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	−	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Stomach	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma														X											
Small intestine	+	−	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	−	+	+	−	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma																									
Adrenal	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+
Follicular cell adenoma																	X								
C-cell adenoma																									
Parathyroid	−	−	+	+	+	+	−	+	−	−	−	+	−	+	+	+	+	+	+	+	−	−	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Uterus	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Endometrial stromal polyp																									X
Ovary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Nerves	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS, invasive																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive			X		X		X	X	X		X		X	X		X		X	X		X	X	X	X	
Adenocarcinoma, NOS, invasive																	X								X
Rhabdomyosarcoma, invasive																									
Carcinosarcoma, invasive																									
SPECIAL SENSE ORGANS																									
Zymbal gland	N	N	N	+	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS				X											X										
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Leukemia, mononuclear cell																									

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: HIGH DOSE (Continued)

ANIMAL NUMBER	003	011	049	016	018	019	005	023	031	044	015	039	042	038	010	022	033	006	050	009	024	004	014	046	047	TOTAL:
WEEKS ON STUDY	071	071	071	072	072	072	073	073	073	073	074	074	074	075	076	076	076	079	080	083	084	087	087	090	097	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma																	X									1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma																						X				1
Trachea	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Nasal cavity	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
Carcinoma, NOS		X	X	X	X		X	X			X	X	X		X					X	X	X		X	X	28
Squamous cell carcinoma						X																		X		2
Adenocarcinoma, NOS														X		X	X		X							6
Rhabdomyosarcoma													X													1
Carcinosarcoma										X																1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, NOS, metastatic															X					X		X				4
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Oral cavity	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell papilloma							X					X			X											4
Squamous cell carcinoma																						X				1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																	X									1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																						X				1
Squamous cell carcinoma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Chromophobe adenoma											X														X	2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma																										1
C-cell adenoma																			X							1
Parathyroid	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	–	–	+	+	+	+	+	+	36
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma													X				X		X	X					X	5
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Endometrial stromal polyp							X																			2
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Nerves	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS, invasive														X								X				2
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive		X	X		X		X	X			X			X					X		X	X		X		25
Adenocarcinoma, NOS, invasive														X			X		X							5
Rhabdomyosarcoma, invasive													X													1
Carcinosarcoma, invasive										X																1
SPECIAL SENSE ORGANS																										
Zymbal gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Leukemia, mononuclear cell																		X								1

* Animals necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Squamous cell papilloma		1 (2%)	
Squamous cell carcinoma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibrosarcoma	2 (4%)	1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(49)	(50)	(49)
Squamous cell carcinoma, metastatic		16 (32%)	11 (22%)
Hepatocellular carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar adenoma	3 (6%)	6 (12%)	4 (8%)
Alveolar/bronchiolar carcinoma	3 (6%)	4 (8%)	5 (10%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, undiffer type			1 (2%)
Malignant lymphoma, lymphocytic type	1 (2%)	1 (2%)	1 (2%)
Malignant lymphoma, histiocytic type		2 (4%)	
Malignant lymphoma, mixed type	3 (6%)	2 (4%)	3 (6%)
Granulocytic leukemia		1 (2%)	
#Spleen	(49)	(50)	(49)
Squamous cell carcinoma, invasive			2 (4%)
Malignant lymphoma, mixed type	1 (2%)		
#Lymph node	(48)	(37)	(35)
Malignant lymphoma, NOS			1 (3%)
#Thoracic lymph node	(48)	(37)	(35)
Squamous cell carcinoma, metastatic		6 (16%)	2 (6%)
#Bronchial lymph node	(48)	(37)	(35)
Alveolar/bronchiolar ca, metastatic		1 (3%)	
#Mediastinal lymph node	(48)	(37)	(35)
Squamous cell carcinoma, metastatic		3 (8%)	5 (14%)
#Hepatic lymph node	(48)	(37)	(35)
Squamous cell carcinoma, invasive		2 (5%)	
#Pancreatic lymph node	(48)	(37)	(35)
Squamous cell carcinoma, invasive		1 (3%)	
#Mesenteric lymph node	(48)	(37)	(35)
Squamous cell carcinoma, invasive			1 (3%)
#Duodenum	(46)	(43)	(47)
Malignant lymphoma, mixed type	1 (2%)		
#Thymus	(39)	(29)	(30)
Squamous cell carcinoma, metastatic		4 (14%)	

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#Spleen	(49)	(50)	(49)
Hemangiosarcoma	1 (2%)		
#Mesenteric lymph node	(48)	(37)	(35)
Hemangioma		1 (3%)	
*Pulmonary artery	(50)	(50)	(50)
Squamous cell carcinoma, metastatic			1 (2%)
*Mesenteric artery	(50)	(50)	(50)
Squamous cell carcinoma, metastatic		1 (2%)	
#Liver	(49)	(50)	(49)
Hemangioma		1 (2%)	1 (2%)
Hemangiosarcoma		1 (2%)	3 (6%)
*Preputial gland	(50)	(50)	(50)
Hemangioma	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(46)	(45)	(48)
Fibrosarcoma, invasive	1 (2%)		
#Liver	(49)	(50)	(49)
Squamous cell carcinoma, invasive		2 (4%)	5 (10%)
Squamous cell carcinoma, metastatic		1 (2%)	
Hepatocellular adenoma	8 (16%)	7 (14%)	8 (16%)
Hepatocellular carcinoma	3 (6%)	6 (12%)	7 (14%)
Liposarcoma	1 (2%)		
#Pancreas	(49)	(50)	(49)
Squamous cell carcinoma, invasive			1 (2%)
#Pancreatic duct	(49)	(50)	(49)
Squamous cell carcinoma, invasive			1 (2%)
#Forestomach	(49)	(50)	(49)
Squamous cell papilloma	1 (2%)	3 (6%)	8 (16%)
Squamous cell carcinoma		42 (84%)	35 (71%)
URINARY SYSTEM			
#Kidney/glomerulus	(49)	(50)	(49)
Squamous cell carcinoma, metastatic		2 (4%)	
ENDOCRINE SYSTEM			
#Adrenal	(49)	(49)	(49)
Alveolar/bronchiolar carcinoma, metastatic			1 (2%)
#Adrenal/capsule	(49)	(49)	(49)
Adenoma, NOS	2 (4%)		
#Adrenal medulla	(49)	(49)	(49)
Pheochromocytoma	2 (4%)	1 (2%)	
#Thyroid	(49)	(48)	(45)
Follicular cell adenoma			1 (2%)
Follicular cell carcinoma	1 (2%)		
#Pancreatic islets	(49)	(50)	(49)
Islet cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Squamous cell carcinoma	1 (2%)	3 (6%)	16 (32%)
#Testis	(49)	(50)	(49)
Interstitial cell tumor	1 (2%)		

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Papillary adenoma	2 (4%)	3 (6%)	3 (6%)
MUSCULOSKELETAL SYSTEM			
*Mandible	(50)	(50)	(50)
Ameloblastoma			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Squamous cell carcinoma, metastatic			1 (2%)
*Pleura	(50)	(50)	(50)
Squamous cell carcinoma, metastatic		5 (10%)	1 (2%)
Alveolar/bronchiolar carcinoma, invasive			1 (2%)
*Mesentery	(50)	(50)	(50)
Squamous cell carcinoma, invasive		2 (4%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Squamous cell carcinoma, invasive		21 (42%)	14 (28%)
Squamous cell carcinoma, metastatic			1 (2%)
Alveolar/bronchiolar carcinoma, metastatic	2 (4%)		
Diaphragm			
Squamous cell carcinoma, invasive			1
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	5	15	17
Moribund sacrifice	7	27	32
Terminal sacrifice	38	8	1
TUMOR SUMMARY			
Total animals with primary tumors**	26	47	43
Total primary tumors	38	87	99
Total animals with benign tumors	14	21	21
Total benign tumors	20	24	26
Total animals with malignant tumors	15	45	42
Total malignant tumors	18	63	73
Total animals with secondary tumors##	3	31	32
Total secondary tumors	3	67	50

* Number of animals receiving complete necropsy examination, all gross lesions including masses examined microscopically
** Primary tumors all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors metastatic tumors or tumors invasive into an adjacent organ

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Keratoacanthoma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Fibrosarcoma		2 (4%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(48)
Squamous cell carcinoma, metastatic		11 (22%)	12 (25%)
Alveolar/bronchiolar adenoma	2 (4%)	1 (2%)	6 (13%)
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)
Adenosquamous carcinoma, metastatic		1 (2%)	
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type	2 (4%)		4 (8%)
Malignant lymphoma, histiocytic type	1 (2%)	1 (2%)	1 (2%)
Malignant lymphoma, mixed type	4 (8%)	1 (2%)	4 (8%)
#Spleen	(50)	(49)	(47)
Squamous cell carcinoma, invasive		1 (2%)	
Malignant lymphoma, mixed type	1 (2%)		1 (2%)
#Splenic capsule	(50)	(49)	(47)
Squamous cell carcinoma, invasive			1 (2%)
#Thoracic lymph node	(50)	(42)	(38)
Squamous cell carcinoma, metastatic		5 (12%)	4 (11%)
#Bronchial lymph node	(50)	(42)	(38)
Squamous cell carcinoma, metastatic		1 (2%)	
#Mediastinal lymph node	(50)	(42)	(38)
Squamous cell carcinoma, metastatic		5 (12%)	2 (5%)
#Mesenteric lymph node	(50)	(42)	(38)
Squamous cell carcinoma, invasive		1 (2%)	1 (3%)
#Liver	(50)	(50)	(48)
Malignant lymphoma, mixed type	1 (2%)		
#Jejunum	(50)	(43)	(42)
Malignant lymphoma, lymphocytic type	1 (2%)		
#Thymus	(41)	(34)	(27)
Squamous cell carcinoma, metastatic		1 (3%)	
CIRCULATORY SYSTEM			
#Spleen	(50)	(49)	(47)
Hemangiosarcoma		1 (2%)	
#Large intestine	(50)	(47)	(46)
Hemangioma			1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(48)
Squamous cell carcinoma, invasive			1 (2%)
Hepatocellular adenoma	4 (8%)	4 (8%)	4 (8%)
*Gallbladder	(50)	(50)	(50)
Squamous cell carcinoma, invasive		1 (2%)	1 (2%)
#Pancreas	(50)	(49)	(47)
Squamous cell carcinoma, invasive			2 (4%)

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Esophagus	(50)	(49)	(47)
Squamous cell carcinoma		1 (2%)	
#Forestomach	(50)	(50)	(48)
Carcinoma, NOS			1 (2%)
Squamous cell papilloma		1 (2%)	3 (6%)
Squamous cell carcinoma		40 (80%)	36 (75%)
Adenosquamous carcinoma		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(50)	(48)
Squamous cell carcinoma, invasive		1 (2%)	
#Kidney/capsule	(50)	(50)	(48)
Squamous cell carcinoma, invasive			1 (2%)
#Kidney/glomerulus	(50)	(50)	(48)
Squamous cell carcinoma, metastatic			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(49)	(47)
Chromophobe adenoma	15 (31%)	2 (4%)	
#Adrenal/capsule	(49)	(50)	(47)
Squamous cell carcinoma, invasive		1 (2%)	1 (2%)
#Adrenal medulla	(49)	(50)	(47)
Pheochromocytoma	1 (2%)		
Pheochromocytoma, malignant			1 (2%)
#Periadrenal tissue	(49)	(50)	(47)
Squamous cell carcinoma, invasive			2 (4%)
#Thyroid	(50)	(43)	(45)
Follicular cell adenoma	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Adenocarcinoma, NOS	1 (2%)	2 (4%)	
#Uterus	(50)	(50)	(46)
Neurilemoma, malignant	1 (2%)		
#Ovary	(49)	(49)	(47)
Squamous cell carcinoma, metastatic		1 (2%)	
Granulosa cell tumor			1 (2%)
Teratoma, NOS		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Papillary adenoma		3 (6%)	5 (10%)
MUSCULOSKELETAL SYSTEM			
*Skull	(50)	(50)	(50)
Osteoma	1 (2%)		
*Abdominal muscle	(50)	(50)	(50)
Squamous cell carcinoma, invasive			1 (2%)

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Squamous cell carcinoma, metastatic		3 (6%)	1 (2%)
*Pleura	(50)	(50)	(50)
Squamous cell carcinoma, metastatic		5 (10%)	9 (18%)
Adenosquamous carcinoma, metastatic		1 (2%)	
*Mesentery	(50)	(50)	(50)
Squamous cell carcinoma, invasive			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Carcinoma, NOS, invasive			1 (2%)
Squamous cell carcinoma, invasive		27 (54%)	23 (46%)
Adenosquamous carcinoma, invasive		1 (2%)	
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	13	14
Moribund sacrifice	5	31	33
Terminal sacrifice	41	5	2
Accidentally killed, nda		1	
Accidentally killed, NOS			1
TUMOR SUMMARY			
Total animals with primary tumors**	32	44	43
Total primary tumors	37	61	71
Total animals with benign tumors	23	10	17
Total benign tumors	24	11	21
Total animals with malignant tumors	13	42	43
Total malignant tumors	13	49	49
Total animals with secondary tumors##		33	32
Total secondary tumors		67	65
Total animals with tumors uncertain--benign or malignant		1	1
Total uncertain tumors		1	1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
** Primary tumors: all tumors except secondary tumors
# Number of animals examined microscopically at this site
Secondary tumors: metastatic tumors or tumors invasive into an adjacent organ

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE: VEHICLE CONTROL

ANIMAL NUMBER	53201	54301	54101	53101	53303	53306	53404	53808	51706	51104	55005	54606	50101	50302	50303	50404	50505	50606	50707	50808	50909	51010	51111	51212	51313
WEEKS ON STUDY	00001	00001	04001	04101	05808	07606	08404	08809	09606	09909	09909	10003	10303	10303	10303	10303	10303	10303	10303	10303	10303	10303	10303	10303	10303
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma												X													X
RESPIRATORY SYSTEM																									
Lungs and bronchi	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma									X											X					
Trachea	A	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Spleen	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Malignant lymphoma, mixed type																									
Lymph nodes	A	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	A	−	−	+	+	+	+	+	+	+	−	−	+	+	+	+	+	−	+	+	−	+	+	+	−
CIRCULATORY SYSTEM																									
Heart	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma, invasive																									X
Liver	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma											X														
Hepatocellular carcinoma							X		X																
Liposarcoma																						X			
Bile duct	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+
Pancreas	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																							X		
Small intestine	A	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																X									
Large intestine	A	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	A	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma											X														
Thyroid	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma															X										
Parathyroid	A	−	−	+	−	−	−	−	+	+	−	−	−	+	+	−	+	−	−	−	−	−	−	−	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+
Testis	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor															X										
Prostate	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma																									
Hemangioma									X																
NERVOUS SYSTEM																									
Brain	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																					X				
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Alveolar/bronchiolar carcinoma, metastatic									X																
Malig. lymphoma, lymphocytic type						X																			
Malignant lymphoma, mixed type															X									X	

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed

No tissue information submitted
C Necropsy, no histology due to protocol
A. Autolysis
M. Animal missing
B No necropsy performed

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	51 15	51 16	51 18	51 19	52 20	52 21	52 22	52 23	52 24	52 25	52 26	52 27	52 28	52 29	53 00	53 35	53 37	53 39	54 40	54 42	54 44	54 45	54 47	54 48	54 49	TOTAL:
WEEKS ON STUDY	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma				X				X													X					3
Alveolar/bronchiolar carcinoma														X												3
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma		X																								1
Malignant lymphoma, mixed type																				X						1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	–	39
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	–	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	46
Fibrosarcoma, invasive																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma			X			X							X						X	X		X	X			8
Hepatocellular carcinoma														X												3
Liposarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma																										1
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Malignant lymphoma, mixed type																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS			X																X							2
Pheochromocytoma																						X				2
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell carcinoma																										1
Parathyroid	+	–	–	+	–	+	+	+	+	+	+	–	–	–	–	–	+	–	+	+	+	+	+	+	+	22
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Interstitial cell tumor																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																X										1
Hemangioma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	*50
Papillary adenoma																										2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Alveolar/bronchiolar carcin, metasta														X												2
Malig. lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type								X																		3

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE: LOW DOSE

ANIMAL NUMBER	54 42	54 44	54 49	53 30	53 38	53 39	51 15	52 29	51 13	53 33	54 40	54 43	53 37	52 20	55 00	53 36	50 04	51 14	52 23	52 27	50 02	50 07	51 19	50 05	50 08
WEEKS ON STUDY	00 02	00 02	00 02	05 00	06 02	07 02	07 03	07 03	07 08	07 09	07 09	07 09	08 00	08 01	08 02	08 03	08 04	08 04	08 04	08 07	08 08	08 08	08 08	09 00	09 00
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																							X		
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																								X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic				X		X	X		X	X			X			X	X						X	X	X
Alveolar/bronchiolar adenoma								X								X			X					X	
Alveolar/bronchiolar carcinoma					X				X																
Trachea	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	−	−	−	−	+	−	+	−	+	+	+	+	−	+	+	−	+	−	−	+	−	+	+	+	+
Squamous cell carcinoma, invasive																			X						
Squamous cell carcinoma, metastatic									X						X									X	
Alveolar/bronchiolar carcinoma, metastatic					X																				
Hemangioma																									
Thymus	+	−	−	+	+	+	−	+	+	+	−	+	−	+	−	−	+	−	+	−	−	+	−	+	+
Squamous cell carcinoma, metastatic						X		X																	
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic																									
DIGESTIVE SYSTEM																									
Salivary gland	+	−	+	+	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																			X						
Squamous cell carcinoma, metastatic																									
Hepatocellular adenoma													X	X					X		X				
Hepatocellular carcinoma																									
Hemangioma																				X					
Hemangiosarcoma																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	N	+	+	+	N	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma									X																
Squamous cell carcinoma				X		X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Small intestine	+	−	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																								X	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	
Pheochromocytoma																									
Thyroid	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	
Parathyroid	+	−	−	−	+	−	−	−	−	+	+	+	−	−	−	+	+	+	+	+	−	−	−	−	
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma														X											
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																									
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic										X													X	X	
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, invasive																						X			
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, invasive				X		X	X	X	X	X			X		X		X						X	X	X
Malig. lymphoma, lymphocytic type																									
Malig. lymphoma, histiocytic type																		X							
Malignant lymphoma, mixed type																									
Granulocytic leukemia											X														

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	52 26	54 45	54 48	50 03	54 41	50 01	51 16	54 47	53 34	52 22	51 12	51 11	50 09	51 10	53 35	54 46	53 31	50 06	51 17	51 18	52 21	52 24	52 25	52 28	53 32	TOTAL TISSUES TUMORS
WEEKS ON STUDY	09 90	09 90	09 90	09 91	09 91	09 93	09 93	09 93	09 94	09 96	09 97	09 99	10 00	10 00	10 00	10 00	10 02	10 03	10 03	10 03	10 03	10 03	10 03	10 03	10 03	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic								X	X		X	X			X		X									16
Alveolar/bronchiolar adenoma																					X	X				6
Alveolar/bronchiolar carcinoma														X							X					4
Trachea	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph nodes	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	37
Squamous cell carcinoma, invasive				X															X							3
Squamous cell carcinoma, metastatic								X	X		X			X	X		X									9
Alveolar/bronchiolar carcin, metastatic																										1
Hemangioma																	X									1
Thymus	–	+	+	+	+	+	–	–	–	–	–	+	–	–	–	+	+	+	+	+	+	+	–	+	+	29
Squamous cell carcinoma, metastatic												X					X									4
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, metastatic					X																					1
DIGESTIVE SYSTEM																										
Salivary gland	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, invasive																						X				2
Squamous cell carcinoma, metastatic						X																				1
Hepatocellular adenoma									X										X						X	7
Hepatocellular carcinoma			X			X			X									X		X				X		6
Hemangioma																		X								1
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	N	+	+	+	+	N	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma									X																X	3
Squamous cell carcinoma	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X		42
Small intestine	–	+	–	+	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	43
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic								X																		2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	46
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma	X																									1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid	–	–	+	+	–	–	+	–	–	+	+	+	–	+	+	–	+	+	+	+	–	+	+	–	+	25
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell adenoma			X																							1
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma																	X							X		3
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma						X									X			X								3
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, metastatic								X									X									5
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive		X																								2
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive							X	X	X		X	X	X	X	X		X									21
Malig lymphoma, lymphocytic type				X																						1
Malig lymphoma, histiocytic type						X																				2
Malignant lymphoma, mixed type									X															X		2
Granulocytic leukemia																										1

* Animals necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE: HIGH DOSE

ANIMAL NUMBER	51 15	52 26	52 28	52 29	53 00	54 00	51 13	51 12	53 34	54 48	51 18	51 16	50 06	50 05	50 03	52 22	53 32	53 35	52 21	52 20	50 09	54 46	51 11	52 25	54 47
WEEKS ON STUDY	00 01	00 02	00 02	00 02	00 02	00 02	05 33	05 44	05 55	05 55	06 00	06 02	06 64	06 67	06 68	06 68	06 69	07 10	07 72	07 74	07 75	07 75	07 77	07 77	07 77
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																								X	
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic									X									X				X		X	X
Hepatocellular carcinoma, metastatic											X														
Alveolar/bronchiolar adenoma																				X					
Alveolar/bronchiolar carcinoma								X																	
Trachea	+	+	+	+	+	A	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive														X											
Lymph nodes	−	−	−	+	−	A	−	+	+	+	+	+	+	−	+	+	−	−	-	+	+	+	+	+	+
Squamous cell carcinoma, invasive																									
Squamous cell carcinoma, metastatic									X	X												X			X
Malignant lymphoma, NOS																									
Thymus	+	+	−	+	+	A	+	+	−	−	+	+	+	+	+	+	+	+	-	+	+	−	+	−	−
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic													X												
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Liver	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																X		X							
Hepatocellular adenoma																			X						
Hepatocellular carcinoma											X							X							
Hemangioma																									
Hemangiosarcoma																	X								
Bile duct	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	N	N	+	N	+	N	+	N	+	+	N	+	+	+	N	N	+	N	+	+	+	+	+
Pancreas	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																									
Esophagus	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma								X					X		X				X			X	X		
Squamous cell carcinoma							X		X	X						X	X	X		X	X		X		X
Small intestine	+	+	+	−	+	A	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	A	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	A	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma, metastatic								X																	
Thyroid	+	+	+	+	+	A	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	−	−	−	−	−	A	+	−	+	−	+	+	−	+	+	+	−	+	+	−	+	+	−	+	−
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	N	N	N	N	N	N	N	N	+	N	N	N	N	N	N	N	+	N	N	N	N	N	N
Testis	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma													X									X			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ameloblastoma													X												
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic																									
Alveolar/bronchiolar carcinoma, invasive																									
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic										X															
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, invasive							X		X	X											X				X
Squamous cell carcinoma, metastatic												X													
Malig lymphoma, undiffer type																							X		
Malig lymphoma, lymphocytic type																				X					
Malignant lymphoma, mixed type															X									X	
Diaphragm, NOS																									
Squamous cell carcinoma, invasive																									

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	51 17	52 23	54 43	50 02	52 44	53 37	54 49	50 08	53 33	55 50	51 10	51 14	50 04	53 31	54 42	53 36	52 27	50 01	53 38	50 07	51 19	54 45	53 41	53 39	54 44	TOTAL TISSUES TUMORS
WEEKS ON STUDY	07 79	07 79	07 79	08 00	08 00	08 00	08 00	08 01	08 01	08 01	08 02	08 82	08 83	08 83	08 88	08 89	09 00	09 01	09 11	09 93	09 93	09 93	09 94	10 33	10 33	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic												X			X	X	X				X			X		11
Hepatocellular carcinoma, metastatic																										1
Alveolar/bronchiolar adenoma																X					X			X		4
Alveolar/bronchiolar carcinoma						X				X					X	X										5
Trachea	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	46
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, invasive													X													2
Lymph nodes	+	−	+	−	+	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	35
Squamous cell carcinoma, invasive																							X			1
Squamous cell carcinoma, metastatic												X			X	X										7
Malignant lymphoma, NOS	X																									1
Thymus	−	−	+	−	−	+	−	−	+	+	+	−	+	+	+	−	+	−	+	+	+	−	−	−	+	30
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Blood vessels	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, metastatic																										1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, invasive		X								X			X													5
Hepatocellular adenoma										X				X	X		X		X			X		X		8
Hepatocellular carcinoma								X		X									X	X			X			7
Hemangioma									X																	1
Hemangiosarcoma				X					X																	3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, invasive			X	X																						2
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma														X												8
Squamous cell carcinoma		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	35
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	47
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar carcin, metastatic																										1
Thyroid	−	+	−	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Follicular cell adenoma																									X	1
Parathyroid	−	+	−	+	+	+	−	+	−	−	−	−	+	+	+	−	+	+	−	+	+	+	−	+	+	27
REPRODUCTIVE SYSTEM																										
Mammary gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Preputial/clitoral gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma	X	X	X		X		X	X	X	X		X	X				X	X		X				X		16
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma													X							X				X		3
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	N	+	+	+	N	N	N	*50
Ameloblastoma																										1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, metastatic															X											1
Alveolar/bronchiolar carcin, invasive										X																1
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, metastatic																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive							X					X		X	X	X		X		X	X	X				14
Squamous cell carcinoma, metastatic																										1
Malig lymphoma, undiffer type																										1
Malig. lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type																									X	3
Diaphragm, NOS																										
Squamous cell carcinoma, invasive				X																						1

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE: VEHICLE CONTROL

ANIMAL NUMBER	54 49	51 16	51 10	50 04	54 45	54 42	54 48	52 26	52 20	50 01	50 02	50 03	50 05	50 06	50 07	50 08	50 09	51 11	51 12	51 13	51 14	51 15	51 17	51 18	51 19
WEEKS ON STUDY	03 32	07 11	08 00	08 86	08 89	09 33	09 44	09 95	09 98	10 33	10 33	10 33	10 33	10 33	10 33	10 33	10 33	10 33	10 33	10 33	10 33	10 33	10 33	10 33	10 33
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma													X		X										
Alveolar/bronchiolar carcinoma						X																			
Trachea	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	−	−	−	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																X									
Malignant lymphoma, mixed type																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	+	+	+	N	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig. lymphoma, lymphocytic type										X															
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma											X			X			X		X	X		X			X
Adrenal	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma											X														
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																		X							
Parathyroid	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	−	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS							X																		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neurilemoma, malignant																									
Ovary	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	N	N	+	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Osteoma								X																	
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Malig. lymphoma, lymphocytic type		X																							
Malig. lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																							X		

+: Tissue examined microscopically
−: Required tissue not examined microscopically
X: Tumor incidence
N: Necropsy, no autolysis, no microscopic examination
S: Animal missexed
.: No tissue information submitted
C: Necropsy, no histology due to protocol
A: Autolysis
M: Animal missing
B: No necropsy performed

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (*Continued*)

ANIMAL NUMBER	52 21	52 22	52 23	52 24	52 25	52 27	52 28	52 29	53 30	53 31	53 32	53 33	53 34	53 35	53 36	53 37	53 38	53 39	54 40	54 41	54 43	54 44	54 46	54 47	55 50	TOTAL TISSUES TUMORS
WEEKS ON STUDY	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	103	
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																										2
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type														X												1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	–	+	+	–	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma															X	X					X					4
Malignant lymphoma, mixed type	X																									1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malig lymphoma, lymphocytic type																										1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Chromophobe adenoma						X			X	X				X			X	X				X			X	15
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell adenoma																										1
Parathyroid	–	–	–	+	+	–	+	–	+	–	–	–	–	–	–	–	+	–	+	+	–	+	+	+	+	30
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neurilemoma, malignant																					X					1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Osteoma																										1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Malig lymphoma, lymphocytic type				X																						2
Malig lymphoma, histiocytic type									X																	1
Malignant lymphoma, mixed type											X						X						X			4

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE: LOW DOSE

ANIMAL NUMBER	518	519	520	534	535	502	514	530	546	506	532	504	508	543	515	531	524	505	525	501	536	527	539	509	541
WEEKS ON STUDY	002	002	002	008	035	046	048	055	055	059	060	064	068	068	070	071	073	076	076	078	078	080	080	081	081
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic														X			X	X		X	X			X	
Alveolar/bronchiolar adenoma																									
Adenosquamous carcinoma, metastatic																						X			
Trachea	+	−	+	+	−	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																			X						
Hemangiosarcoma																									
Lymph nodes	+	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	−	+	+	+	+	+	−
Squamous cell carcinoma, invasive																									
Squamous cell carcinoma, metastatic														X		X		X		X	X				
Thymus	−	+	+	+	−	+	+	+	−	+	+	+	+	−	+	+	+	−	−	+	−	+	+	−	+
Squamous cell carcinoma, metastatic																	X								
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																	X						X		
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																									
Pancreas	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma					X			X	X	X	X		X	X	X	X	X		X	X	X		X	X	X
Adenosquamous carcinoma																						X			
Small intestine	−	−	+	+	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																									
Urinary bladder	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chromophobe adenoma										X															
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive					X																				
Thyroid	+	−	+	+	−	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	−	−	−	−	+	+	−	+	+	+	+	−	−	+	+	+	−	−	+	−	+	−	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+
Adenocarcinoma, NOS								X															X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									
Teratoma, NOS						X																			
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																							X		
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic																	X	X						X	
Adenosquamous carcinoma, metastatic																						X			
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic									X																
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, invasive									X	X	X		X	X		X	X	X		X	X			X	
Adenosquamous carcinoma, invasive																						X			
Malig. lymphoma, histiocytic type							X																		
Malignant lymphoma, mixed type																									

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: LOW DOSE (Continued)

ANIMAL NUMBER	51 16	54 48	51 10	52 94	54 42	52 22	55 50	51 12	51 13	53 37	54 40	52 21	50 03	50 07	51 11	54 49	52 28	52 26	53 33	51 17	52 23	53 38	54 42	54 45	54 47	TOTAL: TISSUES TUMORS
WEEKS ON STUDY	08 82	08 86	08 88	08 88	08 89	09 00	09 00	09 01	09 11	09 91	09 91	09 92	09 93	09 95	09 95	09 96	09 98	09 99	10 00	10 03	10 03	10 03	10 03	10 03	10 03	
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma							X									X										2
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic	X			X						X							X	X								11
Alveolar/bronchiolar adenoma		X																								1
Adenosquamous carcinoma, metastatic																										1
Trachea	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	43
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, invasive																										1
Hemangiosarcoma																							X			1
Lymph nodes	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Squamous cell carcinoma, invasive																						X				1
Squamous cell carcinoma, metastatic	X							X		X	X		X											X		11
Thymus	+	+	+	+	+	+	+	+	−	+	−	−	+	+	+	−	+	−	−	+	−	−	+	+	+	34
Squamous cell carcinoma, metastatic																										1
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																				X	X					4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	N	+	+	*50
Squamous cell carcinoma, invasive			X																							1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma																			X							1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell papilloma							X																			1
Squamous cell carcinoma	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	40
Adenosquamous carcinoma																										1
Small intestine	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Large intestine	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, invasive																			X							1
Urinary bladder	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	49
Chromophobe adenoma													X													2
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, invasive																										1
Thyroid	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Parathyroid	−	−	−	+	−	+	+	−	+	−	+	−	+	+	+	+	+	−	−	+	+	+	+	+	+	30
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell carcinoma, metastatic											X															1
Teratoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma																X						X				3
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, metastatic	X	X																								5
Adenosquamous carcinoma, metastatic																										1
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, metastatic		X											X													3
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive	X	X		X	X	X	X	X	X	X	X	X	X		X		X	X						X		27
Adenosquamous carcinoma, invasive																										1
Malig. lymphoma, histiocytic type																										1
Malignant lymphoma, mixed type																				X						1

* Animals necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE: HIGH DOSE

ANIMAL NUMBER	52 26	51 11	51 13	51 14	51 15	51 16	54 49	51 12	50 02	53 33	50 06	51 19	53 30	50 05	50 08	53 32	54 46	54 43	50 04	50 09	53 36	54 48	52 28	53 35	52 21
WEEKS ON STUDY	00 01	00 02	00 02	00 02	00 02	00 02	00 02	04 00	05 54	05 55	05 59	05 59	06 00	06 06	07 00	07 07	07 22	07 33	07 55	07 55	07 55	07 75	07 78	07 78	07 79
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	N	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic									X	X						X		X			X				
Alveolar/bronchiolar adenoma											X							X					X	X	
Alveolar/bronchiolar carcinoma																									
Trachea	+	−	+	+	+	A	A	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	−	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																									
Malignant lymphoma, mixed type																									
Lymph nodes	−	+	−	+	+	A	A	+	+	+	+	+	+	−	−	−	−	+	+	+	+	+	+	+	−
Squamous cell carcinoma, invasive																									
Squamous cell carcinoma, metastatic												X	X					X	X					X	
Thymus	+	−	+	+	−	A	A	+	+	−	−	−	+	+	−	−	−	−	+	+	−	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	−	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	−	+	−	+	+	+	+
Liver	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																									X
Hepatocellular adenoma																									
Bile duct	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	N	N	N	N	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																				X					
Pancreas	+	−	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																									X
Esophagus	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
Squamous cell papilloma										X				X											
Squamous cell carcinoma									X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
Small intestine	+	−	−	−	+	A	A	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Large intestine	+	−	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
Hemangioma																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																									
Squamous cell carcinoma, metastatic																									
Urinary bladder	+	−	−	+	+	A	A	+	+	−	−	+	+	+	+	−	+	+	+	+	+	+	−	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+
Squamous cell carcinoma, invasive																									
Pheochromocytoma, malignant																									
Thyroid	+	+	+	+	+	A	A	+	−	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	+	−	+	+	−	A	A	−	−	−	−	−	+	+	+	−	+	+	+	−	−	+	+	−	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	N	N	N	+	N	+	N	+	+	N	N	+	+	+	+	N	+	+	+	+
Uterus	+	+	−	−	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovary	+	+	−	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSE ORGANS																									
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Papillary adenoma																									
MUSCULOSKELETAL SYSTEM																									
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, invasive																									X
BODY CAVITIES																									
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic										X		X	X		X	X			X		X				
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, metastatic										X															
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell carcinoma, invasive																									
ALL OTHER SYSTEMS																									
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Carcinoma, NOS, invasive																									
Squamous cell carcinoma, invasive									X	X	X	X	X		X	X	X	X	X		X		X	X	
Malig lymphoma, lymphocytic type								X																	
Malig lymphoma, histiocytic type																									
Malignant lymphoma, mixed type														X											

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: HIGH DOSE (Continued)

ANIMAL NUMBER	53 31	54 45	50 03	51 18	52 24	50 01	53 34	53 39	50 07	52 25	53 37	51 10	54 44	52 22	54 41	54 42	54 40	52 23	51 17	53 38	52 27	54 47	52 20	52 29	55 50	TOTAL. TISSUES TUMORS
WEEKS ON STUDY	08 00	08 00	08 02	08 03	08 03	08 07	08 07	08 08	08 09	08 09	09 00	09 01	09 01	09 02	09 02	09 02	09 03	09 04	09 06	09 07	09 09	10 02	10 03	10 03	10 03	
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Keratoacanthoma																							X			1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, metastatic							X		X			X		X	X					X	X					12
Alveolar/bronchiolar adenoma														X										X		6
Alveolar/bronchiolar carcinoma																									X	1
Trachea	+	+	+	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, invasive												X														1
Malignant lymphoma, mixed type									X																	1
Lymph nodes	+	+	−	+	−	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Squamous cell carcinoma, invasive																	X									1
Squamous cell carcinoma, metastatic																				X						6
Thymus	+	−	+	+	+	+	+	−	+	−	+	+	−	−	+	+	−	+	−	−	−	+	−	+	−	27
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	44
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, invasive																										1
Hepatocellular adenoma					X		X								X							X				4
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	+	+	+	+	+	N	N	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell carcinoma, invasive																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, invasive											X															2
Esophagus	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS			X																							1
Squamous cell papilloma																							X			1
Squamous cell carcinoma	X				X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	36
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	−	42
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Hemangioma																				X						1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Squamous cell carcinoma, invasive																							X			1
Squamous cell carcinoma, metastatic																					X					1
Urinary bladder	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	41
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell carcinoma, invasive													X				X							X		3
Pheochromocytoma, malignant																		X								1
Thyroid	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Follicular cell adenoma											X															1
Parathyroid	+	−	−	−	−	+	−	+	+	−	+	+	+	+	+	+	+	−	−	+	−	+	+	+	−	27
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Granulosa cell tumor								X																		1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSE ORGANS																										
Harderian gland	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Papillary adenoma			X		X		X											X					X			5
MUSCULOSKELETAL SYSTEM																										
Muscle	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive																										1
BODY CAVITIES																										
Pleura	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, metastatic																					X				X	9
Mediastinum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, metastatic																										1
Mesentery	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Squamous cell carcinoma, invasive													X													1
ALL OTHER SYSTEMS																										
Multiple organs, NOS	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	*50
Carcinoma, NOS, invasive			X																							1
Squamous cell carcinoma, invasive	X					X	X							X	X			X		X	X	X			X	23
Malig lymphoma, lymphocytic type															X		X						X			4
Malig lymphoma, histiocytic type								X																		1
Malignant lymphoma, mixed type		X		X															X							4

* Animals necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
Inflammation, acute focal	2 (4%)		
Inflammation, chronic focal	1 (2%)		
Hyperplasia, NOS	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Abscess, NOS		1 (2%)	
Inflammation, pyogranulomatous		1 (2%)	
RESPIRATORY SYSTEM			
#Nasal cavity	(47)	(46)	(32)
Congestion, NOS			1 (2%)
Inflammation, suppurative	15 (32%)	15 (33%)	4 (13%)
Inflammation, acute/chronic	1 (2%)		
Infection, fungal	1 (2%)	1 (2%)	
Atypia, NOS		1 (2%)	
Hyperplasia, epithelial		4 (9%)	
Metaplasia, squamous		2 (4%)	2 (6%)
#Trachea	(50)	(49)	(48)
Inflammation, acute		1 (2%)	
#Lung/bronchus	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
Metaplasia, squamous		1 (2%)	
Metaplasia, osseous	1 (2%)		
#Lung	(50)	(50)	(50)
Aspiration, NOS			2 (4%)
Vegetable foreign body			1 (2%)
Emphysema, NOS			1 (2%)
Congestion, NOS	3 (6%)	3 (6%)	7 (14%)
Edema, NOS	1 (2%)		1 (2%)
Hemorrhage		2 (4%)	
Inflammation, interstitial			2 (4%)
Pneumonia, aspiration			1 (2%)
Bronchopneumonia, acute		2 (4%)	
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, acute focal		1 (2%)	3 (6%)
Inflammation, acute/chronic	1 (2%)	1 (2%)	1 (2%)
Pneumonia, chronic murine	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	
Inflammation, chronic focal		2 (4%)	
Inflammation, granulomatous	2 (4%)		
Hyperplasia, adenomatous	1 (2%)	2 (4%)	2 (4%)
Histiocytosis	2 (4%)	2 (4%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(50)	(48)
Necrosis, NOS		1 (2%)	
Hypoplasia, NOS			1 (2%)
Hyperplasia, NOS		1 (2%)	
#Spleen	(50)	(50)	(50)
Congestion, NOS		1 (2%)	
Fibrosis	1 (2%)		
Infarct, acute		1 (2%)	
Hemosiderosis			3 (6%)
Hematopoiesis	2 (4%)	5 (10%)	2 (4%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mandibular lymph node	(50)	(46)	(45)
Cyst, NOS	1 (2%)		
Hemorrhage			1 (2%)
Inflammation, active chronic		1 (2%)	
Plasmacytosis	1 (2%)	1 (2%)	
#Mediastinal lymph node	(50)	(46)	(45)
Hemorrhage			1 (2%)
#Pancreatic lymph node	(50)	(46)	(45)
Inflammation, acute/chronic		1 (2%)	
#Renal lymph node	(50)	(46)	(45)
Hemorrhage		1 (2%)	1 (2%)
#Liver	(50)	(50)	(50)
Hematopoiesis		2 (4%)	
#Thymus	(40)	(41)	(31)
Cyst, NOS	1 (3%)		
CIRCULATORY SYSTEM			
#Spleen	(50)	(50)	(50)
Thrombus, organized	1 (2%)		
#Lung	(50)	(50)	(50)
Perivasculitis		1 (2%)	
#Heart/atrium	(50)	(50)	(49)
Thrombosis, NOS			1 (2%)
#Myocardium	(50)	(50)	(49)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic	27 (54%)	33 (66%)	29 (59%)
Inflammation, chronic focal			3 (6%)
Fibrosis, focal	4 (8%)	1 (2%)	1 (2%)
Degeneration, NOS	1 (2%)		2 (4%)
Calcification, focal		2 (4%)	
*Mesenteric artery	(50)	(50)	(50)
Thrombus, organized	1 (2%)		
Inflammation, chronic	1 (2%)		
*Pulmonary vein	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
#Liver	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
#Urinary bladder/serosa	(49)	(48)	(48)
Perivasculitis	1 (2%)		
#Adrenal	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
DIGESTIVE SYSTEM			
*Oral cavity	(50)	(50)	(50)
Hyperplasia, epithelial			1 (2%)
*Palate	(50)	(50)	(50)
Hyperplasia, epithelial		1 (2%)	
*Tongue	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
*Periodontal tissues	(50)	(50)	(50)
Abscess, NOS			1 (2%)
#Salivary gland	(50)	(48)	(49)
Dilatation/ducts		2 (4%)	
Inflammation, active chronic		1 (2%)	
Inflammation, acute/chronic	2 (4%)	1 (2%)	1 (2%)
Atrophy, NOS		3 (6%)	1 (2%)
Metaplasia, squamous			1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Liver	(50)	(50)	(50)
Hernia, NOS	1 (2%)	3 (6%)	1 (2%)
Congestion, NOS		3 (6%)	2 (4%)
Inflammation, acute/chronic	1 (2%)		
Cholangiofibrosis			1 (2%)
Necrosis, focal	1 (2%)		
Metamorphosis, fatty	10 (20%)	4 (8%)	2 (4%)
Basophilic cyto change	2 (4%)	1 (2%)	1 (2%)
Ground glass cyto change			1 (2%)
Eosinophilic cyto change		1 (2%)	2 (4%)
Clear cell change	1 (2%)		
Cytologic alteration, NOS		2 (4%)	
Angiectasis	1 (2%)	3 (6%)	
#Hepatic capsule	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Inflammation, acute	1 (2%)		
#Liver/centrilobular	(50)	(50)	(50)
Congestion, NOS			1 (2%)
Inflammation, acute		1 (2%)	
Degeneration, NOS		2 (4%)	2 (4%)
Necrosis, NOS	1 (2%)	1 (2%)	3 (6%)
Metamorphosis, fatty	1 (2%)	4 (8%)	1 (2%)
Cytoplasmic vacuolization			1 (2%)
#Liver/periportal	(50)	(50)	(50)
Metamorphosis, fatty		1 (2%)	1 (2%)
#Bile duct	(50)	(50)	(50)
Cyst, NOS		2 (4%)	
Congestion, NOS		1 (2%)	
Hyperplasia, NOS	43 (86%)	29 (58%)	26 (52%)
#Pancreatic acinus	(50)	(50)	(50)
Atrophy, NOS	14 (28%)	8 (16%)	3 (6%)
Hyperplasia, NOS	5 (10%)	4 (8%)	
#Pancreas/interstitial tissue	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic		1 (2%)	
#Peripancreatic tissue	(50)	(50)	(50)
Necrosis, fat		1 (2%)	
#Esophagus	(50)	(50)	(49)
Inflammation, acute focal			1 (2%)
Perforation, inflammatory			1 (2%)
Hyperplasia, epithelial		6 (12%)	4 (8%)
Hyperkeratosis			1 (2%)
#Stomach	(49)	(50)	(50)
Erosion	1 (2%)		
Calcification, NOS		1 (2%)	
#Gastric mucosa	(49)	(50)	(50)
Necrosis, NOS			1 (2%)
#Gastric serosa	(49)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
#Forestomach	(49)	(50)	(50)
Cyst, NOS		1 (2%)	
Epidermal inclusion cyst		1 (2%)	
Ulcer, NOS		2 (4%)	1 (2%)
Inflammation, acute		2 (4%)	2 (4%)
Ulcer, acute		1 (2%)	
Inflammation, acute/chronic	1 (2%)	4 (8%)	7 (14%)
Hyperplasia, epithelial		24 (48%)	19 (38%)
Hyperkeratosis		1 (2%)	1 (2%)
#Small intestine/mucosa	(45)	(49)	(48)
Metaplasia, osseous	1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Duodenum	(45)	(49)	(48)
Diverticulum			1 (2%)
#Duodenal mucosa	(45)	(49)	(48)
Necrosis, NOS		2 (4%)	6 (13%)
#Large intestine	(49)	(49)	(50)
Inflammation, acute/chronic	1 (2%)		
#Colon	(49)	(49)	(50)
Parasitism	1 (2%)		
#Colonic mucosa	(49)	(49)	(50)
Dilatation, NOS			1 (2%)
#Colonic crypt of Lieberkuhn	(49)	(49)	(50)
Necrosis, NOS		1 (2%)	1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Pyelonephritis, acute/chronic			1 (2%)
Nephropathy	27 (54%)	36 (72%)	33 (66%)
Nephrosis, NOS	1 (2%)	2 (4%)	
#Kidney/interstitial tissue	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
#Kidney/cortex	(50)	(50)	(50)
Calcification, focal			1 (2%)
#Kidney/glomerulus	(50)	(50)	(50)
Nephropathy			1 (2%)
#Kidney/tubule	(50)	(50)	(50)
Dilatation, NOS			2 (4%)
Abscess, NOS		1 (2%)	
Necrosis, focal			1 (2%)
Calcification, NOS		1 (2%)	
#Kidney/pelvis	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
Inflammation, acute/chronic		1 (2%)	
Hyperplasia, epithelial	1 (2%)		
#Urinary bladder	(49)	(48)	(48)
Cast, NOS		1 (2%)	1 (2%)
Hemorrhage		1 (2%)	1 (2%)
Ulcer, NOS			1 (2%)
Inflammation, acute		1 (2%)	1 (2%)
Inflammation, acute/chronic			3 (6%)
Hyperplasia, epithelial			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(50)	(47)
Dilatation/sinus			1 (2%)
Cyst, NOS	3 (6%)	2 (4%)	2 (4%)
Congestion, NOS		1 (2%)	
Hemosiderosis		1 (2%)	
Hyperplasia, focal		1 (2%)	
Hyperplasia, chromophobe cell	5 (10%)	2 (4%)	3 (6%)
Angiectasis		1 (2%)	
#Adrenal cortex	(50)	(50)	(50)
Hemorrhage			1 (2%)
Degeneration, lipoid	2 (4%)	3 (6%)	
Cytoplasmic vacuolization	1 (2%)	2 (4%)	
Hyperplasia, NOS		1 (2%)	
#Adrenal medulla	(50)	(50)	(50)
Calcification, focal		1 (2%)	
Hyperplasia, focal	3 (6%)	4 (8%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(50)	(48)	(47)
Ultimobranchial cyst	1 (2%)	1 (2%)	2 (4%)
Follicular cyst, NOS	4 (8%)	1 (2%)	
Inflammation, chronic focal		1 (2%)	
Hyperplasia, C-cell	4 (8%)	2 (4%)	2 (4%)
Hyperplasia, follicular cell	1 (2%)	1 (2%)	
#Thyroid follicle	(50)	(48)	(47)
Hyperplasia, cystic		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts	5 (10%)	10 (20%)	
Galactocele		1 (2%)	
*Mammary lobule	(50)	(50)	(50)
Hyperplasia, NOS		1 (2%)	
Hyperplasia, epithelial			1 (2%)
*Prepuce	(50)	(50)	(50)
Inflammation, granulomatous focal		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Abscess, NOS	4 (8%)	1 (2%)	
#Prostate	(50)	(50)	(50)
Hemorrhage		1 (2%)	
Inflammation, suppurative	1 (2%)	2 (4%)	2 (4%)
Inflammation, acute		2 (4%)	
Inflammation, acute focal		1 (2%)	
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic	1 (2%)		1 (2%)
Inflammation, chronic suppurative	2 (4%)	1 (2%)	
Inclusion, nuclear	1 (2%)		
Hyperplasia, focal	10 (20%)	13 (26%)	7 (14%)
Metaplasia, squamous		3 (6%)	1 (2%)
#Testis	(49)	(50)	(50)
Inflammation, chronic suppurative		1 (2%)	
Granuloma, spermatic		1 (2%)	
Necrosis, fat		1 (2%)	
Infarct, acute		1 (2%)	
Calcification, focal	1 (2%)	1 (2%)	
Atrophy, NOS	4 (8%)	2 (4%)	5 (10%)
Hyperplasia, interstitial cell	2 (4%)	3 (6%)	13 (26%)
#Testis/tubule	(49)	(50)	(50)
Calcification, focal		2 (4%)	2 (4%)
*Epididymis	(50)	(50)	(50)
Inflammation, chronic suppurative	1 (2%)		
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(50)
Inflammation, chronic			1 (2%)
#Brain	(50)	(50)	(50)
Hemorrhage	1 (2%)	3 (6%)	1 (2%)
Hematoma, NOS		1 (2%)	
Granuloma, foreign body			1 (2%)
Demyelinization		1 (2%)	
#Pons	(50)	(50)	(50)
Compression, NOS		1 (2%)	
*Optic nerve	(50)	(50)	(50)
Degeneration, NOS		1 (2%)	

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
Inflammation, chronic		1 (2%)	
Cataract	36 (72%)	27 (54%)	4 (8%)
*Eye/sclera	(50)	(50)	(50)
Calcification, focal	4 (8%)	2 (4%)	1 (2%)
*Eye/cornea	(50)	(50)	(50)
Inflammation, acute		1 (2%)	2 (4%)
Inflammation, acute/chronic		1 (2%)	
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	35 (70%)	26 (52%)	6 (12%)
MUSCULOSKELETAL SYSTEM			
*Bone	(50)	(50)	(50)
Fibrous osteodystrophy			1 (2%)
*Mandible	(50)	(50)	(50)
Abscess, NOS		1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Vegetable foreign body			1 (2%)
Hemorrhage		1 (2%)	
Inflammation, acute fibrinous			1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Necrosis, fat	1 (2%)		
*Peritoneum	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
*Pleura	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
*Pericardium	(50)	(50)	(50)
Inflammation, acute fibrinous			1 (2%)
*Epicardium	(50)	(50)	(50)
Inflammation, acute/chronic	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, granulomatous focal	1 (2%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Calcification, focal		1 (2%)	
Diaphragm			
Inflammation, acute/chronic		1	
Adipose tissue			
Inflammation, chronic			1
Inflammation, granulomatous	1		1
Inflammation, granulomatous focal		1	
Inflammation, calcified granulomatous	1		
Infarct, NOS		1	
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	50
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst			1 (2%)
Inflammation, acute		1 (2%)	
Abscess, NOS	1 (2%)		
Inflammation, pyogranulomatous	1 (2%)		
Hyperplasia, basal cell	1 (2%)		
RESPIRATORY SYSTEM			
#Nasal cavity	(50)	(49)	(41)
Inflammation, suppurative	6 (12%)	12 (24%)	2 (5%)
Inflammation, acute		1 (2%)	
Inflammation, acute necrotizing		1 (2%)	
Inflammation, acute/chronic	2 (4%)	1 (2%)	
Hyperplasia, atypical			1 (2%)
Hyperplasia, epithelial		3 (6%)	1 (2%)
Metaplasia, squamous	1 (2%)	2 (4%)	4 (10%)
Dysplasia, epithelial			1 (2%)
*Nasal turbinate	(50)	(50)	(50)
Epidermal inclusion cyst		1 (2%)	
#Lung	(50)	(50)	(49)
Aspiration, NOS			1 (2%)
Congestion, NOS	3 (6%)	3 (6%)	2 (4%)
Hemorrhage		1 (2%)	
Bronchopneumonia, acute		2 (4%)	1 (2%)
Inflammation, acute			1 (2%)
Inflammation, acute focal			1 (2%)
Inflammation, acute/chronic			2 (4%)
Pneumonia, chronic murine			1 (2%)
Inflammation, chronic			1 (2%)
Inflammation, chronic focal	1 (2%)	1 (2%)	2 (4%)
Inflammation, granulomatous	1 (2%)	1 (2%)	1 (2%)
Granuloma, NOS	5 (10%)		
Cholesterol deposit	2 (4%)		
Hyperplasia, adenomatous	3 (6%)	1 (2%)	2 (4%)
Histiocytosis	3 (6%)	3 (6%)	2 (4%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(48)	(50)
Myelofibrosis	1 (2%)	1 (2%)	
Myelosclerosis		1 (2%)	
Hypoplasia, erythroid			1 (2%)
#Spleen	(50)	(50)	(49)
Accessory structure		1 (2%)	
Hemosiderosis	1 (2%)	1 (2%)	2 (4%)
Hematopoiesis	2 (4%)	7 (14%)	1 (2%)
#Lymph node	(45)	(46)	(49)
Plasmacytosis	1 (2%)		
#Mandibular lymph node	(45)	(46)	(49)
Cyst, NOS	1 (2%)		2 (4%)
Inflammation, acute		1 (2%)	
Histiocytosis			1 (2%)
Plasmacytosis		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mediastinal lymph node	(45)	(46)	(49)
Inflammation, acute		1 (2%)	
Plasmacytosis		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
#Mesenteric lymph node	(45)	(46)	(49)
Hemosiderosis			1 (2%)
#Liver	(49)	(50)	(50)
Hematopoiesis		1 (2%)	1 (2%)
#Peyers patch	(47)	(50)	(47)
Hyperplasia, lymphoid		1 (2%)	
#Adrenal	(50)	(50)	(49)
Hematopoiesis			1 (2%)
CIRCULATORY SYSTEM			
#Brain	(50)	(50)	(50)
Congenital vascular malformation			1 (2%)
#Hepatic lymph node	(45)	(46)	(49)
Lymphangiectasis		1 (2%)	
#Lung	(50)	(50)	(49)
Thrombosis, NOS		1 (2%)	
#Heart	(50)	(50)	(49)
Endocarditis, bacterial		1 (2%)	
Inflammation, chronic	1 (2%)	3 (6%)	2 (4%)
Inflammation, chronic focal			1 (2%)
#Myocardium	(50)	(50)	(49)
Inflammation, acute/chronic		1 (2%)	1 (2%)
Inflammation, chronic	10 (20%)	20 (40%)	13 (27%)
Inflammation, chronic focal			1 (2%)
Fibrosis			1 (2%)
Calcification, focal		1 (2%)	
#Endocardium	(50)	(50)	(49)
Hemosiderosis			1 (2%)
*Pulmonary artery	(50)	(50)	(50)
Calcification, NOS	1 (2%)		
*Hepatic vein	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
#Liver	(49)	(50)	(50)
Thrombus, organized		1 (2%)	
DIGESTIVE SYSTEM			
*Palate	(50)	(50)	(50)
Inflammation, granulomatous		1 (2%)	
*Tongue	(50)	(50)	(50)
Hyperplasia, atypical			1 (2%)
#Salivary gland	(49)	(50)	(49)
Inflammation, acute/chronic		1 (2%)	
#Parotid gland	(49)	(50)	(49)
Metaplasia, squamous		1 (2%)	
#Liver	(49)	(50)	(50)
Hernia, NOS	1 (2%)	5 (10%)	2 (4%)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic focal		2 (4%)	
Inflammation, granulomatous	2 (4%)		
Granuloma, NOS	7 (14%)		
Fibrosis, focal	1 (2%)		
Cholangiofibrosis		1 (2%)	
Necrosis, NOS			1 (2%)
Metamorphosis, fatty	3 (6%)	3 (6%)	1 (2%)
Cytoplasmic vacuolization			1 (2%)
Basophilic cyto change	19 (39%)	12 (24%)	1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Liver (Continued)	(49)	(50)	(50)
Eosinophilic cyto change	1 (2%)	2 (4%)	2 (4%)
Clear cell change			1 (2%)
Angiectasis	1 (2%)	1 (2%)	1 (2%)
#Portal tract	(49)	(50)	(50)
Lymphocytic inflammatory infiltrate	3 (6%)		
#Liver/centrilobular	(49)	(50)	(50)
Congestion, NOS	1 (2%)		1 (2%)
Degeneration, NOS			2 (4%)
Necrosis, NOS	2 (4%)	2 (4%)	1 (2%)
Necrosis, hemorrhagic		1 (2%)	
Metamorphosis, fatty	1 (2%)		
#Liver/periportal	(49)	(50)	(50)
Lymphocytic inflammatory infiltrate		1 (2%)	
Metamorphosis, fatty		1 (2%)	2 (4%)
#Liver/hepatocytes	(49)	(50)	(50)
Congestion, NOS			1 (2%)
#Bile duct	(49)	(50)	(50)
Cyst, NOS		1 (2%)	
Hyperplasia, NOS	20 (41%)	14 (28%)	12 (24%)
#Pancreatic acinus	(50)	(50)	(48)
Atrophy, NOS	8 (16%)	10 (20%)	4 (8%)
Hyperplasia, NOS		1 (2%)	
#Esophagus	(49)	(50)	(49)
Hyperplasia, atypical			1 (2%)
Hyperplasia, epithelial		7 (14%)	4 (8%)
#Forestomach	(50)	(50)	(49)
Epidermal inclusion cyst		2 (4%)	1 (2%)
Ulcer, NOS		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, acute focal		2 (4%)	
Inflammation, acute/chronic		1 (2%)	
Hyperplasia, epithelial		29 (58%)	24 (49%)
#Small intestine	(47)	(50)	(47)
Inflammation, acute necrotizing		1 (2%)	
#Peyer's patch	(47)	(50)	(47)
Hyperplasia, NOS	1 (2%)		
#Duodenal mucosa	(47)	(50)	(47)
Necrosis, NOS		1 (2%)	7 (15%)
Necrosis, focal			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Hydronephrosis	1 (2%)	1 (2%)	
Pyelonephritis, acute/chronic	1 (2%)		
Nephropathy	3 (6%)	8 (16%)	5 (10%)
Nephrosis, NOS		1 (2%)	
#Kidney/cortex	(50)	(50)	(49)
Cyst, NOS		1 (2%)	
#Kidney/tubule	(50)	(50)	(49)
Dilatation, NOS		3 (6%)	
Cyst, NOS		2 (4%)	
Calcification, focal		2 (4%)	
Pigmentation, NOS		1 (2%)	
#Kidney/pelvis	(50)	(50)	(49)
Calcification, NOS	1 (2%)		
Calcification, focal	1 (2%)		1 (2%)
#Urinary bladder	(50)	(46)	(47)
Inflammation, acute		1 (2%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(48)	(49)
Cyst, NOS	8 (16%)	12 (25%)	3 (6%)
Hemorrhagic cyst	1 (2%)		
Hemosiderosis			1 (2%)
Hyperplasia, focal	1 (2%)	2 (4%)	
Hyperplasia, chromophobe cell	1 (2%)	3 (6%)	3 (6%)
Angiectasis	1 (2%)	5 (10%)	
#Adrenal cortex	(50)	(50)	(49)
Degeneration, lipoid	3 (6%)	3 (6%)	2 (4%)
Infarct, acute		1 (2%)	
Cytoplasmic vacuolization	1 (2%)	1 (2%)	
#Adrenal medulla	(50)	(50)	(49)
Lymphocytic inflammatory infiltrate		1 (2%)	
Hyperplasia, focal	2 (4%)	2 (4%)	
#Thyroid	(49)	(49)	(47)
Ultimobranchial cyst			4 (9%)
Follicular cyst, NOS	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, C-cell	6 (12%)	6 (12%)	2 (4%)
Hyperplasia, follicular cell		1 (2%)	1 (2%)
#Pancreatic islets	(50)	(50)	(48)
Hyperplasia, NOS		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts	14 (28%)	19 (38%)	1 (2%)
Galactocele	1 (2%)	1 (2%)	1 (2%)
Hyperplasia, focal	1 (2%)		
*Mammary lobule	(50)	(50)	(50)
Hyperplasia, NOS	8 (16%)	11 (22%)	1 (2%)
*Clitoral gland	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Hyperplasia, epithelial	1 (2%)		
#Uterus	(50)	(50)	(49)
Hydrometra	2 (4%)		
Abscess, NOS		1 (2%)	
#Cervix uteri	(50)	(50)	(49)
Cyst, NOS	1 (2%)		
#Uterus/endometrium	(50)	(50)	(49)
Cyst, NOS		2 (4%)	2 (4%)
Inflammation, acute focal		1 (2%)	
Hyperplasia, cystic		2 (4%)	
#Ovary/parovarian	(50)	(50)	(49)
Inflammation, granulomatous		1 (2%)	4 (8%)
Inflammation, pyogranulomatous			1 (2%)
Necrosis, fat		1 (2%)	
#Ovary	(50)	(50)	(49)
Cyst, NOS	5 (10%)	5 (10%)	3 (6%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Compression, NOS		1 (2%)	1 (2%)
Spongiosis		1 (2%)	
Hemorrhage		1 (2%)	1 (2%)
Infarct, NOS			1 (2%)
Calcification, focal	1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Hemorrhage	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute		1 (2%)	3 (6%)
Inflammation, chronic			1 (2%)
Cataract	23 (46%)	28 (56%)	12 (24%)
*Eye/sclera	(50)	(50)	(50)
Calcification, focal	2 (4%)	1 (2%)	
*Eye/cornea	(50)	(50)	(50)
Hematoma, NOS			1 (2%)
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic		1 (2%)	1 (2%)
Calcification, NOS		1 (2%)	
Calcification, focal		1 (2%)	
Vascularization			1 (2%)
Metaplasia, squamous			1 (2%)
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	24 (48%)	31 (62%)	19 (38%)
*Eye/lacrimal gland	(50)	(50)	(50)
Porphyrin			1 (2%)
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Hyperkeratosis		1 (2%)	
*Harderian gland	(50)	(50)	(50)
Inflammation, suppurative		1 (2%)	
Hyperplasia, NOS		1 (2%)	
Metaplasia, squamous		1 (2%)	
MUSCULOSKELETAL SYSTEM			
*Skeletal muscle	(50)	(50)	(50)
Inflammation, acute/chronic		1 (2%)	
*Orbicularis oculi muscle	(50)	(50)	(50)
Calcification, focal		1 (2%)	
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Vegetable foreign body	1 (2%)		
Inflammation, acute		1 (2%)	
Inflammation, acute fibrinous	1 (2%)	1 (2%)	
Inflammation, chronic			1 (2%)
Hyperplasia, mesothelial			1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, acute fibrinous		1 (2%)	
Abscess, NOS		1 (2%)	
Inflammation, chronic		1 (2%)	
Inflammation, pyogranulomatous		1 (2%)	
*Pericardium	(50)	(50)	(50)
Abscess, NOS		1 (2%)	
Inflammation, chronic		1 (2%)	
*Mesentery	(50)	(50)	(50)
Inflammation, granulomatous		1 (2%)	
Necrosis, fat			1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
Adipose tissue			
Inflammation, granulomatous		1	
Inflammation, granulomatous focal	3	1	
Necrosis, focal	1		
Necrosis, fat	1		
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Epidermal inclusion cyst	1 (2%)		
Ulcer, NOS	1 (2%)		
Inflammation, acute	1 (2%)		
Inflammation, granulomatous	2 (4%)		
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, calcified granulomatous	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, suppurative	2 (4%)	2 (4%)	1 (2%)
Abscess, NOS	1 (2%)		
#Trachea	(48)	(46)	(46)
Metaplasia, squamous		1 (2%)	
#Lung	(49)	(50)	(49)
Atelectasis			1 (2%)
Congestion, NOS		1 (2%)	
Hemorrhage	2 (4%)	2 (4%)	4 (8%)
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	
Pneumonia, aspiration			1 (2%)
Bronchopneumonia, acute		2 (4%)	1 (2%)
Inflammation, acute focal		1 (2%)	1 (2%)
Inflammation, chronic	3 (6%)	1 (2%)	
Pigmentation, NOS		1 (2%)	
Hyperplasia, focal	1 (2%)		
Hyperplasia, adenomatous	1 (2%)	1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemoid reaction	2 (4%)	9 (18%)	4 (8%)
#Bone marrow	(48)	(50)	(49)
Hypoplasia, NOS		3 (6%)	4 (8%)
Hyperplasia, granulocytic	1 (2%)	13 (26%)	9 (18%)
Hyperplasia, neutrophilic			1 (2%)
#Spleen	(49)	(50)	(49)
Amyloidosis		1 (2%)	
Hyperplasia, lymphoid	4 (8%)	2 (4%)	1 (2%)
Hematopoiesis	1 (2%)	13 (26%)	16 (33%)
#Splenic follicles	(49)	(50)	(49)
Atrophy, NOS			2 (4%)
#Lymph node	(48)	(37)	(35)
Hematopoiesis			1 (3%)
#Mandibular lymph node	(48)	(37)	(35)
Inflammation, acute/chronic			1 (3%)
Hyperplasia, lymphoid		1 (3%)	
#Thoracic lymph node	(48)	(37)	(35)
Plasmacytosis			1 (3%)
#Mediastinal lymph node	(48)	(37)	(35)
Inflammation, acute			1 (3%)
Inflammation, acute/chronic			1 (3%)
Plasmacytosis		1 (3%)	1 (3%)
#Pancreatic lymph node	(48)	(37)	(35)
Plasmacytosis		1 (3%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(48)	(37)	(35)
Congestion, NOS			1 (3%)
Hemorrhage	10 (21%)	4 (11%)	2 (6%)
Inflammation, acute	1 (2%)	2 (5%)	1 (3%)
Multinucleate giant cell		1 (3%)	
Angiectasis	1 (2%)	1 (3%)	
Hyperplasia, lymphoid	1 (2%)		
Hematopoiesis	1 (2%)	4 (11%)	2 (6%)
#Renal lymph node	(48)	(37)	(35)
Plasmacytosis		1 (3%)	
#Inguinal lymph node	(48)	(37)	(35)
Hemorrhage	1 (2%)		
*Nasal cavity	(50)	(50)	(50)
Mastocytosis	1 (2%)		
#Lung	(49)	(50)	(49)
Leukemoid reaction		1 (2%)	
#Liver	(49)	(50)	(49)
Hematopoiesis			2 (4%)
#Kidney	(49)	(50)	(49)
Mastocytosis	1 (2%)		
#Adrenal/capsule	(49)	(49)	(49)
Hematopoiesis		1 (2%)	
#Thymus	(39)	(29)	(30)
Cholesterol deposit			1 (3%)
Hyperplasia, lymphoid	1 (3%)		
#Thymic lymphocytes	(39)	(29)	(30)
Necrosis, NOS		1 (3%)	3 (10%)
CIRCULATORY SYSTEM			
#Lymph node	(48)	(37)	(35)
Thrombosis, NOS	1 (2%)		
Perivasculitis	1 (2%)		
#Mesenteric lymph node	(48)	(37)	(35)
Lymphangiectasis			1 (3%)
Thrombosis, NOS		3 (8%)	1 (3%)
#Lung	(49)	(50)	(49)
Thrombus, organized		1 (2%)	
#Heart	(49)	(50)	(49)
Thrombosis, NOS		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, acute necrotizing			1 (2%)
Periarteritis	2 (4%)		
Calcification, focal		2 (4%)	1 (2%)
#Heart/atrium	(49)	(50)	(49)
Thrombosis, NOS	2 (4%)		
#Liver	(49)	(50)	(49)
Perivasculitis		1 (2%)	
#Hepatic sinusoid	(49)	(50)	(49)
Dilatation, NOS			1 (2%)
Thrombosis, NOS	1 (2%)	2 (4%)	1 (2%)
#Pancreas	(49)	(50)	(49)
Thrombosis, NOS			1 (2%)
#Kidney	(49)	(50)	(49)
Perivasculitis			1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
*Oral cavity	(50)	(50)	(50)
Inflammation, acute	3 (6%)		
Inflammation, acute/chronic	1 (2%)		
*Tooth	(50)	(50)	(50)
Abscess, NOS	1 (2%)		
*Pulp of tooth	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
#Liver	(49)	(50)	(49)
Inflammation, acute fibrinous			1 (2%)
Inflammation, acute/chronic			1 (2%)
Necrosis, NOS			1 (2%)
Necrosis, focal	2 (4%)	14 (28%)	6 (12%)
Infarct, NOS	1 (2%)		
Infarct, healed	1 (2%)		
Metamorphosis, fatty	3 (6%)	1 (2%)	5 (10%)
Cytologic alteration, NOS			1 (2%)
Angiectasis		2 (4%)	1 (2%)
#Hepatic capsule	(49)	(50)	(49)
Inflammation, suppurative			1 (2%)
#Liver/centrilobular	(49)	(50)	(49)
Congestion, NOS	1 (2%)		
Necrosis, NOS		1 (2%)	1 (2%)
Cytoplasmic vacuolization			1 (2%)
#Liver/hepatocytes	(49)	(50)	(49)
Multinucleate giant cell	1 (2%)		2 (4%)
Hypertrophy, focal		1 (2%)	
*Gallbladder	(50)	(50)	(50)
Inflammation, acute		1 (2%)	
#Pancreas	(49)	(50)	(49)
Inflammation, acute fibrinous		1 (2%)	
Abscess, NOS		1 (2%)	
Inflammation, acute/chronic			1 (2%)
#Pancreatic acinus	(49)	(50)	(49)
Atrophy, NOS	5 (10%)	3 (6%)	4 (8%)
#Pancreas/interstitial tissue	(49)	(50)	(49)
Inflammation, acute			1 (2%)
Inflammation, acute/chronic			1 (2%)
*Esophageal lumen	(50)	(50)	(50)
Inflammation, acute			1 (2%)
#Esophagus muscularis propria	(49)	(49)	(49)
Degeneration, NOS			1 (2%)
#Stomach	(49)	(50)	(49)
Ulcer, acute			1 (2%)
Hyperplasia, atypical	1 (2%)		
#Gastric muscularis	(49)	(50)	(49)
Degeneration, NOS		1 (2%)	
#Forestomach	(49)	(50)	(49)
Inflammation, active chronic	2 (4%)		
Inflammation, acute/chronic	1 (2%)		
Adhesion, NOS		1 (2%)	
Hyperplasia, epithelial	2 (4%)	5 (10%)	3 (6%)
Hyperkeratosis		1 (2%)	
#Peyer's patch	(46)	(43)	(47)
Hyperplasia, NOS	1 (2%)		
#Large intestine	(46)	(48)	(48)
Edema, NOS			1 (2%)
#Colon	(46)	(48)	(48)
Inflammation, acute/chronic	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney	(49)	(50)	(49)
Hydronephrosis		1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate	6 (12%)	4 (8%)	1 (2%)
Pyelonephritis, acute	1 (2%)		
Nephrosis, NOS			1 (2%)
Amyloidosis	1 (2%)	1 (2%)	
Calcification, focal		3 (6%)	2 (4%)
Hyperplasia, tubular cell			1 (2%)
Metaplasia, osseous	1 (2%)		
#Kidney/capsule	(49)	(50)	(49)
Inflammation, acute/chronic			2 (4%)
#Kidney/cortex	(49)	(50)	(49)
Hemorrhage	1 (2%)		
Scar	1 (2%)		
#Kidney/tubule	(49)	(50)	(49)
Dilatation, NOS		1 (2%)	1 (2%)
Necrosis, NOS			1 (2%)
Regeneration, NOS	1 (2%)		
#Kidney/pelvis	(49)	(50)	(49)
Inflammation, acute/chronic			1 (2%)
*Ureter	(50)	(50)	(50)
Inflammation, acute focal			1 (2%)
#Urinary bladder	(49)	(50)	(47)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute	1 (2%)		
Inflammation, acute fibrinous			1 (2%)
#Urinary bladder/serosa	(49)	(50)	(47)
Calcification, focal	1 (2%)		
ENDOCRINE SYSTEM			
#Anterior pituitary	(48)	(46)	(47)
Cyst, NOS	2 (4%)		
#Adrenal/capsule	(49)	(49)	(49)
Inflammation, acute			1 (2%)
Inflammation, acute/chronic		1 (2%)	2 (4%)
Inflammation, chronic			1 (2%)
Hyperplasia, NOS	2 (4%)	1 (2%)	
#Adrenal cortex	(49)	(49)	(49)
Hypertrophy, focal	2 (4%)		
Hyperplasia, focal	2 (4%)		
#Adrenal medulla	(49)	(49)	(49)
Hyperplasia, focal	1 (2%)		
#Periadrenal tissue	(49)	(49)	(49)
Inflammation, acute		1 (2%)	
Inflammation, chronic		1 (2%)	
#Thyroid	(49)	(48)	(45)
Follicular cyst, NOS	1 (2%)	10 (21%)	2 (4%)
Lymphocytic inflammatory infiltrate	1 (2%)		
Amyloidosis		1 (2%)	
Hyperplasia, follicular cell	1 (2%)		
REPRODUCTIVE SYSTEM			
*Prepuce	(50)	(50)	(50)
Abscess, NOS		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Cystic ducts	1 (2%)	1 (2%)	3 (6%)
Abscess, NOS	2 (4%)		
Inflammation, acute/chronic		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Prostate	(48)	(49)	(48)
Inflammation, acute	1 (2%)	1 (2%)	1 (2%)
Inflammation, acute fibrinous			1 (2%)
Granuloma, NOS			1 (2%)
*Seminal vesicle	(50)	(50)	(50)
Hypertrophy, NOS		1 (2%)	
#Testis	(49)	(50)	(49)
Necrosis, fat	1 (2%)		
Calcification, focal	8 (16%)	6 (12%)	2 (4%)
Atrophy, NOS		1 (2%)	9 (18%)
Hyperplasia, interstitial cell	1 (2%)		
#Testis/tubule	(49)	(50)	(49)
Calcification, focal			1 (2%)
*Epididymis	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute fibrinous			1 (2%)
NERVOUS SYSTEM			
#Brain	(49)	(50)	(49)
Hemorrhage		2 (4%)	1 (2%)
Calcification, focal	23 (47%)	23 (46%)	21 (43%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Cataract	1 (2%)		
*Eye/cornea	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
Metaplasia, squamous	1 (2%)		
*Eyelid	(50)	(50)	(50)
Edema, NOS	1 (2%)		
*Eye/lacrimal gland	(50)	(50)	(50)
Inflammation, granulomatous	1 (2%)		
*Nasolacrimal duct	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	1 (2%)	
Hyperplasia, epithelial			1 (2%)
MUSCULOSKELETAL SYSTEM			
*Maxilla	(50)	(50)	(50)
Abscess, NOS	1 (2%)		
*Mandible	(50)	(50)	(50)
Inflammation, chronic suppurative			1 (2%)
*Skeletal muscle	(50)	(50)	(50)
Inflammation, chronic suppurative			1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Hemorrhage			1 (2%)
Inflammation, suppurative			1 (2%)
Inflammation, acute/chronic			2 (4%)
*Peritoneum	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
*Mesentery	(50)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
Necrosis, fat			1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Calcification, focal		1 (2%)	
Adipose tissue			
Inflammation, acute necrotizing		1	
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported	2		
Auto/necropsy/histo perf	1		
Auto/necropsy/no histo			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	50	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(50)
Hyperkeratosis		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	3 (6%)	5 (10%)
Infection, fungal	1 (2%)	1 (2%)	
#Lung	(50)	(49)	(48)
Aspiration, NOS	1 (2%)		
Congestion, NOS			1 (2%)
Hemorrhage	1 (2%)	2 (4%)	1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)	2 (4%)	
Inflammation, interstitial			1 (2%)
Pneumonia, aspiration		1 (2%)	2 (4%)
Bronchopneumonia, acute		2 (4%)	6 (13%)
Inflammation, chronic	1 (2%)		1 (2%)
Inflammation, granulomatous			1 (2%)
Hyperplasia, adenomatous			1 (2%)
#Lung/alveoli	(50)	(49)	(48)
Histiocytosis			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemoid reaction	2 (4%)	10 (20%)	4 (8%)
#Bone marrow	(50)	(50)	(48)
Hypoplasia, NOS		3 (6%)	4 (8%)
Hyperplasia, granulocytic	2 (4%)	12 (24%)	14 (29%)
#Spleen	(50)	(49)	(47)
Necrosis, focal	1 (2%)		1 (2%)
Infarct, NOS			1 (2%)
Amyloidosis			1 (2%)
Depletion, lymphoid	1 (2%)		
Hyperplasia, lymphoid	5 (10%)	5 (10%)	2 (4%)
Hematopoiesis	3 (6%)	12 (24%)	12 (26%)
#Splenic capsule	(50)	(49)	(47)
Inflammation, acute			1 (2%)
#Lymph node	(50)	(42)	(38)
Angiectasis	1 (2%)		
Hyperplasia, lymphoid	1 (2%)		
#Mandibular lymph node	(50)	(42)	(38)
Hyperplasia, reticulum cell			1 (3%)
Hyperplasia, lymphoid	1 (2%)		
#Thoracic lymph node	(50)	(42)	(38)
Cholesterol deposit		1 (2%)	
Hematopoiesis		1 (2%)	
#Mediastinal lymph node	(50)	(42)	(38)
Plasmacytosis		1 (2%)	
Hyperplasia, lymphoid		1 (2%)	
#Hepatic lymph node	(50)	(42)	(38)
Hyperplasia, lymphoid	1 (2%)		
#Pancreatic lymph node	(50)	(42)	(38)
Infarct, NOS		1 (2%)	
Russell body		1 (2%)	
Plasmacytosis		1 (2%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Mesenteric lymph node	(50)	(42)	(38)
Congestion, NOS			1 (3%)
Hemorrhage		5 (12%)	1 (3%)
Hematoma, NOS		1 (2%)	
Inflammation, acute		2 (5%)	
Hyperplasia, lymphoid	1 (2%)		1 (3%)
Hematopoiesis		1 (2%)	
#Lung	(50)	(49)	(48)
Leukemoid reaction			1 (2%)
#Liver	(50)	(50)	(48)
Hematopoiesis	1 (2%)	3 (6%)	3 (6%)
#Forestomach	(50)	(50)	(48)
Plasmacytosis		1 (2%)	
#Thymus	(41)	(34)	(27)
Hemorrhage	1 (2%)		
Cholesterol deposit			1 (4%)
Hyperplasia, lymphoid	2 (5%)		
#Thymic lymphocytes	(41)	(34)	(27)
Necrosis, NOS		2 (6%)	2 (7%)
CIRCULATORY SYSTEM			
#Mediastinal lymph node	(50)	(42)	(38)
Lymphangiectasis	1 (2%)		
#Pancreatic lymph node	(50)	(42)	(38)
Thrombosis, NOS		1 (2%)	
#Lung	(50)	(49)	(48)
Thrombosis, NOS			1 (2%)
Perivasculitis		1 (2%)	
#Heart	(50)	(49)	(48)
Thrombosis, NOS	1 (2%)		2 (4%)
Inflammation, acute/chronic		1 (2%)	
Calcification, focal	1 (2%)	1 (2%)	
*Blood vessel	(50)	(50)	(50)
Embolus, septic			1 (2%)
*Artery	(50)	(50)	(50)
Calcification, NOS			1 (2%)
*Renal vein	(50)	(50)	(50)
Thrombosis, NOS			1 (2%)
*Superior mesentric vein	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
#Liver	(50)	(50)	(48)
Thrombosis, NOS		1 (2%)	3 (6%)
#Hepatic sinusoid	(50)	(50)	(48)
Thrombosis, NOS		1 (2%)	
#Pancreas	(50)	(49)	(47)
Thrombosis, NOS		1 (2%)	
#Ovary	(49)	(49)	(47)
Thrombosis, NOS		1 (2%)	3 (6%)
#Adrenal	(49)	(50)	(47)
Thrombosis, NOS	1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM			
#Liver	(50)	(50)	(48)
Cyst, NOS			1 (2%)
Congestion, NOS	1 (2%)		
Lymphocytic inflammatory infiltrate	3 (6%)	1 (2%)	
Inflammation, acute focal	1 (2%)		
Inflammation, acute necrotizing	1 (2%)		1 (2%)
Inflammation, granulomatous focal			1 (2%)
Necrosis, focal	1 (2%)	4 (8%)	7 (15%)
Infarct, NOS	1 (2%)	2 (4%)	1 (2%)
Metamorphosis, fatty	2 (4%)		
Angiectasis		1 (2%)	
#Portal tract	(50)	(50)	(48)
Lymphocytic inflammatory infiltrate	1 (2%)	1 (2%)	
#Liver/centrilobular	(50)	(50)	(48)
Degeneration, NOS		1 (2%)	
#Liver/hepatocytes	(50)	(50)	(48)
Degeneration, NOS	1 (2%)		
*Gallbladder	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
#Bile duct	(50)	(50)	(48)
Hyperplasia, NOS		2 (4%)	
#Pancreas	(50)	(49)	(47)
Cystic ducts	1 (2%)		
Inflammation, acute/chronic		1 (2%)	
Inflammation, granulomatous focal			1 (2%)
#Pancreatic acinus	(50)	(49)	(47)
Atrophy, NOS	3 (6%)	1 (2%)	3 (6%)
Hyperplasia, focal			1 (2%)
#Pancreas/interstitial tissue	(50)	(49)	(47)
Inflammation, acute	1 (2%)		
Inflammation, acute/chronic			1 (2%)
#Peripancreatic tissue	(50)	(49)	(47)
Inflammation, acute/chronic			1 (2%)
#Stomach	(50)	(50)	(48)
Ulcer, acute			1 (2%)
#Gastric mucosa	(50)	(50)	(48)
Cyst, NOS	1 (2%)		
#Forestomach	(50)	(50)	(48)
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic	1 (2%)		
Adhesion, NOS		1 (2%)	
Atypia, NOS		1 (2%)	
Russell body		1 (2%)	
Hyperplasia, atypical		1 (2%)	1 (2%)
Hyperplasia, epithelial	3 (6%)	1 (2%)	2 (4%)
Hyperkeratosis			1 (2%)
#Small intestinal crypt of Lieberkuhn	(50)	(43)	(42)
Abscess, NOS	1 (2%)		
#Duodenal mucosa	(50)	(43)	(42)
Necrosis, NOS			1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM			
#Kidney	(50)	(50)	(48)
Hydronephrosis	1 (2%)	2 (4%)	2 (4%)
Lymphocytic inflammatory infiltrate	5 (10%)	2 (4%)	
Pyelonephritis, acute		1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	
Glomerulonephritis, chronic		1 (2%)	
Inflammation, granulomatous focal			1 (2%)
Nephrosis, NOS	1 (2%)		
Infarct, NOS		1 (2%)	
Infarct, healed		1 (2%)	
Calcification, focal		1 (2%)	2 (4%)
Metaplasia, osseous	2 (4%)		
#Renal papilla	(50)	(50)	(48)
Necrosis, focal			1 (2%)
#Kidney/glomerulus	(50)	(50)	(48)
Amyloidosis	1 (2%)		1 (2%)
#Kidney/tubule	(50)	(50)	(48)
Pigmentation, NOS	1 (2%)		
Cytoplasmic vacuolization			1 (2%)
Atrophy, focal	1 (2%)	1 (2%)	
#Urinary bladder	(49)	(47)	(41)
Lymphocytic inflammatory infiltrate	4 (8%)	2 (4%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(49)	(47)
Cyst, NOS	1 (2%)	1 (2%)	
Congestion, NOS	1 (2%)		
Hyperplasia, NOS	7 (14%)	2 (4%)	
Hyperplasia, focal	1 (2%)		
Angiectasis	1 (2%)		
#Adrenal	(49)	(50)	(47)
Necrosis, NOS		3 (6%)	4 (9%)
#Adrenal/capsule	(49)	(50)	(47)
Inflammation, acute/chronic		1 (2%)	1 (2%)
Inflammation, chronic		1 (2%)	
Hyperplasia, NOS	1 (2%)		
#Adrenal cortex	(49)	(50)	(47)
Congestion, NOS	1 (2%)		
Inflammation, chronic	1 (2%)		
Degeneration, lipoid	2 (4%)		
Cytoplasmic vacuolization	1 (2%)		
Cytologic alteration, NOS		1 (2%)	5 (11%)
#Periadrenal tissue	(49)	(50)	(47)
Steatitis			1 (2%)
#Thyroid	(50)	(43)	(45)
Ultimobranchial cyst			1 (2%)
Follicular cyst, NOS	1 (2%)	4 (9%)	2 (4%)
Hyperplasia, follicular cell	1 (2%)	2 (5%)	
#Parathyroid	(30)	(30)	(27)
Cyst, NOS			1 (4%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts	5 (10%)	5 (10%)	4 (8%)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, active chronic		1 (2%)	
Hyperplasia, NOS	1 (2%)		1 (2%)
*Clitoral gland	(50)	(50)	(50)
Dilatation/ducts			1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM (Continued)			
#Uterus	(50)	(50)	(46)
Hydrometra	2 (4%)	3 (6%)	
Inflammation, suppurative			1 (2%)
Necrosis, fat	1 (2%)		
Decidual alteration, NOS	1 (2%)		
#Uterus/endometrium	(50)	(50)	(46)
Cyst, NOS	4 (8%)	8 (16%)	8 (17%)
Hyperplasia, cystic	40 (80%)	24 (48%)	12 (26%)
#Endometrial stroma	(50)	(50)	(46)
Hyperplasia, NOS	1 (2%)		
#Fallopian tube	(50)	(50)	(46)
Hyperplasia, NOS			1 (2%)
#Ovary/parovarian	(49)	(49)	(47)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Ovary	(49)	(49)	(47)
Cyst, NOS	21 (43%)	16 (33%)	8 (17%)
Hemorrhage		1 (2%)	5 (11%)
Hemorrhagic cyst			1 (2%)
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute	1 (2%)		
Inflammation, acute/chronic		3 (6%)	
Inflammation, chronic focal		1 (2%)	
Necrosis, NOS		1 (2%)	
Calcification, focal	1 (2%)		
Melanin	1 (2%)		
Hyperplasia, stromal	1 (2%)	1 (2%)	
Angiectasis	1 (2%)	1 (2%)	
NERVOUS SYSTEM			
#Brain/meninges	(50)	(50)	(48)
Inflammation, chronic		1 (2%)	
#Brain	(50)	(50)	(48)
Hemorrhage		3 (6%)	
Lymphocytic inflammatory infiltrate	1 (2%)		
Abscess, NOS		1 (2%)	1 (2%)
Cholesterol deposit	1 (2%)		
Calcification, focal	28 (56%)	24 (48%)	15 (31%)
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
*Maxilla	(50)	(50)	(50)
Inflammation, chronic suppurative			1 (2%)
Fibrous osteodystrophy	1 (2%)		
*Sternum	(50)	(50)	(50)
Fibrous osteodystrophy	43 (86%)	21 (42%)	12 (24%)
Osteosclerosis	1 (2%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	VEHICLE CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*Mediastinum	(50)	(50)	(50)
Vegetable foreign body			1 (2%)
Inflammation, suppurative			1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
*Parietal pleura	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
*Mesentery	(50)	(50)	(50)
Inflammation, acute necrotizing	1 (2%)		
Inflammation, acute/chronic		1 (2%)	1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Bacterial septicemia	1 (2%)		
Adipose tissue			
Inflammation, chronic	1		
Inflammation, chronic necrotizing	1		
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported		1	
Auto/necropsy/histo perf			1
Auto/necropsy/no histo			1

* Number of animals receiving complete necropsy examination; all gross lesions including masses examined microscopically.
# Number of animals examined microscopically at this site

APPENDIX E

ANALYSES OF PRIMARY TUMORS IN RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
Skin: Squamous Cell Papilloma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	10.5%	15.6%	0.0%
Terminal Rates (c)	4/38 (11%)	1/9 (11%)	0/0
Week of First Observation	104	97	
Life Table Tests (d)	P=0.410	P=0.410	(e)
Incidental Tumor Tests (d)	P=0.574	P=0.574	(e)
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.339N	P=0.059N
Subcutaneous Tissue: Fibroma			
Overall Rates (a)	4/50 (8%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	9.9%	8.0%	0.0%
Terminal Rates (c)	3/38 (8%)	0/9 (0%)	0/0
Week of First Observation	94	94	
Life Table Tests (d)	P=0.555	P=0.555	(e)
Incidental Tumor Tests (d)	P=0.407N	P=0.407N	(e)
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.339N	P=0.059N
Subcutaneous Tissue: Fibroma or Neurofibroma			
Overall Rates (a)	6/50 (12%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	15.1%	17.2%	0.0%
Terminal Rates (c)	5/38 (13%)	0/9 (0%)	0/0
Week of First Observation	94	94	
Life Table Tests (d)	P=0.269	P=0.269	(e)
Incidental Tumor Tests (d)	P=0.482N	P=0.482N	(e)
Cochran-Armitage Trend Test (d)	P=0.014N		
Fisher Exact Test (d)		P=0.370N	P=0.013N
Subcutaneous Tissue: Fibroma, Neurofibroma, or Sarcoma			
Overall Rates (a)	6/50 (12%)	4/50 (8%)	1/50 (2%)
Adjusted Rates (b)	15.1%	17.2%	7.1%
Terminal Rates (c)	5/38 (13%)	0/9 (0%)	0/0
Week of First Observation	94	94	70
Life Table Tests (d)	P=0.080	P=0.269	P=0.268
Incidental Tumor Tests (d)	P=0.551N	P=0.482N	P=0.982
Cochran-Armitage Trend Test (d)	P=0.042N		
Fisher Exact Test (d)		P=0.370N	P=0.056N
Nasal Cavity: Carcinoma			
Overall Rates (a)	0/47 (0%)	12/46 (26%)	(f) 24/32 (75%)
Adjusted Rates (b)	0.0%	36.7%	93.5%
Terminal Rates (c)	0/38 (0%)	0/9 (0%)	0/0
Week of First Observation		70	58
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.004	P=0.071	P=0.235
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Nasal Cavity: Squamous Cell Carcinoma			
Overall Rates (a)	0/47 (0%)	3/46 (7%)	0/32 (0%)
Adjusted Rates (b)	0.0%	15.0%	0.0%
Terminal Rates (c)	0/38 (0%)	0/9 (0%)	0/0 (0%)
Week of First Observation		93	
Life Table Tests (d)	P=0.027	P=0.027	(e)
Incidental Tumor Tests (d)	P=0.324	P=0.324	(e)
Cochran-Armitage Trend Test (d)	P=0.541		
Fisher Exact Test (d)		P=0.117	(e)

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Nasal Cavity: Carcinoma or Squamous Cell Carcinoma			
Overall Rates (a)	0/47 (0%)	15/46 (33%)	24/32 (75%)
Adjusted Rates (b)	0.0%	46.3%	93.5%
Terminal Rates (c)	0/38 (0%)	0/9 (0%)	0/0
Week of First Observation		70	58
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.001	P=0.021	P=0.235
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Nasal Cavity: Adenocarcinoma			
Overall Rates (a)	0/47 (0%)	(g) 8/46 (17%)	4/32 (13%)
Adjusted Rates (b)	0.0%	46.8%	100.0%
Terminal Rates (c)	0/38 (0%)	3/9 (33%)	0/0
Week of First Observation		79	45
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.005	P=0.003	P=0.572
Cochran-Armitage Trend Test (d)	P=0.028		
Fisher Exact Test (d)		P=0.003	P=0.024
Nasal Cavity: Adenocarcinoma, Carcinoma, or Squamous Cell Carcinoma			
Overall Rates (a)	0/47 (0%)	23/46 (50%)	28/32 (88%)
Adjusted Rates (b)	0.0%	71.8%	100.0%
Terminal Rates (c)	0/38 (0%)	3/9 (33%)	0/0
Week of First Observation		70	45
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P=0.117
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	3/50 (6%)	6/50 (12%)	1/50 (2%)
Adjusted Rates (b)	7.6%	31.8%	9.1%
Terminal Rates (c)	2/38 (5%)	1/9 (11%)	0/0
Week of First Observation	102	78	72
Life Table Tests (d)	P=0.002	P=0.011	P=0.222
Incidental Tumor Tests (d)	P=0.612N	P=0.408	P=0.982
Cochran-Armitage Trend Test (d)	P=0.274N		
Fisher Exact Test (d)		P=0.243	P=0.309N
Tongue: Squamous Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	0.0%	7.5%	100.0%
Terminal Rates (c)	0/38 (0%)	0/9 (0%)	0/0
Week of First Observation		71	41
Life Table Tests (d)	P=0.006	P=0.100	P=0.030
Incidental Tumor Tests (d)	P=0.527	P=0.748	P=0.718
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test (d)		P=0.121	P=0.247
Tongue: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	0.0%	7.5%	100.0%
Terminal Rates (c)	0/38 (0%)	0/9 (0%)	0/0
Week of First Observation		71	41
Life Table Tests (d)	P<0.001	P=0.100	P=0.005
Incidental Tumor Tests (d)	P=0.449	P=0.748	P=0.661
Cochran-Armitage Trend Test (d)	P=0.101		
Fisher Exact Test (d)		P=0.121	P=0.121

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Oral Cavity: Squamous Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	5/50 (10%)	2/50 (4%)
Adjusted Rates (b)	0.0%	21.9%	100.0%
Terminal Rates (c)	0/38 (0%)	1/9 (11%)	0/0
Week of First Observation		71	41
Life Table Tests (d)	P<0.001	P=0.007	P=0.030
Incidental Tumor Tests (d)	P=0.209	P=0.133	P=0.718
Cochran-Armitage Trend Test (d)	P=0.238		
Fisher Exact Test (d)		P=0.028	P=0.247
Oral Cavity: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	5/50 (10%)	4/50 (8%)
Adjusted Rates (b)	0.0%	21.9%	100.0%
Terminal Rates (c)	0/38 (0%)	1/9 (11%)	0/0
Week of First Observation		71	41
Life Table Tests (d)	P<0.001	P=0.007	P=0.001
Incidental Tumor Tests (d)	P=0.153	P=0.133	P=0.614
Cochran-Armitage Trend Test (d)	P=0.070		
Fisher Exact Test (d)		P=0.028	P=0.059
Esophagus: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	3/49 (6%)
Adjusted Rates (b)	0.0%	16.7%	20.8%
Terminal Rates (c)	0/38 (0%)	1/9 (11%)	0/0
Week of First Observation		99	61
Life Table Tests (d)	P<0.001	P=0.043	P=0.011
Incidental Tumor Tests (d)	P=0.111	P=0.162	P=0.829
Cochran-Armitage Trend Test (d)	P=0.079		
Fisher Exact Test (d)		P=0.247	P=0.117
Esophagus: Squamous Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	1/49 (2%)
Adjusted Rates (b)	0.0%	28.1%	4.3%
Terminal Rates (c)	0/38 (0%)	2/9 (22%)	0/0
Week of First Observation		90	66
Life Table Tests (d)	P=0.001	P=0.004	P=0.366
Incidental Tumor Tests (d)	P=0.054	P=0.025	P=0.981
Cochran-Armitage Trend Test (d)	P=0.383		
Fisher Exact Test (d)		P=0.059	P=0.495
Esophagus: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	6/50 (12%)	4/49 (8%)
Adjusted Rates (b)	0.0%	42.2%	24.3%
Terminal Rates (c)	0/38 (0%)	3/9 (33%)	0/0
Week of First Observation		90	61
Life Table Tests (d)	P<0.001	P<0.001	P=0.004
Incidental Tumor Tests (d)	P=0.009	P=0.003	P=0.763
Cochran-Armitage Trend Test (d)	P=0.076		
Fisher Exact Test (d)		P=0.013	P=0.056
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	0/49 (0%)	7/50 (14%)	0/50 (0%)
Adjusted Rates (b)	0.0%	52.2%	0.0%
Terminal Rates (c)	0/38 (0%)	4/9 (44%)	0/0
Week of First Observation		90	
Life Table Tests (d)	P<0.001	P<0.001	(h)
Incidental Tumor Tests (d)	P=0.001	P<0.001	(h)
Cochran-Armitage Trend Test (d)	P=0.585N		
Fisher Exact Test (d)		P=0.007	(h)

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Forestomach: Squamous Cell Carcinoma			
Overall Rates (a)	0/49 (0%)	7/50 (14%)	0/50 (0%)
Adjusted Rates (b)	0.0%	30.4%	0.0%
Terminal Rates (c)	0/38 (0%)	1/9 (11%)	0/0
Week of First Observation		82	
Life Table Tests (d)	P<0.001	P<0.001	(h)
Incidental Tumor Tests (d)	P=0.219	P=0.086	(h)
Cochran-Armitage Trend Test (d)	P=0.585N		
Fisher Exact Test (d)		P=0.007	(h)
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/49 (0%)	14/50 (28%)	0/50 (0%)
Adjusted Rates (b)	0.0%	70.1%	0.0%
Terminal Rates (c)	0/38 (0%)	5/9 (56%)	0/0
Week of First Observation		82	
Life Table Tests (d)	P<0.001	P<0.001	(h)
Incidental Tumor Tests (d)	P<0.001	P<0.001	(h)
Cochran-Armitage Trend Test (d)	P=0.556N		
Fisher Exact Test (d)		P<0.001	(h)
Pancreas: Acinar Cell Adenoma			
Overall Rates (a)	8/50 (16%)	7/50 (14%)	0/50 (0%)
Adjusted Rates (b)	20.4%	30.5%	0.0%
Terminal Rates (c)	7/38 (18%)	1/9 (11%)	0/0
Week of First Observation	97	89	
Life Table Tests (d)	P=0.076	P=0.076	(e)
Incidental Tumor Tests (d)	P=0.310N	P=0.440N	(e)
Cochran-Armitage Trend Test (d)	P=0.006N		
Fisher Exact Test (d)		P=0.500N	P=0.003N
Pituitary Gland: Chromophobe Adenoma			
Overall Rates (a)	17/50 (34%)	8/50 (16%)	1/47 (2%)
Adjusted Rates (b)	40.3%	35.9%	3.0%
Terminal Rates (c)	13/38 (34%)	2/9 (22%)	0/0
Week of First Observation	95	77	60
Life Table Tests (d)	P=0.178	P=0.313	P=0.434
Incidental Tumor Tests (d)	P=0.026N	P=0.068N	P=0.979
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.032N	P<0.001N
Pituitary Gland: Chromophobe Adenoma or Carcinoma			
Overall Rates (a)	17/50 (34%)	9/50 (18%)	1/47 (2%)
Adjusted Rates (b)	40.3%	39.1%	3.0%
Terminal Rates (c)	13/38 (34%)	2/9 (22%)	0/0
Week of First Observation	95	77	60
Life Table Tests (d)	P=0.113	P=0.209	P=0.434
Incidental Tumor Tests (d)	P=0.038N	P=0.097N	P=0.979
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.055N	P<0.001N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	11/50 (22%)	6/50 (12%)	3/50 (6%)
Adjusted Rates (b)	27.4%	42.8%	100.0%
Terminal Rates (c)	9/38 (24%)	3/9 (33%)	0/0
Week of First Observation	97	94	54
Life Table Tests (d)	P=0.003	P=0.145	P=0.005
Incidental Tumor Tests (d)	P=0.290	P=0.605	P=0.910
Cochran-Armitage Trend Test (d)	P=0.014N		
Fisher Exact Test (d)		P=0.143N	P=0.020N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Adrenal Gland: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	13/50 (26%)	7/50 (14%)	3/50 (6%)
Adjusted Rates (b)	32.4%	52.3%	100.0%
Terminal Rates (c)	11/38 (29%)	4/9 (44%)	0/0
Week of First Observation	97	94	54
Life Table Tests (d)	P=0.002	P=0.101	P=0.005
Incidental Tumor Tests (d)	P=0.219	P=0.493	P=0.910
Cochran-Armitage Trend Test (d)	P=0.004N		
Fisher Exact Test (d)		P=0.105N	P=0.006N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/50 (6%)	1/48 (2%)	0/47 (0%)
Adjusted Rates (b)	7.4%	2.6%	0.0%
Terminal Rates (c)	2/38 (5%)	0/9 (0%)	0/0
Week of First Observation	95	84	
Life Table Tests (d)	P=0.632N	P=0.642N	(e)
Incidental Tumor Tests (d)	P=0.181N	P=0.204N	(e)
Cochran-Armitage Trend Test (d)	P=0.067N		
Fisher Exact Test (d)		P=0.324N	P=0.133N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/50 (10%)	3/48 (6%)	0/47 (0%)
Adjusted Rates (b)	12.2%	18.8%	0.0%
Terminal Rates (c)	3/38 (8%)	1/9 (11%)	0/0
Week of First Observation	95	84	
Life Table Tests (d)	P=0.373	P=0.366	(e)
Incidental Tumor Tests (d)	P=0.323N	P=0.357N	(e)
Cochran-Armitage Trend Test (d)	P=0.027N		
Fisher Exact Test (d)		P=0.381N	P=0.033N
Pancreatic Islets: Islet Cell Adenoma			
Overall Rates (a)	5/50 (10%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	12.7%	6.3%	0.0%
Terminal Rates (c)	4/38 (11%)	0/9 (0%)	0/0
Week of First Observation	102	99	
Life Table Tests (d)	P=0.586N	P=0.586N	(e)
Incidental Tumor Tests (d)	P=0.236N	P=0.236N	(e)
Cochran-Armitage Trend Test (d)	P=0.011N		
Fisher Exact Test (d)		P=0.102N	P=0.028N
Mammary Gland: Adenoma or Fibroadenoma			
Overall Rates (a)	3/50 (6%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	7.9%	13.7%	0.0%
Terminal Rates (c)	3/38 (8%)	1/9 (11%)	0/0
Week of First Observation	104	90	
Life Table Tests (d)	P=0.369	P=0.369	(e)
Incidental Tumor Tests (d)	P=0.681	P=0.637	(e)
Cochran-Armitage Trend Test (d)	P=0.082N		
Fisher Exact Test (d)		P=0.500N	P=0.121N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	40/49 (82%)	41/50 (82%)	6/50 (12%)
Adjusted Rates (b)	90.9%	100.0%	100.0%
Terminal Rates (c)	34/38 (89%)	9/9 (100%)	0/0
Week of First Observation	94	77	66
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.390N	P=0.188	P=0.712
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.584	P<0.001N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Preputial Gland: Adenoma, Carcinoma, or Squamous Cell Carcinoma			
Overall Rates (a)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	7.6%	4.0%	0.0%
Terminal Rates (c)	2/38 (5%)	0/9 (0%)	0/0
Week of First Observation	103	94	
Life Table Tests (d)	P=0.717	P=0.717	(e)
Incidental Tumor Tests (d)	P=0.349N	P=0.349N	(e)
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.309N	P=0.121N
Zymbal Gland: Adenoma, Carcinoma, or Squamous Cell Carcinoma			
Overall Rates (a)	2/50 (4%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	4.4%	9.9%	0.0%
Terminal Rates (c)	0/38 (0%)	0/9 (0%)	0/0
Week of First Observation	48	79	
Life Table Tests (d)	P=0.527	P=0.346	P=0.508N
Incidental Tumor Tests (d)	P=0.075N	P=0.334N	P=0.282N
Cochran-Armitage Trend Test (d)	P=0.202N		
Fisher Exact Test (d)		P=0.500	P=0.247N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value could be determined because all animals in the 200 mg/kg group died before the first tumor was observed in the vehicle control group.
(f) A squamous cell papilloma was also observed in one of these animals.
(g) An adenoma was also observed in one of these animals.
(h) No P value is reported because no tumors were observed in the 200 mg/kg and vehicle control groups.

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
Subcutaneous Tissue: Fibroma or Sarcoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	6.7%	0.0%	0.0%
Terminal Rates (c)	2/43 (5%)	0/11 (0%)	0/0
Week of First Observation	84		
Life Table Tests (d)	P=0.287N	P=0.307N	P=0.915N
Incidental Tumor Tests (d)	P=0.084N	P=0.125N	P=0.252N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Nasal Cavity: Carcinoma			
Overall Rates (a)	0/50 (0%)	11/49 (22%)	28/41 (68%)
Adjusted Rates (b)	0.0%	44.3%	100.0%
Terminal Rates (c)	0/43 (0%)	3/11 (27%)	0/0
Week of First Observation		72	55
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.004	P=0.005
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Nasal Cavity: Carcinoma or Squamous Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	13/49 (27%)	29/41 (71%)
Adjusted Rates (b)	0.0%	49.9%	100.0%
Terminal Rates (c)	0/43 (0%)	3/11 (27%)	0/0
Week of First Observation		72	55
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.003	P=0.003
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Nasal Cavity: Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	3/49 (6%)	6/41 (15%)
Adjusted Rates (b)	0.0%	20.1%	40.0%
Terminal Rates (c)	0/43 (0%)	1/11 (9%)	0/0
Week of First Observation		98	67
Life Table Tests (d)	P<0.001	P=0.011	P<0.001
Incidental Tumor Tests (d)	P=0.057	P=0.202	P=0.423
Cochran-Armitage Trend Test (d)	P=0.005		
Fisher Exact Test (d)		P=0.117	P=0.007
Nasal Cavity: Adenoma or Adenocarcinoma			
Overall Rates (a)	0/50 (0%)	4/49 (8%)	6/41 (15%)
Adjusted Rates (b)	0.0%	23.0%	40.0%
Terminal Rates (c)	0/43 (0%)	1/11 (9%)	0/0
Week of First Observation		96	67
Life Table Tests (d)	P<0.001	P=0.004	P<0.001
Incidental Tumor Tests (d)	P=0.058	P=0.185	P=0.423
Cochran-Armitage Trend Test (d)	P=0.006		
Fisher Exact Test (d)		P=0.056	P=0.007
Nasal Cavity: Adenocarcinoma, Carcinoma, or Squamous Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	16/49 (33%)	35/41 (85%)
Adjusted Rates (b)	0.0%	61.6%	100.0%
Terminal Rates (c)	0/43 (0%)	4/11 (36%)	0/0
Week of First Observation		72	55
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Nasal Cavity: Adenoma, Adenocarcinoma, Carcinoma, or Squamous Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	17/49 (35%)	35/41 (85%)
Adjusted Rates (b)	0.0%	62.9%	100.0%
Terminal Rates (c)	0/43 (0%)	4/11 (36%)	0/0
Week of First Observation		72	55
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	1/49 (2%)
Adjusted Rates (b)	0.0%	18.6%	25.0%
Terminal Rates (c)	0/43 (0%)	1/11 (9%)	0/0
Week of First Observation		88	87
Life Table Tests (d)	P<0.001	P=0.011	P=0.061
Incidental Tumor Tests (d)	P=0.195	P=0.178	P=0.748
Cochran-Armitage Trend Test (d)	P=0.383		
Fisher Exact Test (d)		P=0.059	P=0.495
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	5/50 (10%)	7/50 (14%)	1/50 (2%)
Adjusted Rates (b)	11.0%	25.6%	12.5%
Terminal Rates (c)	3/43 (7%)	0/11 (0%)	0/0
Week of First Observation	91	84	79
Life Table Tests (d)	P=0.021	P=0.059	P=0.223
Incidental Tumor Tests (d)	P=0.090N	P=0.149N	P=0.296N
Cochran-Armitage Trend Test (d)	P=0.107N		
Fisher Exact Test (d)		P=0.380	P=0.102N
Hematopoietic System: Leukemia			
Overall Rates (a)	5/50 (10%)	8/50 (16%)	1/50 (2%)
Adjusted Rates (b)	11.0%	28.7%	12.5%
Terminal Rates (c)	3/43 (7%)	0/11 (0%)	0/0
Week of First Observation	91	84	79
Life Table Tests (d)	P=0.010	P=0.030	P=0.223
Incidental Tumor Tests (d)	P=0.097N	P=0.172N	P=0.296N
Cochran-Armitage Trend Test (d)	P=0.114N		
Fisher Exact Test (d)		P=0.277	P=0.102N
Oral Mucosa: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	0.0%	19.6%
Terminal Rates (c)	0/43 (0%)	0/11 (0%)	0/0
Week of First Observation			73
Life Table Tests (d)	P=0.002	(e)	P=0.007
Incidental Tumor Tests (d)	P=0.409	(e)	P=0.738
Cochran-Armitage Trend Test (d)	P=0.037		
Fisher Exact Test (d)		(e)	P=0.121
Oral Cavity: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	0.0%	0.0%	21.9%
Terminal Rates (c)	0/43 (0%)	0/11 (0%)	0/0
Week of First Observation			65
Life Table Tests (d)	P<0.001	(e)	P=0.004
Incidental Tumor Tests (d)	P=0.336	(e)	P=0.661
Cochran-Armitage Trend Test (d)	P=0.015		
Fisher Exact Test (d)		(e)	P=0.059

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Oral Cavity: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	0.0%	8.1%	41.4%
Terminal Rates (c)	0/43 (0%)	0/11 (0%)	0/0
Week of First Observation		95	65
Life Table Tests (d)	P<0.001	P=0.126	P<0.001
Incidental Tumor Tests (d)	P=0.164	P=0.808	P=0.491
Cochran-Armitage Trend Test (d)	P=0.016		
Fisher Exact Test (d)		P=0.247	P=0.028
Esophagus: Squamous Cell Carcinoma			
Overall Rates (a)	0/49 (0%)	3/50 (6%)	1/49 (2%)
Adjusted Rates (b)	0.0%	16.4%	12.5%
Terminal Rates (c)	0/42 (0%)	1/11 (9%)	0/0
Week of First Observation		95	79
Life Table Tests (d)	P=0.002	P=0.024	P=0.157
Incidental Tumor Tests (d)	P=0.097	P=0.205	P=0.748
Cochran-Armitage Trend Test (d)	P=0.378		
Fisher Exact Test (d)		P=0.125	P=0.500
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	1/49 (2%)
Adjusted Rates (b)	2.0%	25.5%	25.0%
Terminal Rates (c)	0/43 (0%)	2/11 (18%)	0/0
Week of First Observation	74	98	87
Life Table Tests (d)	P=0.005	P=0.027	P=0.356
Incidental Tumor Tests (d)	P=0.436	P=0.224	P=0.340N
Cochran-Armitage Trend Test (d)	P=0.593		
Fisher Exact Test (d)		P=0.181	P=0.747
Forestomach: Squamous Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	5/50 (10%)	1/49 (2%)
Adjusted Rates (b)	0.0%	22.2%	2.7%
Terminal Rates (c)	0/43 (0%)	1/11 (9%)	0/0
Week of First Observation		90	64
Life Table Tests (d)	P=0.002	P=0.004	P=0.444
Incidental Tumor Tests (d)	P=0.348	P=0.163	P=0.947
Cochran-Armitage Trend Test (d)	P=0.391		
Fisher Exact Test (d)		P=0.028	P=0.495
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	1/50 (2%)	9/50 (18%)	2/49 (4%)
Adjusted Rates (b)	2.0%	43.6%	27.0%
Terminal Rates (c)	0/43 (0%)	3/11 (27%)	0/0
Week of First Observation	74	90	64
Life Table Tests (d)	P<0.001	P<0.001	P=0.142
Incidental Tumor Tests (d)	P=0.233	P=0.044	P=0.409N
Cochran-Armitage Trend Test (d)	P=0.415		
Fisher Exact Test (d)		P=0.008	P=0.492
Pituitary Gland: Chromophobe Adenoma			
Overall Rates (a)	16/50 (32%)	12/48 (25%)	2/49 (4%)
Adjusted Rates (b)	35.4%	41.8%	100.0%
Terminal Rates (c)	14/43 (33%)	1/11 (9%)	0/0
Week of First Observation	74	83	74
Life Table Tests (d)	P=0.010	P=0.061	P=0.050
Incidental Tumor Tests (d)	P=0.040N	P=0.134N	P=0.489N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.294N	P<0.001N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Pituitary Gland: Adenoma or Chromophobe Adenoma			
Overall Rates (a)	16/50 (32%)	13/48 (27%)	2/49 (4%)
Adjusted Rates (b)	35.4%	43.4%	100.0%
Terminal Rates (c)	14/43 (33%)	1/11 (9%)	0/0
Week of First Observation	74	83	74
Life Table Tests (d)	P=0.007	P=0.040	P=0.050
Incidental Tumor Tests (d)	P=0.034N	P=0.157N	P=0.489N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.378N	P<0.001N
Pituitary Gland: Chromophobe Carcinoma			
Overall Rates (a)	1/50 (2%)	4/48 (8%)	0/49 (0%)
Adjusted Rates (b)	2.3%	20.0%	0.0%
Terminal Rates (c)	1/43 (2%)	1/11 (9%)	0/0
Week of First Observation	104	96	
Life Table Tests (d)	P=0.024	P=0.021	(f)
Incidental Tumor Tests (d)	P=0.394	P=0.314	(f)
Cochran-Armitage Trend Test (d)	P=0.398N		
Fisher Exact Test (d)		P=0.168	P=0.505N
Pituitary Gland: Chromophobe Adenoma or Carcinoma			
Overall Rates (a)	17/50 (34%)	16/48 (33%)	2/49 (4%)
Adjusted Rates (b)	37.7%	54.0%	100.0%
Terminal Rates (c)	15/43 (35%)	2/11 (18%)	0/0
Week of First Observation	74	83	74
Life Table Tests (d)	P<0.001	P=0.006	P=0.050
Incidental Tumor Tests (d)	P=0.083N	P=0.280N	P=0.489N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.557N	P<0.001N
Pituitary Gland: Adenoma, Chromophobe Adenoma, or Chromophobe Carcinoma			
Overall Rates (a)	17/50 (34%)	17/48 (35%)	2/49 (4%)
Adjusted Rates (b)	37.7%	55.2%	100.0%
Terminal Rates (c)	15/43 (35%)	2/11 (18%)	0/0
Week of First Observation	74	83	74
Life Table Tests (d)	P<0.001	P=0.004	P=0.050
Incidental Tumor Tests (d)	P=0.072N	P=0.311N	P=0.489N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.526	P<0.001N
Adrenal Gland: Cortical Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/49 (0%)
Adjusted Rates (b)	7.0%	0.0%	0.0%
Terminal Rates (c)	3/43 (7%)	0/11 (0%)	0/0
Week of First Observation	104		
Life Table Tests (d)	P=0.436N	P=0.436N	(f)
Incidental Tumor Tests (d)	P=0.436N	P=0.436N	(f)
Cochran-Armitage Trend Test (d)	P=0.038N		
Fisher Exact Test (d)		P=0.121N	P=0.125N
Thyroid Gland: Follicular Cell Carcinoma			
Overall Rates (a)	1/49 (2%)	5/49 (10%)	0/47 (0%)
Adjusted Rates (b)	2.4%	34.7%	0.0%
Terminal Rates (c)	1/42 (2%)	3/10 (30%)	0/0
Week of First Observation	104	95	
Life Table Tests (d)	P=0.003	P=0.002	(f)
Incidental Tumor Tests (d)	P=0.022	P=0.013	(f)
Cochran-Armitage Trend Test (d)	P=0.415N		
Fisher Exact Test (d)		P=0.102	P=0.510N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	1/49 (2%)	5/49 (10%)	1/47 (2%)
Adjusted Rates (b)	2.4%	34.7%	2.9%
Terminal Rates (c)	1/42 (2%)	3/10 (30%)	0/0
Week of First Observation	104	95	67
Life Table Tests (d)	P=0.001	P=0.002	P=0.427
Incidental Tumor Tests (d)	P=0.027	P=0.013	P=0.944
Cochran-Armitage Trend Test (d)	P=0.576		
Fisher Exact Test (d)		P=0.102	P=0.742
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/49 (6%)	4/49 (8%)	1/47 (2%)
Adjusted Rates (b)	7.1%	18.2%	14.3%
Terminal Rates (c)	3/42 (7%)	0/10 (0%)	0/0
Week of First Observation	104	88	80
Life Table Tests (d)	P=0.014	P=0.089	P=0.135
Incidental Tumor Tests (d)	P=0.639	P=0.640N	P=0.748
Cochran-Armitage Trend Test (d)	P=0.267N		
Fisher Exact Test (d)		P=0.500	P=0.324N
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	4/49 (8%)	0/49 (0%)	0/47 (0%)
Adjusted Rates (b)	9.0%	0.0%	0.0%
Terminal Rates (c)	3/42 (7%)	0/10 (0%)	0/0
Week of First Observation	74		
Life Table Tests (d)	P=0.212N	P=0.249N	P=0.735N
Incidental Tumor Tests (d)	P=0.019N	P=0.198N	P=0.056N
Cochran-Armitage Trend Test (d)	P=0.016N		
Fisher Exact Test (d)		P=0.059N	P=0.064N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	6/49 (12%)	4/49 (8%)	1/47 (2%)
Adjusted Rates (b)	13.7%	18.2%	14.3%
Terminal Rates (c)	5/42 (12%)	0/10 (0%)	0/0
Week of First Observation	74	88	80
Life Table Tests (d)	P=0.123	P=0.310	P=0.401
Incidental Tumor Tests (d)	P=0.138N	P=0.270N	P=0.342N
Cochran-Armitage Trend Test (d)	P=0.047N		
Fisher Exact Test (d)		P=0.370N	P=0.062N
Mammary Gland: Fibroadenoma			
Overall Rates (a)	10/50 (20%)	18/50 (36%)	5/50 (10%)
Adjusted Rates (b)	23.3%	71.6%	100.0%
Terminal Rates (c)	10/43 (23%)	6/11 (55%)	0/0
Week of First Observation	104	84	74
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.025	P=0.015	P=0.175
Cochran-Armitage Trend Test (d)	P=0.139N		
Fisher Exact Test (d)		P=0.059	P=0.131N
Mammary Gland: Adenocarcinoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	2.0%	19.2%	0.0%
Terminal Rates (c)	0/43 (0%)	1/11 (9%)	0/0
Week of First Observation	74	94	
Life Table Tests (d)	P=0.112	P=0.055	P=0.735N
Incidental Tumor Tests (d)	P=0.350N	P=0.540	P=0.051N
Cochran-Armitage Trend Test (d)	P=0.390N		
Fisher Exact Test (d)		P=0.181	P=0.500N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (a)	11/50 (22%)	21/50 (42%)	5/50 (10%)
Adjusted Rates (b)	24.8%	74.9%	100.0%
Terminal Rates (c)	10/43 (23%)	6/11 (55%)	0/0
Week of First Observation	74	84	74
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.119	P=0.034	P=0.579
Cochran-Armitage Trend Test (d)	P=0.101N		
Fisher Exact Test (d)		P=0.026	P=0.086N
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	7.0%	0.0%	0.0%
Terminal Rates (c)	3/43 (7%)	0/11 (0%)	0/0
Week of First Observation	104		
Life Table Tests (d)	P=0.436N	P=0.436N	(f)
Incidental Tumor Tests (d)	P=0.436N	P=0.436N	(f)
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	8/50 (16%)	11/50 (22%)	2/49 (4%)
Adjusted Rates (b)	18.6%	41.4%	8.9%
Terminal Rates (c)	8/43 (19%)	2/11 (18%)	0/0
Week of First Observation	104	81	71
Life Table Tests (d)	P<0.001	P=0.004	P=0.091
Incidental Tumor Tests (d)	P=0.539N	P=0.376	P=0.835
Cochran-Armitage Trend Test (d)	P=0.061N		
Fisher Exact Test (d)		P=0.306	P=0.049N
Uterus: Endometrial Stromal Polyp or Sarcoma			
Overall Rates (a)	8/50 (16%)	12/50 (24%)	2/49 (4%)
Adjusted Rates (b)	18.6%	43.5%	8.9%
Terminal Rates (c)	8/43 (19%)	2/11 (18%)	0/0
Week of First Observation	104	81	71
Life Table Tests (d)	P<0.001	P=0.002	P=0.091
Incidental Tumor Tests (d)	P=0.547N	P=0.356	P=0.835
Cochran-Armitage Trend Test (d)	P=0.065N		
Fisher Exact Test (d)		P=0.227	P=0.049N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).
(e) No P value is reported because no tumors were observed in the 200 mg/kg and vehicle control groups.
(f) No P value could be determined because all 200 mg/kg animals died before the first tumor was observed in the vehicle control group.

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	3/48 (6%)	6/47 (13%)	4/44 (9%)
Adjusted Rates (b)	7.9%	33.5%	63.7%
Terminal Rates (c)	3/38 (8%)	2/8 (25%)	1/2 (50%)
Week of First Observation	103	73	74
Life Table Tests (d)	P<0.001	P=0.013	P<0.001
Incidental Tumor Tests (d)	P=0.145	P=0.128	P=0.100
Cochran-Armitage Trend Test (d)	P=0.377		
Fisher Exact Test (d)		P=0.232	P=0.451
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	3/48 (6%)	4/47 (9%)	5/44 (11%)
Adjusted Rates (b)	7.5%	22.9%	28.0%
Terminal Rates (c)	2/38 (5%)	1/8 (13%)	0/2 (0%)
Week of First Observation	96	62	54
Life Table Tests (d)	P=0.002	P=0.100	P=0.004
Incidental Tumor Tests (d)	P=0.466	P=0.481	P=0.671N
Cochran-Armitage Trend Test (d)	P=0.247		
Fisher Exact Test (d)		P=0.488	P=0.309
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/48 (13%)	9/47 (19%)	8/44 (18%)
Adjusted Rates (b)	15.2%	41.3%	70.9%
Terminal Rates (c)	5/38 (13%)	2/8 (25%)	1/2 (50%)
Week of First Observation	96	62	54
Life Table Tests (d)	P<0.001	P=0.008	P<0.001
Incidental Tumor Tests (d)	P=0.292	P=0.254	P=0.234
Cochran-Armitage Trend Test (d)	P=0.272		
Fisher Exact Test (d)		P=0.272	P=0.320
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	5/48 (10%)	2/47 (4%)	3/44 (7%)
Adjusted Rates (b)	13.2%	17.6%	53.1%
Terminal Rates (c)	5/38 (13%)	1/8 (13%)	1/2 (50%)
Week of First Observation	103	94	68
Life Table Tests (d)	P=0.023	P=0.432	P=0.055
Incidental Tumor Tests (d)	P=0.194	P=0.618	P=0.272
Cochran-Armitage Trend Test (d)	P=0.312N		
Fisher Exact Test (d)		P=0.226N	P=0.407N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	6/48 (13%)	5/47 (11%)	6/44 (14%)
Adjusted Rates (b)	15.1%	27.5%	58.1%
Terminal Rates (c)	5/38 (13%)	1/8 (13%)	1/2 (50%)
Week of First Observation	76	84	68
Life Table Tests (d)	P=0.002	P=0.126	P=0.015
Incidental Tumor Tests (d)	P=0.452	P=0.634N	P=0.609
Cochran-Armitage Trend Test (d)	P=0.501		
Fisher Exact Test (d)		P=0.515N	P=0.557
Hematopoietic System: Lymphoma or Leukemia			
Overall Rates (a)	6/48 (13%)	6/47 (13%)	6/44 (14%)
Adjusted Rates (b)	15.1%	29.3%	58.1%
Terminal Rates (c)	5/38 (13%)	1/8 (13%)	1/2 (50%)
Week of First Observation	76	79	68
Life Table Tests (d)	P=0.003	P=0.076	P=0.015
Incidental Tumor Tests (d)	P=0.524	P=0.656	P=0.609
Cochran-Armitage Trend Test (d)	P=0.498		
Fisher Exact Test (d)		P=0.605	P=0.557

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Circulatory System: Hemangiosarcoma			
Overall Rates (a)	1/48 (2%)	1/47 (2%)	3/44 (7%)
Adjusted Rates (b)	2.6%	12.5%	12.5%
Terminal Rates (c)	1/38 (3%)	1/8 (13%)	0/2 (0%)
Week of First Observation	103	103	69
Life Table Tests (d)	P=0.009	P=0.387	P=0.050
Incidental Tumor Tests (d)	P=0.110	P=0.387	P=0.686
Cochran-Armitage Trend Test (d)	P=0.179		
Fisher Exact Test (d)		P=0.747	P=0.276
Circulatory System: Hemangioma or Hemangiosarcoma			
Overall Rates (a)	2/48 (4%)	3/47 (6%)	4/44 (9%)
Adjusted Rates (b)	4.9%	24.7%	17.6%
Terminal Rates (c)	1/38 (3%)	1/8 (13%)	0/2 (0%)
Week of First Observation	96	87	69
Life Table Tests (d)	P=0.002	P=0.088	P=0.018
Incidental Tumor Tests (d)	P=0.335	P=0.622	P=0.663N
Cochran-Armitage Trend Test (d)	P=0.228		
Fisher Exact Test (d)		P=0.490	P=0.298
Liver: Hepatocellular Adenoma			
Overall Rates (a)	8/48 (17%)	7/47 (15%)	8/44 (18%)
Adjusted Rates (b)	20.4%	37.3%	75.4%
Terminal Rates (c)	7/38 (18%)	2/8 (25%)	1/2 (50%)
Week of First Observation	99	80	72
Life Table Tests (d)	P<0.001	P=0.047	P<0.001
Incidental Tumor Tests (d)	P=0.136	P=0.566	P=0.267
Cochran-Armitage Trend Test (d)	P=0.482		
Fisher Exact Test (d)		P=0.518N	P=0.532
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	3/48 (6%)	6/47 (13%)	7/44 (16%)
Adjusted Rates (b)	7.1%	46.2%	59.5%
Terminal Rates (c)	1/38 (3%)	3/8 (38%)	0/2 (0%)
Week of First Observation	84	90	60
Life Table Tests (d)	P<0.001	P=0.008	P<0.001
Incidental Tumor Tests (d)	P=0.075	P=0.251	P=0.681
Cochran-Armitage Trend Test (d)	P=0.099		
Fisher Exact Test (d)		P=0.232	P=0.125
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	11/48 (23%)	12/47 (26%)	13/44 (30%)
Adjusted Rates (b)	26.5%	71.3%	88.3%
Terminal Rates (c)	8/38 (21%)	5/8 (63%)	1/2 (50%)
Week of First Observation	84	80	60
Life Table Tests (d)	P<0.001	P=0.002	P<0.001
Incidental Tumor Tests (d)	P=0.039	P=0.309	P=0.342
Cochran-Armitage Trend Test (d)	P=0.273		
Fisher Exact Test (d)		P=0.477	P=0.313
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	1/48 (2%)	3/47 (6%)	8/44 (18%)
Adjusted Rates (b)	2.6%	19.6%	25.8%
Terminal Rates (c)	1/38 (3%)	1/8 (13%)	0/2 (0%)
Week of First Observation	103	78	54
Life Table Tests (d)	P<0.001	P=0.054	P=0.001
Incidental Tumor Tests (d)	P=0.102	P=0.201	P=0.388
Cochran-Armitage Trend Test (d)	P=0.005		
Fisher Exact Test (d)		P=0.301	P=0.011

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Forestomach: Squamous Cell Carcinoma			
Overall Rates (a)	0/48 (0%)	42/47 (89%)	35/44 (90%)
Adjusted Rates (b)	0.0%	95.3%	100.0%
Terminal Rates (c)	0/38 (0%)	6/8 (75%)	2/2 (100%)
Week of First Observation		50	53
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	1/48 (2%)	43/47 (91%)	41/44 (93%)
Adjusted Rates (b)	2.6%	97.7%	100.0%
Terminal Rates (c)	1/38 (3%)	7/8 (88%)	2/2 (100%)
Week of First Observation	103	50	53
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Preputial Gland: Squamous Cell Carcinoma			
Overall Rates (a)	1/48 (2%)	3/47 (6%)	16/44 (36%)
Adjusted Rates (b)	2.6%	21.4%	82.5%
Terminal Rates (c)	1/38 (3%)	1/8 (13%)	1/2 (50%)
Week of First Observation	103	81	64
Life Table Tests (d)	P<0.001	P=0.044	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.254	P=0.012
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.301	P<0.001
Harderian Gland: Papillary Adenoma			
Overall Rates (a)	2/48 (4%)	3/47 (6%)	3/44 (7%)
Adjusted Rates (b)	5.3%	23.3%	61.5%
Terminal Rates (c)	2/38 (5%)	1/8 (13%)	1/2 (50%)
Week of First Observation	103	93	83
Life Table Tests (d)	P<0.001	P=0.060	P=0.001
Incidental Tumor Tests (d)	P=0.023	P=0.292	P=0.084
Cochran-Armitage Trend Test (d)	P=0.372		
Fisher Exact Test (d)		P=0.490	P=0.458

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE

	Vehicle Control	100 mg/kg	200 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	2/50 (4%)	1/46 (2%)	6/43 (14%)
Adjusted Rates (b)	4.9%	4.2%	46.3%
Terminal Rates (c)	2/41 (5%)	0/6 (0%)	1/3 (33%)
Week of First Observation	103	86	59
Life Table Tests (d)	P<0.001	P=0.556	P=0.001
Incidental Tumor Tests (d)	P=0.034	P=0.754N	P=0.165
Cochran-Armitage Trend Test (d)	P=0.048		
Fisher Exact Test (d)		P=0.532N	P=0.091
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	3/50 (6%)	1/46 (2%)	7/43 (16%)
Adjusted Rates (b)	7.0%	4.2%	73.2%
Terminal Rates (c)	2/41 (5%)	0/6 (0%)	2/3 (67%)
Week of First Observation	93	86	59
Life Table Tests (d)	P<0.001	P=0.657	P<0.001
Incidental Tumor Tests (d)	P=0.027	P=0.385N	P=0.126
Cochran-Armitage Trend Test (d)	P=0.059		
Fisher Exact Test (d)		P=0.341N	P=0.104
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	3/50 (6%)	0/47 (0%)	4/43 (9%)
Adjusted Rates (b)	6.8%	0.0%	46.9%
Terminal Rates (c)	2/41 (5%)	0/6 (0%)	1/3 (33%)
Week of First Observation	71		40
Life Table Tests (d)	P=0.015	P=0.400N	P=0.019
Incidental Tumor Tests (d)	P=0.129	P=0.097N	P=0.331
Cochran-Armitage Trend Test (d)	P=0.343		
Fisher Exact Test (d)		P=0.133N	P=0.415
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	6/50 (12%)	1/47 (2%)	5/43 (12%)
Adjusted Rates (b)	14.6%	16.7%	28.1%
Terminal Rates (c)	6/41 (15%)	1/6 (17%)	0/3 (0%)
Week of First Observation	103	103	66
Life Table Tests (d)	P=0.008	P=0.684	P=0.013
Incidental Tumor Tests (d)	P=0.149	P=0.684	P=0.500
Cochran-Armitage Trend Test (d)	P=0.515N		
Fisher Exact Test (d)		P=0.066N	P=0.607N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	10/50 (20%)	2/47 (4%)	10/43 (23%)
Adjusted Rates (b)	23.5%	18.6%	64.0%
Terminal Rates (c)	9/41 (22%)	1/6 (17%)	1/3 (33%)
Week of First Observation	71	48	40
Life Table Tests (d)	P<0.001	P=0.613N	P<0.001
Incidental Tumor Tests (d)	P=0.034	P=0.315N	P=0.230
Cochran-Armitage Trend Test (d)	P=0.432		
Fisher Exact Test (d)		P=0.018N	P=0.448
Liver: Hepatocellular Adenoma			
Overall Rates (a)	4/50 (8%)	4/47 (9%)	4/43 (9%)
Adjusted Rates (b)	9.8%	37.5%	37.7%
Terminal Rates (c)	4/41 (10%)	2/6 (33%)	0/3 (0%)
Week of First Observation	103	73	83
Life Table Tests (d)	P=0.004	P=0.030	P=0.008
Incidental Tumor Tests (d)	P=0.171	P=0.141	P=0.466
Cochran-Armitage Trend Test (d)	P=0.485		
Fisher Exact Test (d)		P=0.607	P=0.555

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Forestomach: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	1/47 (2%)	3/43 (7%)
Adjusted Rates (b)	0.0%	5.0%	36.7%
Terminal Rates (c)	0/41 (0%)	0/6 (0%)	1/3 (33%)
Week of First Observation		90	55
Life Table Tests (d)	P=0.006	P=0.338	P=0.019
Incidental Tumor Tests (d)	P=0.048	P=0.826	P=0.090
Cochran-Armitage Trend Test (d)	P=0.046		
Fisher Exact Test (d)		P=0.485	P=0.095
Forestomach: Squamous Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	40/47 (85%)	36/43 (84%)
Adjusted Rates (b)	0.0%	97.5%	97.0%
Terminal Rates (c)	0/41 (0%)	5/6 (83%)	2/3 (67%)
Week of First Observation		35	54
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Forestomach: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	40/47 (85%)	38/43 (88%)
Adjusted Rates (b)	0.0%	97.5%	100.0%
Terminal Rates (c)	0/41 (0%)	5/6 (83%)	3/3 (100%)
Week of First Observation		35	54
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Forestomach: Carcinoma, Squamous Cell Carcinoma, or Adenosquamous Carcinoma			
Overall Rates (a)	0/50 (0%)	41/47 (87%)	37/43 (86%)
Adjusted Rates (b)	0.0%	97.6%	97.2%
Terminal Rates (c)	0/41 (0%)	5/6 (83%)	2/3 (67%)
Week of First Observation		35	54
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Forestomach: Carcinoma, Adenosquamous Carcinoma, or Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	41/47 (87%)	39/43 (91%)
Adjusted Rates (b)	0.0%	97.6%	100.0%
Terminal Rates (c)	0/41 (0%)	5/6 (83%)	3/3 (100%)
Week of First Observation		35	54
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Pituitary Gland: Chromophobe Adenoma			
Overall Rates (a)	15/49 (31%)	2/46 (4%)	0/42 (0%)
Adjusted Rates (b)	37.5%	9.9%	0.0%
Terminal Rates (c)	15/40 (38%)	0/5 (0%)	0/3 (0%)
Week of First Observation	103	59	
Life Table Tests (d)	P=0.133N	P=0.551N	P=0.249N
Incidental Tumor Tests (d)	P=0.040N	P=0.259N	P=0.249N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P<0.001N	P<0.001N

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF DIMETHYLVINYL CHLORIDE (Continued)

	Vehicle Control	100 mg/kg	200 mg/kg
Harderian Gland: Papillary Adenoma			
Overall Rates (a)	0/50 (0%)	3/47 (6%)	5/43 (12%)
Adjusted Rates (b)	0.0%	27.6%	49.4%
Terminal Rates (c)	0/41 (0%)	1/6 (17%)	1/3 (33%)
Week of First Observation		80	82
Life Table Tests (d)	P<0.001	P=0.005	P<0.001
Incidental Tumor Tests (d)	P=0.009	P=0.097	P=0.055
Cochran-Armitage Trend Test (d)	P=0.014		
Fisher Exact Test (d)		P=0.110	P=0.019

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence at terminal kill
(d) Beneath the vehicle control incidence are the P values associated with the trend test. Beneath the dosed group incidence are the P values corresponding to pairwise comparisons between that dosed group and the vehicle controls. The life table analysis regards tumors in animals dying prior to terminal kill as being (directly or indirectly) the cause of death. The incidental tumor test regards these lesions as nonfatal. The Cochran-Armitage and Fisher exact tests compare directly the overall incidence rates. A negative trend or lower incidence in a dosed group is indicated by (N).

APPENDIX F

HISTORICAL INCIDENCES OF TUMORS IN F344/N RATS AND B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE

TABLE F1. HISTORICAL INCIDENCE OF NASAL CAVITY TUMORS IN F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	No. of Animals Examined	No. of Tumors	Site	Diagnosis
Incidence at Litton Bionetics, Inc.				
No nasal cavity tumors observed in 350 male or 350 female vehicle control animals.				
Overall Historical Incidence				
Male				
	1,100	1	Nares	Squamous cell papilloma
		1	Nose, NOS	Squamous cell carcinoma
TOTAL		2 (0.2%)		
Female				
	1,100	0		

(a) Data as of August 3, 1984, for studies of at least 104 weeks. The greatest observed incidence of nasal cavity tumors in any male vehicle control group was 2/50 in the chlorodibromomethane study.

TABLE F2. HISTORICAL INCIDENCE OF ESOPHAGEAL AND ORAL CAVITY TUMORS IN F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Esophagus	No. of Animals Examined	No. of Tumors	Diagnosis
Historical Incidence at Litton Bionetics, Inc.			
No esophageal tumors have been observed in 350 male and 350 female vehicle control animals.			
Overall Historical Incidence			
Male			
	1,037	1	Squamous cell carcinoma
TOTAL		1 (0.1%)	
Female			
	1,036	0	

Oral Cavity	No. of Animals Examined	No. of Tumors	Site	Diagnosis
Historical Incidence at Litton Bionetics, Inc.				
No oral cavity tumors have been observed in 350 male or 350 female vehicle controls.				
Male				
	1,100	1	Soft palate	Squamous cell papilloma
		1	Tongue	Squamous cell papilloma
TOTAL		2 (0.2%)		
Female				
	1,100	1	Soft palate	Squamous cell papilloma
		1	Tongue	Squamous cell papilloma
		1	Dorsum of tongue	Squamous cell papilloma
TOTAL		3 (0.3%)		

(a) Data as of August 3, 1984, for studies of at least 104 weeks. No male vehicle control group had more than one oral cavity or esophageal tumor. The greatest observed incidence in any female vehicle control group was 2/50.

TABLE F3. HISTORICAL INCIDENCE OF STOMACH TUMORS IN F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

	No. of Animals Examined	No. of Tumors	Site	Diagnosis
Incidence at Litton Bionetics, Inc.				
Male				
No stomach tumors have been observed in 350 male vehicle control animals.				
Female				
	349	(b) 1	Stomach, NOS	Squamous cell papilloma
Overall Historical Incidence				
Male				
	1,091	3	Forestomach	Squamous cell papilloma
		1	Cardiac stomach	Squamous cell papilloma
TOTAL		4 (0.4%)		
Female				
	1,096	2	Stomach, NOS	Squamous cell papilloma
		1	Gastric mucosa	Squamous cell papilloma
		1	Forestomach	Squamous cell papilloma
TOTAL		4 (0.4%)		

(a) Data as of August 3, 1984, for studies of at least 104 weeks. No more than one tumor was observed in any vehicle control group.
(b) Observed in the 2,4-toluene diisocyanate study (NTP TR 251)

TABLE F4. HISTORICAL INCIDENCE OF MAMMARY GLAND TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls	
	All Benign (b)	All Malignant (c)
Historical Incidence at Litton Bionetics, Inc.		
Diallylphthalate	12/50	1/50
Dimethyl morpholinophosphoramidate	11/50	0/50
Tris(2-ethylhexyl)phosphate	11/50	1/50
Dimethyl hydrogen phosphite	9/50	0/50
3-Chloro-2-methylpropene	19/50	2/50
4-Vinylcyclohexene	7/50	0/50
2,4-Toluene diisocyanate	17/50	0/50
TOTAL	86/350 (24.6%)	4/350 (1.1%)
SD (d)	8.54%	1.57%
Range (e)		
High	19/50	2/50
Low	7/50	0/50
Overall Historical Incidence		
TOTAL	280/1,100 (25.5%)	17/1,100 (1.5%)
SD (d)	8.08%	1.50%
Range (e)		
High	19/50	2/50
Low	7/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes diagnoses of fibroadenoma, adenoma, papillary adenoma, cystadenoma, and papillary cystadenoma
(c) Includes diagnoses of adenocarcinoma and papillary cystadenocarcinoma
(d) Standard deviation
(e) Range and SD are reported for groups of 35 or more animals.

TABLE F5. HISTORICAL INCIDENCE OF THYROID GLAND FOLLICULAR CELL TUMORS IN FEMALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma (b)	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Diallylphthalate	0/48	0/48	0/48
Dimethyl morpholinophosphoramidate	0/50	0/50	0/50
Tris(2-ethylhexyl)phosphate	1/46	1/46	2/46
Dimethyl hydrogen phosphite	1/49	0/49	1/49
3-Chloro-2-methylpropene	0/50	1/50	1/50
4-Vinylcyclohexene	0/49	0/49	0/49
2,4-Toluene diisocyanate	0/50	1/50	1/50
TOTAL	2/342 (0.6%)	3/342 (0.9%)	5/342 (1.5%)
SD (c)	1.03%	1.10%	1.62%
Range (d)			
High	1/46	1/46	2/46
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	10/1,076 (0.9%)	5/1,076 (0.5%)	15/1,076 (1.4%)
SD (c)	1.65%	0.88%	1.74%
Range (d)			
High	3/48	1/46	3/48
Low	0/50	0/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes cystadenoma and papillary cystadenoma of the thyroid gland follicle and thyroid gland follicular cell adenoma and papillary adenoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE F6. HISTORICAL INCIDENCE OF STOMACH TUMORS IN B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	No. of Animals Examined	No. of Tumors	Diagnosis
Incidence at Litton Bionetics, Inc.			
Male			
Dimethyl hydrogen phosphite	50	1	Squamous cell carcinoma
2,4-Toluene diisocyanate	48	1	Papilloma, NOS
Diallylphthalate	49	0	
Dimethyl morpholinophosphoramidate	50	0	
Tris(2-ethylhexyl)phosphate	50	1	Squamous cell papilloma
3-Chloro-2-methylpropene	49	2	Squamous cell papilloma
4-Vinylcyclohexene	47	2	Squamous cell papilloma
TOTAL	343	7 (2.0%)	
Female			
No stomach tumors have been observed in 343 vehicle control animals.			
Overall Historical Incidence			
Male			
	1,070	1	Papilloma, NOS
		8	Squamous cell papilloma
		5	Squamous cell carcinoma
TOTAL		(b) 14 (1.3%)	
Female			
	1,073	3	Squamous cell papilloma
		1	Adenoma, NOS
		1	Adenomatous polyp
TOTAL		(c) 5 (0.5%)	

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Greatest incidence observed in any vehicle control group: 2/46
(c) Greatest incidence observed in any vehicle control group: 2/50

TABLE F7. HISTORICAL INCIDENCE OF PREPUTIAL GLAND TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

	No. of Animals Examined	No. of Tumors	Diagnosis
Incidence at Litton Bionetics, Inc.			
No preputial gland tumors have been observed in 350 male vehicle control animals.			
Overall Historical Incidence			
	1,097	1 (0.1%)	Adenoma, NOS

(a) Data as of August 3, 1984, for studies of at least 104 weeks

TABLE F8. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Dimethyl hydrogen phosphite	2/50	2/50	4/50
2,4-Toluene diisocyanate	0/49	0/49	0/49
Diallylphthalate	1/50	0/50	1/50
Dimethyl morpholinophosphoramidate	2/50	2/50	4/50
Tris(2-ethylhexyl)phosphate	2/48	0/48	2/48
3-Chloro-2-methylpropene	3/50	0/50	3/50
4-Vinylcyclohexene	5/50	1/50	6/50
TOTAL	15/347 (4.3%)	5/347 (1.4%)	20/347 (5.8%)
SD (b)	3.15%	1.90%	4.06%
Range (c)			
High	5/50	2/50	6/50
Low	0/49	0/50	0/49
Overall Historical Incidence			
TOTAL	45/1,087 (4.1%)	12/1,087 (1.1%)	57/1,087 (5.2%)
SD (b)	2.88%	1.60%	3.47%
Range (c)			
High	5/50	2/50	6/50
Low	0/50	0/50	0/49

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F9. HISTORICAL INCIDENCE OF HARDERIAN GLAND TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls	
	Adenoma	Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.		
Dimethyl hydrogen phosphite	0/50	0/50
2,4-Toluene diisocyanate	1/50	1/50
Diallylphthalate	2/50	2/50
Dimethyl morpholinophosphoramidate	0/50	0/50
Tris(2-ethylhexyl)phosphate	0/49	0/49
3-Chloro-2-methylpropene	1/50	1/50
4-Vinylcyclohexene	0/50	0/50
TOTAL	(b) 4/349 (1.1%)	4/349 (1.1%)
SD (c)	1.57%	1.57%
Range (d)		
High	2/50	2/50
Low	0/50	0/50
Overall Historical Incidence		
TOTAL	(e) 20/1,096 (1.8%)	21/1,096 (1.9%)
SD (c)	2.38%	2.51%
Range (d)		
High	5/50	5/50
Low	0/50	0/50

(a) Data as of August 3, 1984, for studies of at least 104 weeks
(b) Includes one papillary adenoma
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.
(e) Includes one papillary adenoma and one papillary cystadenoma

APPENDIX G

GENETIC TOXICOLOGY OF DIMETHYLVINYL CHLORIDE

TABLE G1. MUTAGENICITY OF DIMETHYLVINYL CHLORIDE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	150 ± 10.3	189 ± 3.0	183 ± 2.8
	33	133 ± 2.3	---	---
	100	121 ± 9.4	192 ± 13.6	186 ± 0.7
	333	115 ± 11.3	180 ± 8.3	152 ± 12.9
	1,000	142 ± 4.5	195 ± 3.5	155 ± 12.0
	3,333	187 ± 5.5	180 ± 2.0	156 ± 7.8
	10,000	---	190 ± 1.2	172 ± 4.0
TA1535	0	11 ± 2.1	12 ± 2.0	13 ± 1.9
	100	12 ± 1.0	13 ± 1.2	13 ± 3.2
	333	12 ± 3.0	9 ± 2.3	11 ± 0.3
	1,000	20 ± 1.2	11 ± 3.1	15 ± 1.2
	3,333	21 ± 2.9	11 ± 0.9	14 ± 1.2
	10,000	5 ± 4.7	13 ± 2.8	15 ± 1.0
TA1537	0	7 ± 0.9	15 ± 0.3	6 ± 1.5
	100	6 ± 1.8	12 ± 1.8	8 ± 2.2
	333	9 ± 1.2	10 ± 0.3	9 ± 3.2
	1,000	11 ± 0.9	7 ± 1.8	11 ± 3.2
	3,333	10 ± 0.3	8 ± 1.3	8 ± 1.2
	10,000	9 ± 1.9	10 ± 1.5	14 ± 0.9
TA98	0	19 ± 0.3	29 ± 2.1	20 ± 0.7
	100	16 ± 0.3	26 ± 1.2	21 ± 4.4
	333	17 ± 1.2	23 ± 1.5	28 ± 2.6
	1,000	14 ± 0.6	27 ± 1.5	22 ± 4.4
	3,333	21 ± 2.5	29 ± 2.9	26 ± 2.3
	10,000	19 ± 5.2	29 ± 2.7	20 ± 3.6

(a) The S9 fractions were prepared from the livers of Aroclor 1254-induced male Sprague-Dawley rats and male Syrian hamsters. Cells and study compound or solvent (water) were incubated for 20 minutes at 37° C in the presence of either S9 or buffer. After the addition of soft agar, the contents of each tube were poured onto minimal medium, and the plates were incubated at 37° C for 48 hours (Haworth et al., 1983). The experiment was performed twice, each in triplicate; because the results were similar, data from only one experiment are shown.
(b) Revertants are presented as mean ± standard error.

TABLE G2. MUTAGENICITY OF DIMETHYLVINYL CHLORIDE IN L5178Y/TK$^{+/-}$ MOUSE LYMPHOMA CELLS IN THE ABSENCE OF S9 (a)

Compound	Dose (μg/ml)	Total Mutant Clones	Cloning Efficiency (percent)	Relative Total Growth (percent)	Mutation Frequency (mutants/10^6 clonable cells)
Absolute ethanol (1%)					
		43	90.7	81	16
		56	116.2	101	16
		70	94.3	120	25
		69	102.0	97	23
Methyl methanesulfonate					
	5	437	82.7	61.2	176
		450	89.7	66.3	167
		480	79.5	75.0	201
Dimethylvinyl chloride					
	0.1	55	84.8	68.6	22
		41	85.0	80.5	16
		68	92.0	74.1	25
	0.2	76	71.0	61.5	36
		64	85.8	64.0	25
		48	66.5	37.9	24
	0.4	131	75.7	28.9	58
		192	77.7	32.9	82
		185	108.8	11.3	57
	0.6	396	54.5	7.7	242
		417	79.8	9.9	174
		373	106.5	14.2	117

(a) Experiments were performed twice, and all doses were tested in triplicate, except the solvent control (100% ethanol) which was tested in quadruplicate. Because the results were similar, data from only one experiment are shown. The protocol was basically that of Clive et al. (1979). Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium supplemented with trifluorothymidine for selection of cells that were mutant at the thymidine kinase (TK) locus, and 600 cells were plated in nonselective medium to determine the percentage of viable cells.

TABLE G3. INDUCTION OF SISTER-CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY DIMETHYLVINYL CHLORIDE (a)

−S9 (b)		+S9 (c)	
Dose (μg/ml)	SCE/Cell (d)	Dose (μg/ml)	SCE/Cell (d)
DMSO		DMSO	
(10 μl)	6.98	(10 μl)	8.78
Dimethylvinyl chloride			
100	9.60	250	8.14
250	11.40	500	9.34
500	14.20	750	11.88
Mitomycin C		Cyclophosphamide	
0.05	20.10	1.5	30.66
		2.0	37.36

(a) SCE = sister chromatid exchange
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent at 37° C; 2 hours after initiation of treatment, 10 μM BrdU was added, and incubation was continued for an additional 22-24 hours. Cells were washed, fresh medium containing BrdU (10 μM) and colcemid (0.1 μg/ml) was added, and incubation was continued for 2-3 hours (Galloway et al., 1985).
(c) In the presence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then cells were washed, and medium containing 10 μM BrdU was added. Cells were incubated for a further 26 hours, with colcemid (0.1 μg/ml) present for the final 2-3 hours. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).
(d) Cells were collected by mitotic shake-off, treated for 3 minutes with potassium chloride (75 mM), washed twice with fixative, and dropped onto slides and air-dried (Galloway et al., 1985).

TABLE G4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY DIMETHYLVINYL CHLORIDE (a)

−S9 (b)		+S9 (c)	
Dose (μg/ml)	Abs/100 Cells (percent cells w/abs)	Dose (μg/ml)	Abs/100 Cells (percent cells w/abs)
DMSO		DMSO	
(10 μl)	1 (1)	(10 μl)	0 (0)
Dimethylvinyl chloride		Dimethylvinyl chloride	
50	0 (0)	50	0 (0)
100	1 (1)	160	0 (0)
250	0 (0)	500	1 (1)
500	2 (2)	1,600	1 (1)
Mitomycin C		Cyclophosphamide	
0.25	21 (20)	50	34 (25)

(a) Abs = aberrations
(b) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid (0.1 μg/ml) was added. After a further 2-3 hours of incubation, cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa (Galloway et al., 1985).
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, fresh medium was added, and incubation was continued for 8-10 hours. Colcemid (0.1 μg/ml) was added for the last 2-3 hours of incubation; then cells were harvested by mitotic shake-off, fixed, and stained in 6% Giemsa. S9 was from the livers of Aroclor 1254-induced male Sprague-Dawley rats (Galloway et al., 1985).

TABLE G5. INDUCTION OF SEX-LINKED RECESSIVE LETHAL MUTATIONS IN DROSOPHILA BY DIMETHYLVINYL CHLORIDE

Route of Exposure	Dose (ppm)	No. of Lethals/No. of X Chromosomes Tested (a)			
		Mating 1	Mating 2	Mating 3	Total (percent)
Feeding	0	3/2,922	6/2,916	5/2,570	14/8,408 (0.17)
	12,750	7/3,128	16/2,927	10/2,249	33/8,304 (0.40)

(a) The sex-linked recessive lethal assay was performed essentially as described by Abrahamson and Lewis (1971). Exposure by feeding was done by allowing 24-hour-old Canton-S males to feed for 3 days on a solution of the study chemical dissolved in 5% sucrose. Exposed males were mated to three *Basc* females for 3 days and given fresh females at 2-day intervals to produce three broods of 3, 2, and 2 days, after which the parents were discarded. F_1 heterozygous females were crossed to their siblings and placed in individual vials. F_1 daughters from the same parental males were kept together to identify clusters. After 17 days, presumptive lethal mutations were identified as vials containing no wild-type males; these were retested. The treated group was found to be significantly different from the controls at the 1% level (Margolin et al., 1983).

TABLE G6. INDUCTION OF RECIPROCAL TRANSLOCATIONS IN DROSOPHILA BY DIMETHYLVINYL CHLORIDE (a)

Route of Exposure	Dose (ppm)	Storages (Translocations/Tests)						Total No. of Tests	Total No. of Trans-locations	Percent Trans-locations
		1	2	3	4	5	6			
Feeding	12,750	8/873	6/821	8/698	3/253	1/30	0/0	2,675	26	0.9720
Historical control	0	0/6,187	0/6,085	0/6,635	1/6,381	0/4,738	0/250	30,276	1	0.0033

(a) The reciprocal translocation assay was performed essentially as described by Abrahamson and Lewis (1971). Males were fed for 3 days; then each male was mated to a harem of bw;st;p^p females for 3 days. Females were subsequently discarded, and each male was transferred to a fresh harem for 4 days. This mating regimen allowed sampling of the spermatid population, the most sensitive stage of germ cell maturation, as indicated by the sex-linked recessive lethal mutation data (Table G5). Males were then discarded. The females were transferred to fresh medium every 3-4 days to produce a total of five cultures, and then they were discarded. In this manner, successive cultures sample sperm were stored for increasing lengths of time. Individual F_1 males were backcrossed to bw;st;p^p females, and the F_2 were screened for pseudolinkage. This procedure allows the recovery of translocations involving the Y, second, or third chromosomes in any combination. Presumptive translocations were retested. The treated group was found to be significantly different from the controls at the 1% level (Kastenbaum and Bowman, 1970).

APPENDIX H

CHEMICAL CHARACTERIZATION OF DIMETHYLVINYL CHLORIDE

APPENDIX H. CHEMICAL CHARACTERIZATION

I. Identity and Purity Determinations of Dimethylvinyl Chloride Performed by the Analytical Chemistry Laboratory

	Determined	Literature Values
A. Lot no. 062537		
1. Physical properties		
a. Boiling point:	62° ± 1(δ)° C at 729 torr (visual, micro boiling point) 72.5°-75° C (Dupont 900 DTA)	68.1° C (Merck, 1976)
b. Index of refraction:	n_D^{20}: 1.4212 ± 0.004(δ)	n_D^{20}: 1.4221 (Merck, 1976)
c. Density:	$d_{22}^{24.5}$: 0.9188 ± 0.0007(δ)	d_4^{20}: 0.9186 g/ml (Merck, 1976)
d. Appearance:	Clear, pale orange liquid	
2. Spectral data		
a. Infrared		
Instrument:	Beckman IR-12	
Cell:	0.054 cm liquid cell with sodium chloride windows	
Results:	See Figure 5	No literature reference found. Spectrum consistent with commercial spectrum from manufacturer (Aldrich, 1975) and with structure.
b. Ultraviolet/visible		
Instrument:	Cary 118	
Solvent:	Hexane (1%)	
Results:	No absorbance between 800 and 350 nm. No maximum between 350 and 212 nm but a gradual increase in absorbance and slight inflections toward the solvent cutoff at 212 nm.	No literature reference found.

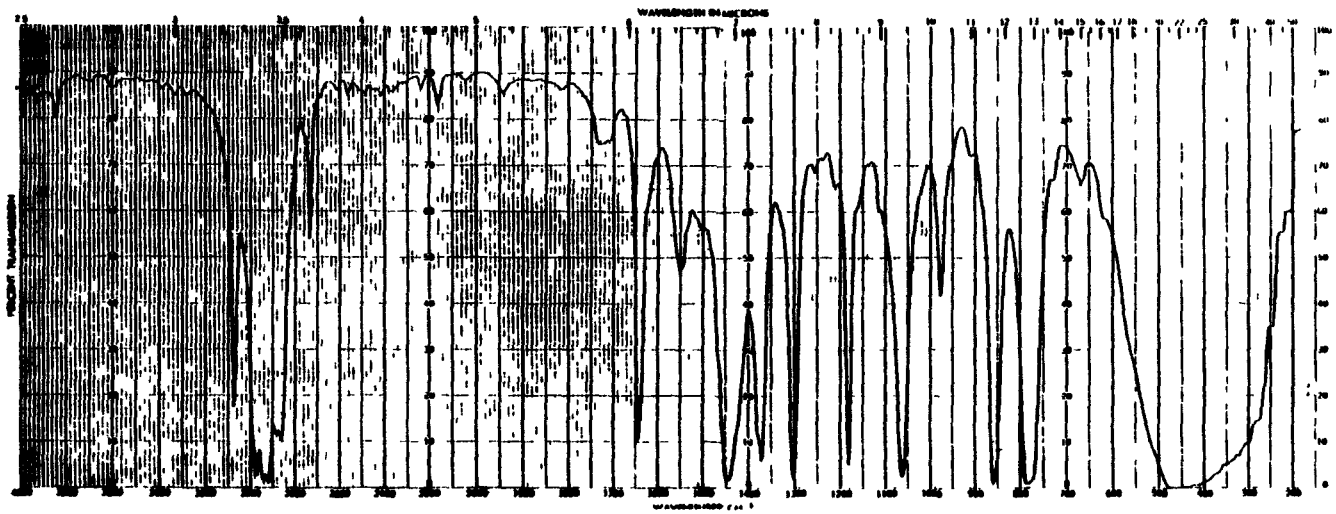


FIGURE 5. INFRARED ABSORPTION SPECTRUM OF DIMETHYLVINYL CHLORIDE (LOT NO. 062537)

	Determined	Literature Values
c. Nuclear magnetic resonance		
Instrument:	Varian HA-100	
Solvent:	Neat, tetramethylsilane added	
Assignments:	See Figure 6	No literature spectrum found. Sample spectrum consistent with spectrum from manufacturer (Aldrich, 1974) and with structure.
Chemical shift (δ):	a d, 1.67 ppm b d, 1.70 ppm c m, 5.63 ppm d d, 1.17 ppm e 1.52 ppm f 1.57 ppm g 3.46 ppm h 3.56 ppm i 3.85 ppm	
	(Peaks d through i are impurities. Peak i is consistent in chemical shift with one of the resonant frequencies for 3-chloro-2-methylpropene, but this tentative assignment was not confirmed.)	
Coupling constants:	J_{ac} = 1.5 Hz J_{bc} = 1.5 Hz J = 3 Hz	
Integration ratios:	a + b 5.97 c 1.03 d 0.15 e + f 0.24 g + h + i 0.02	

3. **Water analysis (Karl Fischer):** 0.029% ± 0.002(δ)%
4. **Titration for acidic components:** 210 ± 10(δ) ppm (assumed to be hydrochloric acid)
5. **Elemental analysis**

Element	C	H	Cl
Theory	53.06	7.79	39.15
Determined	52.83	7.84	38.95
	53.05	7.98	39.13

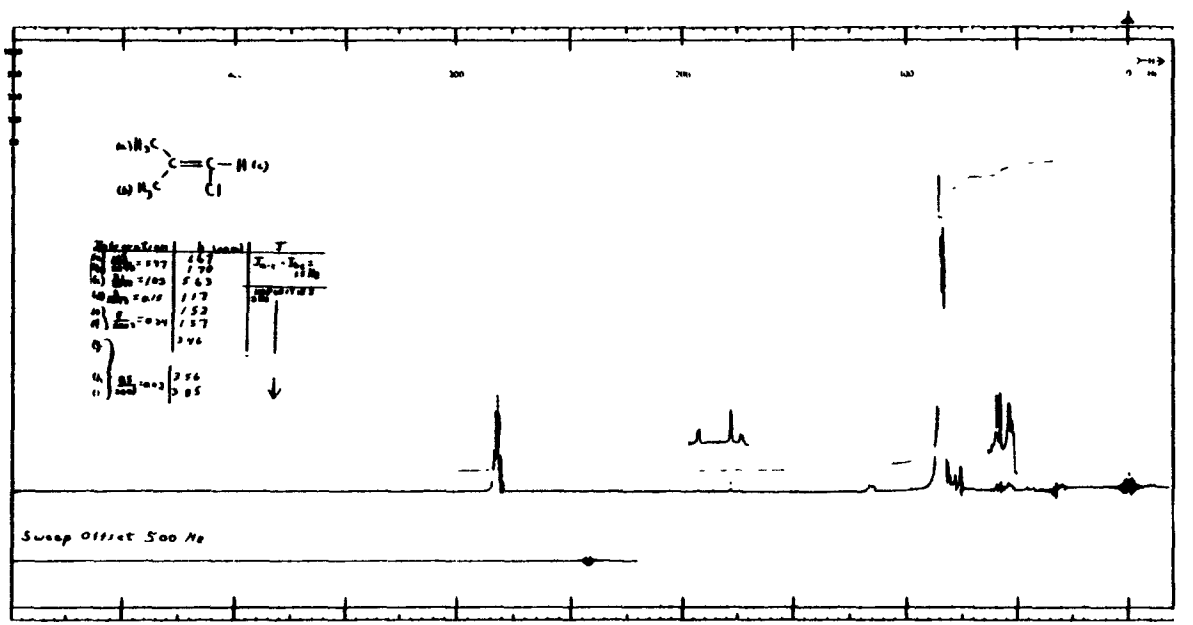


FIGURE 6. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DIMETHYLVINYL CHLORIDE (LOT NO. 062537)

6. **Gas chromatography**

Instrument: Tracor MT 220
Detector: Flame ionization
Inlet temperature: 200° C
Detector temperature: 270° C
Sample injected: 6 µl neat, diluted to 1% and 0.5% in *o*-dichlorobenzene to quantitate the major peak and check for overloading

System 1

Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 × 4 mm ID, glass
Oven temperature program: 50° C for 5 min, then to 170° C at 10° C/min

Results: A major peak and 36 impurities were observed. The six largest impurities had areas of 1%, 0.9%, 0.9%, 0.3%, 0.1%, and 0.1% that of the major peak. The areas of the other 30 impurities totaled <0.5% of the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.6	0.3	0.10
2	1.2	0.5	0.10
3	1.5	0.6	0.30
4	1.8	0.8	1.00
5	2.4	1.0	100
6	4.7	1.9	0.01
7	4.9	2.0	0.02
8	5.3	2.2	0.02
9	5.9	2.5	0.03
10	6.6	2.7	0.90
11	7.6	3.1	< 0.01
12	8.5	3.5	< 0.01
13	8.7	3.6	0.04
14	9.3	3.9	< 0.01
15	9.5	4.0	< 0.01
16	9.8	4.1	< 0.01
17	10.0	4.2	0.90
18	10.3	4.3	0.01
19	10.6	4.4	0.01
20	11.0	4.5	0.01
21	11.2	4.6	< 0.01
22	11.8	4.9	0.04
23	12.3	5.1	0.04
24	12.5	5.2	< 0.01
25	12.9	5.3	0.01
26	13.4	5.5	0.01
27	13.6	5.6	0.03
28	14.1	5.8	< 0.01
29	14.3	5.9	0.01
30	14.9	6.2	< 0.01
31	15.0	6.2	0.01
32	15.3	6.3	0.01
33	15.5	6.4	< 0.01
34	15.7	6.5	< 0.01
35	16.2	6.7	< 0.01
36	16.3	6.8	0.05
37	16.8	7.0	< 0.01

System 2

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), 1.8 m × 4 mm, ID
Oven temperature program: 50° C for 5 min, then 50° to 200° C at 10° C/min

Results: A major peak and 34 impurities were observed. The areas of six of these impurities are 0.8%, 0.6%, 0.5%, 0.2%, 0.1%, and 0.1% that of the major peak. The areas of the other 28 impurities total less than 0.3% of the major peak area.

Under these conditions 3-chloro-2-methylpropene had a retention time of 1.6 minutes. It is possible that peak no. 4 is 3-chloro-2-methylpropene, but this was not confirmed.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.3	0.3	0.10
2	0.5	0.5	0.80
3	1.1	1.0	100
4	1.5	1.4	0.20
5	2.8	2.5	0.01
6	3.4	3.1	0.50
7	4.4	4.0	0.60
8	7.7	6.9	0.10
9	8.3	7.5	
10	9.3	8.4	< 0.01
11	9.6	8.7	< 0.01
12	9.8	8.8	0.02
13	10.2	9.2	< 0.01
14	10.5	9.4	0.04
15	10.6	9.6	< 0.01
16	11.0	9.9	< 0.01
17	11.3	10.2	< 0.01
18	11.5	10.4	< 0.01
19	11.9	10.7	0.01
20	12.1	10.9	< 0.01
21	12.4	11.1	0.01
22	12.6	11.3	0.04
23	13.0	11.7	0.01
24	13.4	12.0	< 0.01
25	13.6	12.2	< 0.01
26	13.8	12.5	0.05
27	14.1	12.7	< 0.01
28	14.3	12.8	< 0.01
29	14.6	13.1	0.01
30	14.9	13.5	< 0.01
31	15.1	13.6	< 0.01
32	15.3	13.8	< 0.01
33	15.5	14.0	< 0.01
34	15.7	14.1	< 0.01
35	16.1	14.5	< 0.01

7. **Conclusions:** The results of the elemental analysis agreed with the theoretical values. Gas chromatography with one system indicated 36 impurities. The six largest impurities had areas 1%, 0.9%, 0.9%, 0.3%, 0.1%, and 0.1% of the area of the major peak. The areas of the other 30 impurities totaled less than 0.5% of the major peak. A second system indicated 34 impurities. The six largest impurities had areas 0.8%, 0.6%, 0.5%, 0.2%, 0.1%, and 0.1% of the area of the major peak. The areas of the other 28 impurities totaled less than 0.3% of the major peak. Titration for acidic components indicated 210 ± 10 ppm acidity (assumed to be hydrochloric acid). The infrared and nuclear magnetic resonance spectra were consistent with the structure, but six impurity peaks were observed in the nuclear magnetic resonance spectrum.

	Determined	Literature Values
B. Lot No. KD090967		
1. Physical properties		
Appearance:	Clear, pale yellow liquid	
2. Spectral data		
a. Infrared		
Instrument:	Perkin-Elmer 283	
Cell:	Thin film between silver chloride windows	
Results:	See Figure 7	Consistent with structure and literature reference (Aldrich, 1975)
b. Ultraviolet/visible		
Instrument:	Cary 219	
Solvent:	Hexane	
Results:	No absorbance maxima were observed in the visible region (800-350 nm) with a 1% solution. There was a gradual increase in absorbance in the ultraviolet region (350-200 nm), but no resolved maxima were observed.	No literature reference found. Spectrum consistent with structure.
c. Nuclear magnetic resonance		
Instrument:	Varian EM-360A	
Solvent:	Neat liquid containing tetramethylsilane as internal standard	
Assignments:	See Figure 8	Consistent with structure and literature reference (Aldrich, 1974)

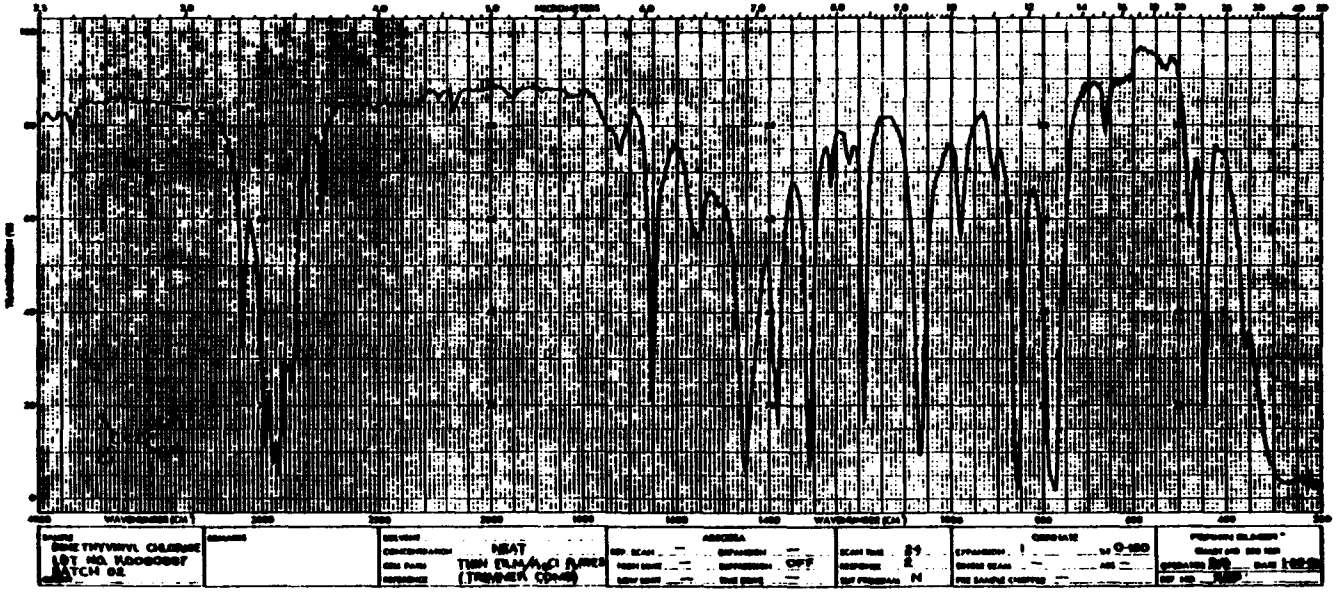


FIGURE 7. INFRARED ABSORPTION SPECTRUM OF DIMETHYLVINYL CHLORIDE (LOT NO. KD090967)

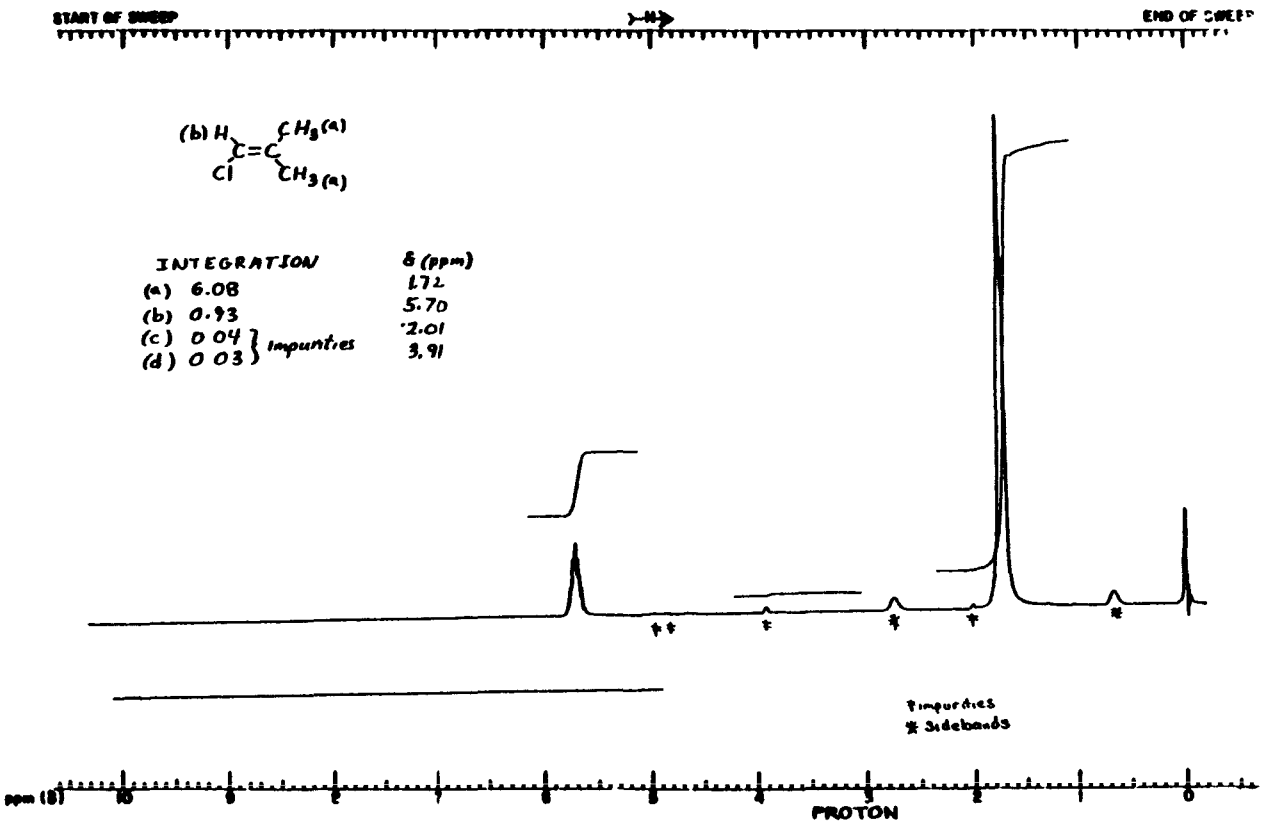


FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DIMETHYLVINYL CHLORIDE (LOT NO. KD090967)

Chemical shift (δ):	a	m,	1.72
	b	m,	5.70
	c	impurity,	2.01
	d	impurity,	3.91
Integration ratios:	a	6.08	
	b	0.93	
	c	0.04 }	impurities
	d	0.03 }	

3. **Water analysis (Karl Fischer):** 0.005% ± 0.002(δ)%

4. **Titration of acidic components:** Neat dimethylvinyl chloride (4 ml) was added to 25 ml of 95% ethanol (previously neutralized to the phenolphthalein endpoint). As the titration vessel headspace was purged with nitrogen gas, the sample was titrated with 0.01 N sodium hydroxide to the phenolphthalein endpoint.

   419 ± 18 ppm (as hydrochloric acid)

5. **Elemental analysis**

Element	C	H	Cl
Theory (T)	53.06	7.79	39.15
Determined (D)	53.10	7.88	39.03
	53.15	7.81	39.13
Percent D/T	100.12	100.71	99.82

6. **Gas chromatography**

   a. ***Impurity detection***

   Instrument: Varian 3700
   Detector: Flame ionization
   Carrier gas: Nitrogen, 70 ml/min

   System 1

   Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
   Inlet temperature: 200° C
   Detector temperature: 270° C
   Oven temperature program: 50° C for 5 min, then 50° to 170° C at 10° C/min
   Sample injected: Neat liquid (5 µl) and 1% and 0.5% solutions in *o*-dichlorobenzene to quantitate impurities and check detector linearity

Results: A major peak and 14 impurities with relative areas greater than 0.01% of the major peak area were observed. The two largest impurities had areas 0.16% and 0.11% of the major peak area. The remaining 12 impurities had a cumulative area of 0.29% relative to the major peak. Two additional impurities were observed eluting after the major peak with individual areas less than 0.01% of the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	1.0	0.34	0.16
2	1.8	0.62	0.03
3	2.3	0.79	0.04
4	2.9	1.00	100
5	4.1	1.41	0.01
6	4.9	1.69	0.03
7	6.8	2.34	0.01
8	11.3	3.90	0.02
9	14.8	5.10	0.02
10	16.3	5.52	
11	16.6	5.72	0.05
12	16.9	5.83	
13	18.6	6.41	0.12
14	20.8	7.17	0.06
15	24.1-24.2	8.31-8.34	0.01

System 2

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb, 1.8 m × 4 mm ID, glass
Inlet temperature: 200° C
Detector temperature: 250° C
Oven temperature program: 50° C for 5 min, then 50° C to 200° C at 10° C/min
Sample injected: Neat liquid (4 µl) and 1% and 0.5% solutions in o-dichlorobenzene to quantitate impurities and check detector linearity

Results: A major peak and nine impurities with areas greater than 0.01% relative to the major peak area were observed. The three largest impurities had areas 0.10%, 0.12%, and 2.88% of the major peak area. The largest impurity was subsequently identified as 3-chloro-2-methylpropene (Section I.B.6.b.). The remaining six impurities had a cumulative area of 0.31% relative to the major peak. Three additional impurities, one before and two after the major peak, were observed with individual areas less than 0.01% of the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	1.25	1.00	100
2	1.90	1.52	2.88
3	3.09	2.47	0.10
4	5.10	4.08	0.04
5	9.90	7.92	0.02
6	11.5	9.20	0.10
7	12.2	9.80	0.03
8	13.0	10.4	0.12
9	14.4-14.7	11.5-11.8	0.07
10	15.7	12.6	0.06

System 3

Column: 80/100 Carbopack C/0.1% SP1000, 1.8 m × 4 mm ID, glass
Inlet temperature: 180° C
Detector temperature: 250° C
Oven temperature program: 50° C for 5 min, then 50° C to 250° C at 10° C/min
Sample injected: Neat liquid (3 µl) and 1% and 0.5% solutions in methylene chloride to quantitate impurities and check detector linearity

Results: A major peak and 11 impurities, 5 eluting before and 6 eluting after the major peak were observed. The largest impurity (identified as 3-chloro-2-methylpropene) was 2.3% of the major peak area. The cumulative area of the remaining nine impurities was 0.60% of the major peak area. Three additional impurities were observed, one before and two after the major peak, with individual areas less than 0.01% of the major peak area.

Analysis of lot no. 062537 by the system described above indicated a markedly different chromatographic profile than that reported for lot no. KD090967. A major peak and 14 impurities were observed, 7 eluting before and 7 eluting after the major peak. Three of the largest impurities had areas 0.87%, 0.78%, and 0.89% of the major peak area. The peak with a retention time corresponding to 3-chloro-2-methylpropene, observed in lot no. KD090967, had an area 0.50% relative to the major peak area in lot no. 062537. The cumulative area of the impurities in lot no. 062537 was 4.13% as compared with 2.9% observed for lot no. KD090967.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
Lot no. KD090967			
(a) 1	1.9	0.17	0.20
(a) 2	7.1	0.65	0.03
(a) 3	8.0	0.73	0.20
(a) 4	8.8	(b) 0.81	2.30
(a) 5	9.3	0.85	0.06
6	10.9	1.00	100
7	12.2	1.12	0.02
8	14.5	1.33	0.01
9	15.7-16.1	1.44-1.48	0.02
10	17.9	1.64	0.01
11	24.2	2.22	0.02
12	26.2	2.40	0.03
Lot no. 062537			
(a) 1	1.9	0.17	0.23
(a) 2	2.2	0.20	
(a) 3	4.3	0.39	0.29
(a) 4	5.2	0.48	0.87
(a) 5	8.0	0.73	0.09
(a) 6	8.9	(b) 0.82	0.50
(a) 7	9.2	0.84	0.01
8	10.9	1.00	100
9	11.6	1.07	0.02
10	12.2	1.12	0.78
11	19.0	1.74	0.38
12	19.2	1.77	0.89
13	20.5	1.88	0.03
14	21.6	1.98	0.01
15	23.2	2.13	0.03

(a) Column overloading occurred on several peaks eluting before the major peak with both lots of dimethylvinyl chloride. Those peaks eluting before the major peak were quantitated from injections of 1% dimethylvinyl chloride in *o*-dichlorobenzene. Impurity peaks eluting after the major peak were quantitated from injections of the neat sample.
(b) 3-Chloro-2-methylpropene

b. Identification and quantitation of 3-chloro-2-methylpropene

Identification by gas chromatography/electron impact mass spectrometry

Instrument: Varian MAT CH4B mass spectrometer interfaced via a single-stage glass jet separator to a Varian 3700 gas chromatograph. Data processed by an Incos 2300 data system.
Column: Carbopack C/0.1% SP1000, 1.8 m × 2 mm ID, glass
Oven temperature program: 50° C for 5 min, then 50° to 210° C at 10° C/min
Inlet temperature: 180° C
Transfer temperature: 240° C
Separator temperature: 230° C
Electron energy: 70 eV
Trap current: 40 μA
Accelerator voltage: 3,000 V
Resolution: 1000
Scan range: 16-220 amu
Scan times (sec): Up: 1.75 Top: 0.10
Down: 0.75 Bottom: 0.40

Results: Reconstructed ion chromatogram--One major peak and two impurity peaks were observed.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak
1	1.20	0.12
2	7.05	0.72
3	9.85	1.0

Peak no. 1 spectrum--A spectrum obtained for peak no. 1 was consistent with the expected fragmentation and with a literature spectrum of acetone (Eight Peak Index, 1970).

Spectrum Obtained from Peak No. 1		Literature Spectrum of Acetone	
m/e	Relative Abundance (percent of m/e 43)	m/e	Relative Abundance (percent of m/e 43)
43	100	43	100
58	47	58	33
44	23	15	20
42	6	42	6
29	5	28	5
27	4	27	4
38	3	26	3
39	3	29	3
36	3		

Peak no. 2 spectrum--A spectrum obtained from peak no. 2 was consistent with the expected fragmentation pattern and with a literature spectrum of 3-chloro-2-methylpropene (Eight Peak Index, 1970).

Spectrum Obtained from Peak No. 2		Literature Spectrum of 3-Chloro-2-methylpropene	
m/e	Relative Abundance (percent of m/e 55)	m/e	Relative Abundance (percent of m/e 55)
55	100	55	100
39	69	39	69
90	49	27	38
41	48	90	33
29	41	29	31
54	35	54	28
27	33	53	23
53	19	41	23
44	16		
36	15		
70	15		
92	15		
75	13		
38	11		

Peak no. 3 spectrum--A spectrum obtained from peak no. 3, the major peak in the reconstructed ion chromatogram, was consistent with the fragmentation pattern expected of dimethylvinyl chloride.

Spectrum Obtained from Peak No. 3

m/e	Relative Abundance (percent of m/e 55)
55	100
90	66
39	50
53	26
54	23
27	22
92	21
29	20
75	19
41	18

c. **Quantitation by gas chromatography:** 3-chloro-2-methylpropene in lot no. KD090967 was quantitated against standards of dimethylvinyl chloride

Instrument: Varian 3700
Detector: Flame ionization
Carrier gas: Nitrogen, 70 ml/min
Column: 80/100 Carbopack C/0.1% SP1000, 1.8 m × 4 mm ID, glass
Inlet temperature: 180° C
Detector temperature: 250° C
Oven temperature program: 50° C for 5 min, then 50° C to 250° C at 10° C/min
Sample injected: Neat liquid (3 µl) and 1% and 0.5% solutions in methylene chloride to quantitate impurities and check detector linearity

Results: 2.48% ± 0.08 (δ)% (v/v) 3-chloro-2-methylpropene

The peak identified as acetone in the mass spectrometry section was not quantitated. The relative area of this impurity was 0.20% of the major peak area as obtained with the same gas chromatographic system.

7. **Conclusions:** The results of the elemental analysis for carbon, hydrogen, and chlorine agreed with theoretical values. Water content by Karl Fischer titration was 0.005% ± 0.002(δ)%. Neutralization of acidic components (assumed to be hydrochloric acid) indicated 419 ± 18(δ) ppm. One gas chromatographic system (20% SP2100/0.1% Carbowax 1500) resolved a major peak and 14 impurities, the largest impurity having an area of 0.16% of the major peak area. The remaining 13 impurities totaled 0.40% relative to the major peak. A second gas chromatographic system (10% Carbowax 20M-TPA) resolved a major peak and nine impurities, all eluting after the major peak. The largest impurity (2.88%) was identified as 3-chloro-2-methylpropene with standards and spiking solutions. The combined area of the remaining eight impurities was 0.54% of the major peak area. A third gas chromatographic system (80/100 Carbopack C/0.1% SP1000) resolved a major peak and 11 impurities, the largest of which had an area of 2.30% of the major peak area. The remaining 10 impurities had a combined area of 0.60% of the major peak area. When lot no. 062537 was analyzed on this system, a major peak and 14 impurities were observed. Three of the larger impurities had areas of 0.87%, 0.78%, and 0.89% of the major peak.

The impurity with a retention time corresponding to the 2.30% impurity in lot no. KD090967 was at a concentration of 0.5% in lot no. 062537. The cumulative area of all impurities in lot no. 062537 was 4.13%, as compared with 2.9% in lot no. KD090967. Two impurities and the major component were identified by gas chromatography (80/100 Carbopack C/0.1% SP1000)/mass spectrometry. The first impurity, acetone, was not quantitated against standards, as its relative area was only 0.20% of the major peak area. The second impurity, 3-chloro-2-methylpropene (2.3% of the major peak area), was quantitated against standards and found to be present in the sample at a concentration of 2.48% ± 0.08% (v/v). The infrared, ultraviolet/visible, nuclear magnetic resonance, and mass spectral data were consistent with the structure of dimethylvinyl chloride.

	Determined	Literature Values
C. Lot no. 1103BH		
1. Physical properties		
Appearance:	Clear, amber liquid	
2. Spectral data		
a. Infrared		
Instrument:	Perkin-Elmer 283	
Cell:	Thin film between silver chloride windows	
Results:	See Figure 9	Consistent with structure and literature reference (Aldrich, 1975)
b. Ultraviolet/visible		
Instrument:	Cary 219	
Solvent:	Hexane	
Results:	There was no absorbance observed in the visible region (800-350 nm) with a 1% solution in hexane.	No literature reference found. Spectrum consistent with structure.

λ_{max} (nm)	ε
275	~3.94

c. Nuclear magnetic resonance		
Instrument:	Varian 360-A	
Solvent:	Neat liquid containing tetramethylsilane as internal standard	
Assignments:	See Figure 10	Consistent with structure and literature reference (Aldrich, 1974)

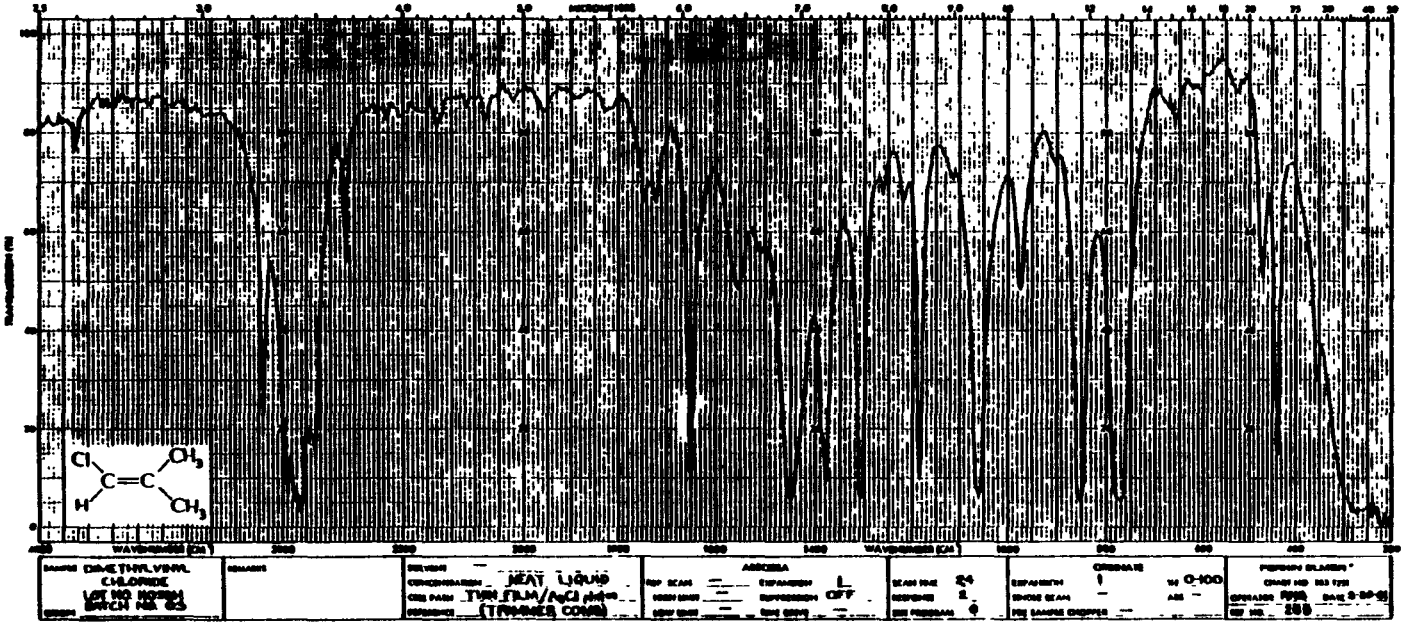


FIGURE 9. INFRARED ABSORPTION SPECTRUM OF DIMETHYLVINYL CHLORIDE (LOT NO. 1103BH)

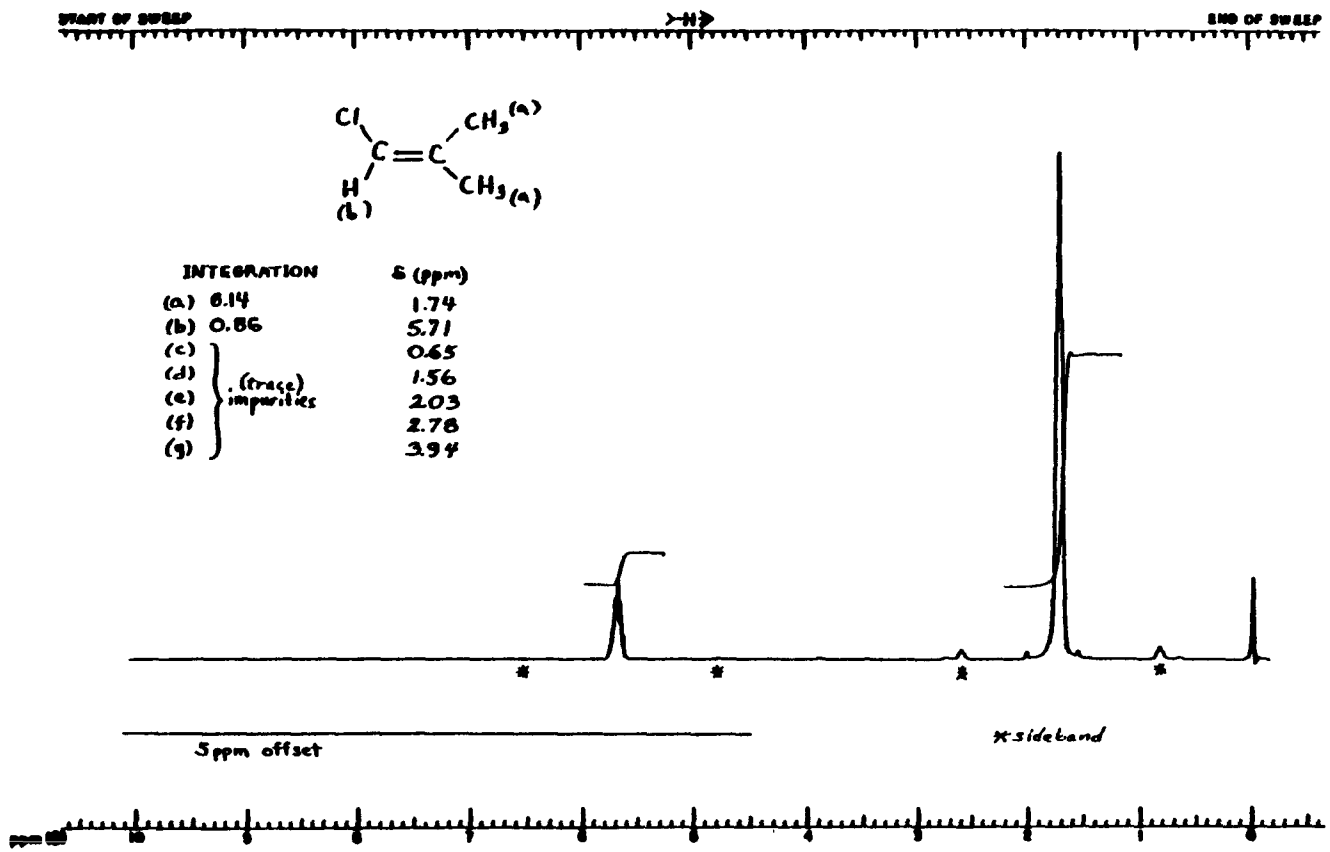


FIGURE 10. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF DIMETHYLVINYL CHLORIDE (LOT NO. 1103BH)

Chemical shift (δ):	a	m,	1.74
	b	m,	5.71
	c	impurity,	0.65
	d	impurity,	1.56
	e	impurity,	2.03
	f	impurity,	2.78
	g	impurity,	3.94
Integration ratios:	a	6.14	
	b	0.86	
	c-g	impurities	

3. **Water analysis (Karl Fischer):** ≤0.01%

4. **Titration of acidic components:** The sample was diluted with 95% ethanol that had been pretitrated to the phenolphthalein endpoint. Titration was performed under nitrogen with 0.01 N sodium hydroxide, back to the phenolphthalein endpoint.

   844 ± 16(δ) ppm (as hydrochloric acid)

5. **Elemental analysis**

Element	C	H	Cl
Theory (T)	53.06	7.79	39.15
Determined (D)	53.15	7.43	39.37
	52.91	7.75	39.47
Percent D/T	99.94	97.43	100.7

6. **Gas chromatography**

   a. **Impurity detection**

   Instrument: Varian 3700
   Detector: Flame ionization
   Carrier gas: Nitrogen, 70 ml/min

   System 1

   Column: 80/100 Carbopack C/0.1% SP1000
   Inlet temperature: 180° C
   Detector temperature: 250° C
   Oven temperature program: 50° C for 5 min, then 50° C to 210° C at 10° C/min
   Sample injected: Neat liquid (3 µl), and 1% and 0.5% solutions of dimethylvinyl chloride in *o*-dichlorobenzene to quantitate impurities and check detector linearity

Results: A major peak and nine impurities were observed, six eluting before and three eluting after the major peak. Two of the largest impurities had areas of 0.30% and 0.76% of the major peak area. The largest impurity (0.76%) was identified as 3-chloro-2-methylpropene. The combined area of the remaining seven impurities was 0.65% of the major peak area. Two additional impurities were observed, one before and one after the major peak, with individual areas less than 0.01% of the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	1.9	0.17 }	0.42
2	2.2	0.20 }	
3	5.2	0.47	0.09
4	6.8-7.6	0.61-0.68	0.02
5	8.0	0.72	0.30
6	8.8	0.79	0.76
7	11.1	1.00	100
8	11.6	1.05	0.03
9	12.1	1.09	0.08
10	14.8-15.2	1.33-1.37	0.01

System 2

Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW), 1.8 m × 4 mm ID, glass
Inlet temperature: 200° C
Detector temperature: 270° C
Oven temperature program: 50° C for 5 min, then 50° C to 200° C at 10° C/min
Sample injected: Neat liquid (4 µl) and 1% and 0.5% solutions of dimethylvinyl chloride in *o*-dichlorobenzene to quantitate impurities and check detector linearity

Results: A major peak and eight impurities were observed, one before and seven after the major peak. The relative areas of the two larger impurities were 0.72% and 0.32%. The impurity with a retention time of 1.81 minutes (peak no. 3) was identified as 3-chloro-2-methylpropene (Section I.B.6.b.) The remaining six impurities had a combined area of 0.40% of the major peak. One impurity with a relative area less than 0.01% was observed eluting before the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	0.63	0.53	0.10
2	1.18	1.00	100
3	1.81	1.53	0.72
4	2.83	2.40	0.32
5	3.74	3.17	0.15
6	4.80	4.07	0.06
7	9.61	8.13	0.05
8	10.39	8.80	0.02
9	15.20	12.87	0.02

b. **Quantitation of 3-chloro-2-methylpropene:** 3-Chloro-2-methylpropene (retention time 8.8 minutes) was identified by retention time and quantitated against standards with the system described in Section I.C.6.a.

The concentration of this impurity was determined to be 0.75% ± 0.02(δ)%.

7. **Conclusions:** Cumulative data indicated a purity of approximately 98%. The results of the elemental analysis for carbon, hydrogen, and chlorine agreed with the theoretical values. Water content by Karl Fischer titration was equal to or less than 0.01%. Titration indicated 844 ± 16(δ) ppm acidic components, calculated as hydrochloric acid. One gas chromatographic system resolved a major peak and nine impurity peaks. The two largest peaks had areas of 0.30% and 0.76% relative to that of the major peak. The combined relative area for the remaining impurities was 0.65%. A second gas chromatographic system resolved a major peak and eight impurity peaks. The two largest peaks had relative areas of 0.72% and 0.32%; the combined relative area of the other peaks was 0.40%. The concentration of 3-chloro-2-methylpropene was found to be 0.75% ± 0.02(δ)% quantitated by gas chromatography.

D. Identification and quantitation of impurities in dimethylvinyl chloride

The purpose of this work was to identify and quantitate impurities, including epichlorohydrin, in two samples of dimethylvinyl chloride (lot nos. 062537 and 1103BH).

The two samples of dimethylvinyl chloride were analyzed by gas chromatography/mass spectrometry. The impurities were quantitated by gas chromatography with flame ionization detection. The identity and concentration of impurities with concentrations greater than or equal to 0.1% (w/w) are reported.

1. **Analytical methods**

a. **Identification by gas chromatography/mass spectrometry**

Gas chromatography

Instrument: Varian 3700
Column: 1% SP1000 on 60/80 Carbopack B, 2.4 m × 2 mm ID, glass
Injector temperature: 200° C
Carrier Gas: Helium, 30 ml/min
Oven temperature program: 40° C for 4 min, then 220° C at 10° C/min
Volume Injected: 1 µl
Samples injected: dimethylvinyl chloride (lot nos. 062537 and 1103BH) neat liquid and 10% (v/v) solutions in methanol; available impurity standards (0.4% v/v) in methanol

Mass spectrometry

Instrument: Finnigan MAT CH4-B (interfaced to the gas chromatograph with a single-stage glass jet separator)
Temperatures:
Transfer line: 250° C
Helium separator: 250° C
Ion source: 220° C
Electron energy: 70 eV
Trap current: 40μA
Accelerating voltage: 3,000 V
Resolution: 400
Scan range: 10 to 300 amu
Scan rate: 3 sec/scan
Scan times (sec): Up - 1.75, Top - 0.05, Down - 0.70, Bottom - 0.50
Data system: Incos 2400

b. Quantitation by gas chromatography/flame ionization detection

The gas chromatographic system described in Section I.D.1.a was used for impurity quantitation with the following changes:

Detector: Flame ionization
Detector temperature: 250° C
Carrier gas: Nitrogen, 30 ml/min
Volume injected: ~ 1.5 μl
Solutions injected: 5% (v/v) solutions of dimethylvinyl chloride (lot nos. 062537 and 1103BH) in methanol, standards, in methanol, at concentrations bracketing those observed for impurities and containing *n*-butanol internal standard

c. Epichlorohydrin analysis by gas chromatography/flame ionization detection

The following gas chromatography/flame ionization detection system was developed to confirm the results of gas chromatographic/mass spectrometric analysis of epichlorohydrin.

The gas chromatographic system described above (Section I.D.2) was used with the following changes.

Column: 20% SP2401/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
Column temperature program: 40° C, isothermal
Carrier gas: Nitrogen, 70 ml/min
Volume injected: ~2.5 μl
Solutions injected: 10% (v/v) solutions of dimethylvinyl chloride (lot nos. 062537 and 1103BH) in methanol; 0.005% (v/v) solutions of epichlorohydrin in methanol

2. Results

a. Dimethylvinyl chloride: lot no. 062537

The reconstructed ion current (RIC) and gas chromatograms obtained for this lot indicated that the sample contained numerous (≥ 19) impurities (Figure 11). The six impurity peaks estimated to be present at concentrations greater than or equal to 0.1% (w/w) were identified.

The identification and quantitation of these six impurity peaks, as well as analyses for epichlorohydrin, are discussed below.

Impurity peak no. 1

Peak no. 1 in the RIC was composed of two coeluting impurities: acetone and methylpropene. The identity of acetone was confirmed by comparison of mass spectral and retention time data with an authentic standard and a reference spectrum (EPA/NIH, 1978). The coeluting impurity, methylpropene, was tentatively identified by comparing its mass spectrum to a literature reference (EPA/NIH, 1978).

When quantitated against an acetone standard, the combined concentration of these two impurities was estimated at 0.12% ± 0.01(s)% (w/w).

Impurity peak no. 2: *t*-butanol (2-methyl-2-propanol)

Impurity peak no. 2 was identified as *t*-butanol on the basis of mass spectral and retention time coincidence to an authentic standard and a literature reference (EPA/NIH, 1978). When quantitated against a *t*-butanol standard, this impurity was determined to be present at a concentration of 0.16% ± 0.01(s)% (w/w).

Impurity peak no. 3: *t*-butyl chloride (2-chloro-2-methylpropane)

Impurity peak no. 3 was identified as *t*-butyl chloride (2-chloro-2-methylpropane). The identity of this impurity was confirmed by comparison of the mass spectral and retention time coincidence with an authentic standard and a reference spectrum (EPA/NIH, 1978). When quantitated against a *t*-butyl chloride standard, this impurity was determined to be present at a concentration of 0.91 ± 0.02(s)% (w/w).

An impurity, tentatively identified as chloroform from a comparison of its mass spectrum and a reference spectrum (EPA/NIH, 1978), was observed to coelute with the *t*-butyl chloride impurity. This impurity was estimated to be present at a concentration of less than 0.1% (w/w), on the basis of gas chromatographic/mass spectrometric data.

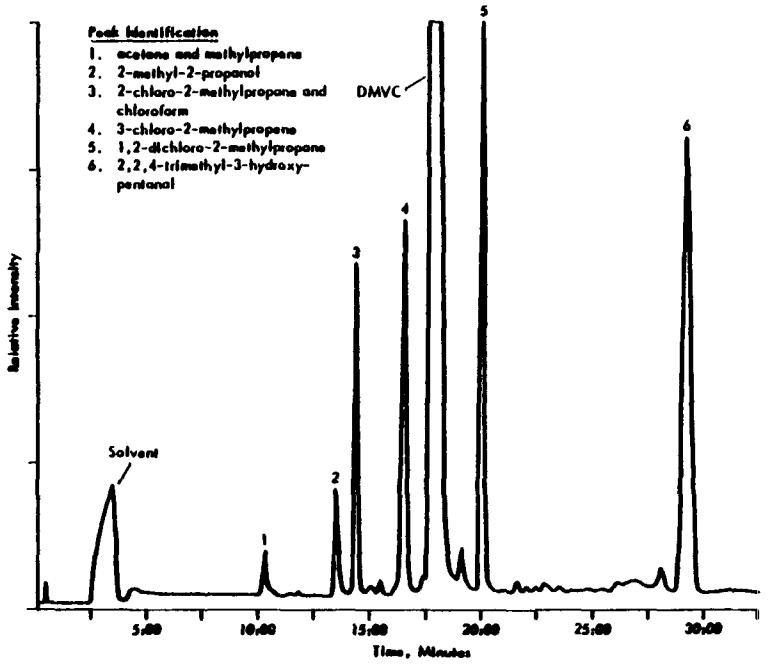


FIGURE 11. RECONSTRUCTED ION CURRENT CHROMATOGRAM OF DIMETHYLVINYL CHLORIDE (LOT NO. 062537)

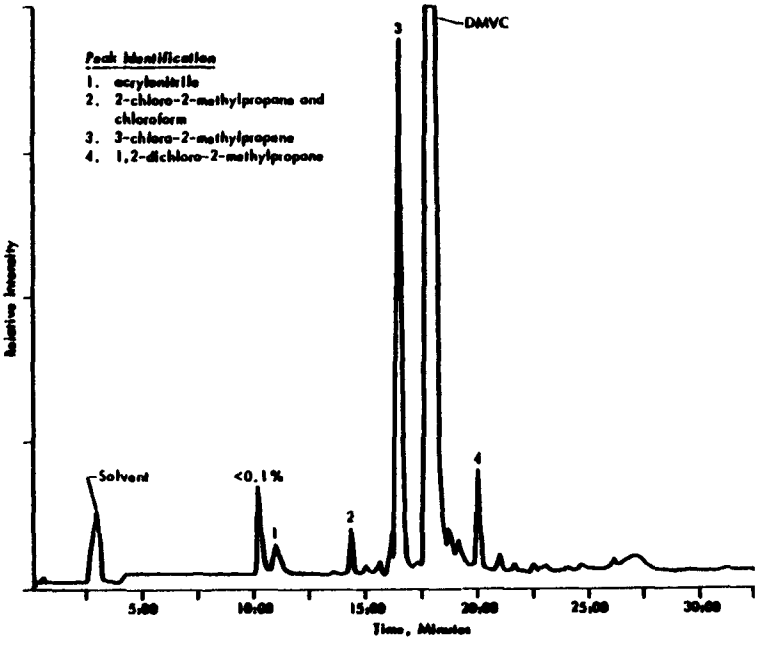


FIGURE 12. RECONSTRUCTED ION CURRENT CHROMATOGRAM OF DIMETHYLVINYL CHLORIDE (LOT NO. 1103BH)

Impurity peak no. 4: 3-chloro-2-methylpropene

Impurity peak no. 4 was identified as 3-chloro-2-methylpropene. The identity of this impurity was confirmed by comparison of the mass spectral and retention time data with that of a concurrently analyzed standard and a reference spectrum (EPA/NIH, 1978). Quantitation of this impurity against a 3-chloro-2-methylpropene standard indicated that 3-chloro-2-methylpropene was present in the sample at a concentration of 0.68% ± 0.01(s)% (w/w).

Impurity peak no. 5: 1,2-dichloro-2-methylpropane

The retention time as mass spectrum of impurity no. 5 was consistent with that observed for a concurrently analyzed 1,2-dichloro-2-methylpropane standard. The reference spectrum (EPA/NIH, 1978) did not match either the impurity spectrum or a spectrum of the standard. However, infrared and nuclear magnetic resonance spectra for the standard were consistent with the structure of 1,2-dichloro-2-methylpropane and agreed with literature spectra (Sadtler Standard Spectra) for this compound.

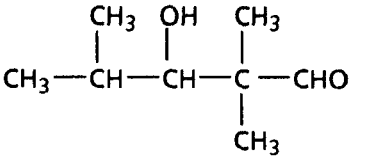
Diagnostic ions in the spectrum of the impurity and standard were as follows:

	Intensity (percent of base peak)	
m/z	Impurity	Standard
126 (M^+)	(not observed)	
111 (M^+-CH_3)	2.4	2.3
91 (M^+-Cl)	8.8	8.5
79	31.3	30.3
77 (M^+-CH_2Cl)	100	100
55	17.2	18.6
49	5.0	5.2
41	25.4	27.3
39	12.6	13.7

On the basis of quantitation against a 1,2-dichloro-2-methylpropane standard, this impurity was determined to be present at a concentration of 1.04% ± 0.08(s)% (w/w). The presence of this impurity in the sample can be rationalized as arising from the addition of hydrochloric acid (present as a precursor during synthesis or as a trace impurity) to the double bond of dimethylvinyl chloride.

Impurity peak no. 6: 2,2,4-trimethyl-3-hydroxypentanal

The mass spectrum of impurity no. 6 was consistent with 2,2,4-trimethyl-3-hydroxypentanal, an aldol condensation product of isobutyraldehyde. The presence of this impurity can be rationalized from the probable synthetic route for dimethylvinyl chloride (Merck, 1983) (e.g., reaction of isobutyraldehyde with hydrochloric acid).



2,2,4-TRIMETHYL-3-HYDROXYPENTANAL

No standard was found for comparative analysis. No literature reference spectrum was found.

Diagnostic ions in the spectrum for this impurity were as follows:

m/z	Intensity (percent of base peak)
144 $(M)^+$	(not observed)
143 $(M-H)^+$	1.5
129 $(M-CH_3)^+$	1.0
111 $(M-CH_3-H_2O)^+$	0.5
101 $(M-C_3H_7)^+$	100
86 $(M-C_3H_7-CH_3)^+$	4.8
73 $(C_4H_9O)^+$	60.5
71 $(C_4H_7O)^+$	12.8
56 $(M-C_4H_9O-CH_2O)^+$	49.6
55 $(M-C_4H_9O-H_2O)^+$	74.9

This impurity was quantitated at 0.92% ± 0.03(s)% (w/w) against a 3-chloro-2-methylpropene standard by gas chromatography/flame ionization detection.

Epichlorohydrin determination

Epichlorohydrin was not observed in the gas chromatographic/mass spectrometry analysis of lot no. 062537. Due to the presence of numerous impurities, the detection limit for the chromatographic/mass spectrometric analysis was 0.05% (w/w). When the dimethylvinyl chloride was analyzed by gas chromatography/flame ionization detection by the instrument parameters described in Section II.D.3., the detection limit for epichlorohydrin in dimethylvinyl chloride, lot no. 062537 was 0.03% (w/w).

Based on these results, lot no. 062537 does not contain epichlorohydrin at a concentration of greater than or equal to 0.03% (w/w).

b. Dimethylvinyl chloride: lot no. 1103BH

The reconstructed ion current (Figure 12) and gas chromatograms obtained from analysis of this lot indicated that the sample contained numerous ($\geq$ 12) impurities. Four of these impurity peaks were determined to be present at concentrations greater than or equal to 0.1% (w/w). The identification and quantitation of these four impurity peaks, as well as analysis for epichlorohydrin, are discussed below.

Impurity peak no. 1: acrylonitrile

The retention time and mass spectrum of peak no. 1 were consistent with those of a concurrently analyzed acrylonitrile standard. The mass spectra of the impurity and the standard agreed with a reference spectrum (EPA/NIH, 1978). This impurity was quantitated at 0.14% $\pm$ 0.01(s)% (w/w) against an acrylonitrile standard.

Impurity peak no. 2: *t*-butyl chloride (2-chloro-2-methylpropane)

The retention time and mass spectrum of peak no. 2 were consistent with those of a concurrently analyzed *t*-butyl chloride standard and with a reference spectrum (EPA/NIH, 1978). A coeluting impurity, tentatively identified as chloroform, was also observed. Chloroform was also tentatively detected in lot no. 062537. The cumulative concentration of the *t*-butyl chloride and chloroform impurities was quantitated at 0.10% $\pm$ 0.00(s)% (w/w) against a *t*-butyl chloride standard.

Impurity peak no. 3: 3-chloro-2-methylpropene

The retention time and mass spectrum of peak no. 3 were consistent with those observed for a concurrently analyzed 3-chloro-2-methylpropene standard. The mass spectra of the impurity and the standard were consistent with a reference spectrum (EPA/NIH, 1978) for 3-chloro-2-methylpropene. Quantitation of this impurity versus a 3-chloro-2-methylpropene standard indicated it was present in the sample at a concentration of 1.18% $\pm$ 0.02(s)% (w/w).

Impurity peak no. 4: 1,2-dichloro-2-methylpropane

The retention time and mass spectrum of peak no. 4 were consistent with those observed for a concurrently analyzed 1,2-dichloro-2-methylpropane standard. As discussed above for lot no. 062537, the EPA/NIH literature spectrum did not match that of the impurity or the spectrum of the standard. The fragmentation observed for this impurity agreed with that observed for the 1,2-dichloro-2-methylpropane standard and the impurity observed in lot no. 062537. This impurity was quantitated at 0.10% $\pm$ 0.01(s)% (w/w) versus a 1,2-dichloro-2-methylpropane standard.

Epichlorohydrin determination

No evidence for the presence of epichlorohydrin was observed in this sample of dimethylvinyl chloride. Due to the presence of numerous impurities, the detection limit for epichlorohydrin was 0.02% (w/w) by gas chromatography/mass spectrometry.

Similar analyses could not be performed with gas chromatography/flame ionization detection (Section II.D.3) because of the presence of impurities coeluting with epichlorohydrin.

Based on these results, lot no. 1103BH did not contain epichlorohydrin at levels greater than or equal to 0.02% (w/w).

3. Summary of results

Analysis of lot no. 062537 indicated six impurity peaks with concentrations greater than 0.1% of the total weight. These six peaks represent eight compounds. Five of these impurities were identified by comparison of the retention times and mass spectra with authentic standards. These impurities were acetone, *t*-butanol, *t*-butyl chloride, 3-chloro-2-methylpropene, and 1,2-dichloro-2-methylpropane. Tentative identification of three additional impurities was based on mass spectral interpretation and consideration of the route of synthesis. These impurities were chloroform, methylpropene, and 2,2,4-trimethyl-3-hydroxypentanal, an aldol condensation product of isobutyraldehyde.

Analysis of lot no. 1103BH indicated four impurity peaks with concentrations greater than 0.1% of the total weight. These four peaks represent five compounds. Four of these impurities were identified by comparison of the retention times and mass spectra with authentic standards. These impurities were acrylonitrile, *t*-butyl chloride, 3-chloro-2-methylpropene, and 1,2-dichloro-2-methylpropane. The fifth impurity, tentatively identified as chloroform, coeluted with *t*-butyl chloride.

The results of the identification and quantitation of impurities in these lots of dimethylvinyl chloride are presented in Table H1.

Epichlorohydrin was not detected in either lot of dimethylvinyl chloride. The estimated detection limits for epichlorohydrin were: 0.03%, w/w (gas chromatography/flame ionization detection) in lot no. 062537; and 0.02%, w/w (gas chromatography/mass spectrometry) in lot no. 1103BH.

TABLE H1. IDENTITY AND CONCENTRATION OF IMPURITIES OBSERVED IN DIMETHYLVINYL CHLORIDE (a)

Peak No.	Impurity	Concentration (percent, w/w)
Lot no. 062537 (b)		
1	Acetone Methylpropene	(c) 0.12 ± 0.01(s)
2	*t*-Butanol	0.16 ± 0.01(s)
3	*t*-Butyl chloride Chloroform	0.91 ± 0.02(s)
4	3-Chloro-2-methylpropene	0.68 ± 0.01(s)
5	1,2-Dichloro-2-methylpropane	1.04 ± 0.08(s)
6	2,2,4-Trimethyl-3-hydroxypentanal	(d) 0.92 ± 0.03(s)
Lot no. 1103BH (e)		
1	Acrylonitrile	0.14 ± 0.01(s)
2	*t*-Butyl chloride Chloroform	0.10 ± 0.00(s)
3	3-Chloro-2-methylpropene	1.18 ± 0.02(s)
4	1,2-Dichloro-2-methylpropane	0.10 ± 0.01(s)

(a) Detected at concentrations greater than 0.1% (w/w)
(b) Figure 11
(c) Quantitated by comparison to an acetone standard
(d) Quantitated by comparison to a 3-chloro-2-methylpropene standard
(e) Figure 12

II. Stability of Dimethylvinyl Chloride Lot No. 062537 Performed by the Analytical Chemistry Laboratory

A. Sample storage: Samples were stored for 2 weeks at −20°, 5°, 25°, or 60° C.

B. Analytical method: Gas chromatography

Instrument: Bendix 2500
Detector: Flame ionization
Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, 4 mm × 1.8 m, glass
Inlet temperature: 100° C
Detector temperature: 28.5° C
Oven temperature: 30° C, isothermal
Carrier gas: Nitrogen, 40 ml/min
Retention time of major component: 2.4 min

C. Results: Six impurities were detected and quantified at the detection level used for this study. The areas of the impurity peaks were identical within the error of the analysis in the −20°, 5°, and 25° C samples. The results for the 60° C samples indicated lower areas for impurities with retention times from 0.34 to 1.37 minutes as compared with the major peak and larger areas for those impurities with retention times greater than three times the major peak. This difference in the 60° C samples was probably due to the volatility of these components (boiling point of the major component, 62° C).

Storage Temperature	Area of the Major Peak Relative to the −20° C Sample
−20° C	100% ± 4%
5° C	100% ± 4%
25° C	100% ± 4%
60° C	99% ± 4%

D. Conclusion: Dimethylvinyl chloride is stable as the bulk chemical when stored for 2 weeks at temperatures up to 25° C. At 60° C, the major component and some impurities are probably volatilized from the container.

III. Stability Study of Dimethylvinyl Chloride at the Study Laboratory

A. Storage conditions: Bulk, 4° C
Reference, −20° C or less

B. Analytical methods

1. **Gas chromatography**

Instrument: Hewlett Packard 5880 or 5840 with 7672A liquid sampler
Detector: Flame ionization
Inlet temperature: 200°-270° C
Detector temperature: 200°-270° C
Carrier gas: Nitrogen, 20 or 40 ml/min
Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, 1.8 m × 2 mm ID, silanized glass
Oven temperature: 50° C for 5 min; 50°-200° C at 10° C/min; 200° C for 0, 5, or 10 min
Sample injection: 1 or 3 µl neat liquid; 1.0% and 0.5% dimethylvinyl chloride in *o*-dichlorobenzene to quantitate the major peak and to check for column and/or detector overloading

2. **Infrared spectroscopy**

Instrument: Perkin Elmer Model 398, 457, or 283B
Cell: Neat liquid between potassium bromide or sodium chloride plates

C. Results

1. **Gas chromatography**

Date of Analysis	Lot No.	Percent Purity				Number of Impurities			
		Bulk		Reference		Bulk		Reference	
		Neat	1% Solution	Neat	1% Solution	Neat	1% Solution	Neat	1% Solution
10/07/78 (a)	062537	96.3	--	95.8	--	14	--	14	--
10/07/78		99.1	--	99.2	--	13	--	15	--
06/13/78 (a)		--	--	95.7	--	--	--	8	--
07/09/79		94.0	--	94.3	--	11	--	12	--
12/18/79 (b)		--	--	--	96.6	--	--	--	3
05/08/80 (b)		--	96.8	--	96.4	--	4	--	3
09/09/80 (b)		--	96.7	--	96.7	--	7	--	7
01/09/81		89.7	94.8	95.6	97.0	53	10	43	5
01/09/81	KD090967	98.9	99.6	--	--	39	5	--	--
03/05/81	1103BH	99.0	99.7	--	--	14	2	--	--
07/08/81		98.5	99.5	98.8	99.6	25	--	19	--
10/06/81		98.4	99.5	97.9	99.5	28	--	28	--
02/24/82		98.4	99.8	98.4	99.8	19	--	21	--
06/11/82		98.9	99.5	98.5	99.4	14	--	26	--
10/25/82		98.8	99.3	98.4	99.4	13	--	22	--
02/25/83		98.1	99.5	98.8	99.5	37	--	17	--

(a) Column used: 10% Carbowax 20M-TPA Supelcoport W(AW), 1.8 m × 2 mm ID, glass
(b) Values for 1% solution alone reported due to overloading of analytical column during analysis of neat material

2. **Infrared spectroscopy:** All bulk spectra were comparable to the reference spectra and with the spectra supplied by the analytical chemistry laboratory.

APPENDIX I

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX I. PREPARATION AND CHARACTERIZATION

I. Room Temperature Stability Study Conducted at the Analytical Chemistry Laboratory (Lot no. 062537)

A. Sample preparation and storage: Two milliliters of corn oil was transferred into an 8.5-ml septum vial, which was then sealed and weighed. Approximately 120 mg of dimethylvinyl chloride was then injected with a microliter syringe, and the vial was reweighed. The sample was agitated on a vortex mixer for 30 seconds and then stored at room temperature in the dark for the appropriate period of time. Solutions (6.0% w/v) of dimethylvinyl chloride in corn oil were prepared in duplicate for storage at 0, 5, 6, and 7 days.

B. Sample extraction and analysis: At the end of each storage period, the appropriate samples were extracted with 2 ml of absolute methanol that was injected into the vials with a 2-ml syringe. The two-phase mixtures were thoroughly agitated on a vortex mixer for 1 minute and placed in an ultrasonic vibratory bath for 1 minute. Aliquots for analysis were removed directly from the upper (methanol) layer of each sample by microliter syringe and analyzed by the gas chromatographic system described below.

Instrument: Bendix 2500
Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, 4 m × 1.8 mm, glass
Detection: Flame ionization
Inlet temperature: 100° C
Oven temperature: 30° C, isothermal
Detector temperature: 28.5° C
Carrier gas: Nitrogen, 40 ml/min
Retention time: 2.4 min

C. Results

Storage Time (days)	Average Percent Chemical Found in Chemical/Vehicle Mixture (a, b)
0	6.0 ± 0.5
5	4.8 ± 0.4
6	5.5 ± 0.4
7	5.4 ± 0.4

(a) Corrected for a spiked recovery of 83.0% ± 9.0%.
(b) Target concentration of chemical in corn oil, 6.04% ± 0.04%.

D. Conclusion: Dimethylvinyl chloride mixed with corn oil at the 6.0% concentration is stable, within the error limits of this study, when stored in the dark at room temperature (25° C) for 7 days.

II. Stability Study of Dimethylvinyl Chloride in Corn Oil Conducted by the Study Laboratory

A. Methods: Solutions of dimethylvinyl chloride in corn oil were prepared at concentrations of 20 mg/ml and 40 mg/ml and stored at 25° C. Samples were analyzed 5, 20, and 44 days after preparation. The analytical procedure was the same as that described in Appendix J, Section I.

B. Results

Storage Time (days)	Target Concentration (mg/ml)	Actual Concentration (a)	Percent of Target Concentration
5	20	20.4	102.0
20	20	23.8	119.0
44	20	18.5	92.5
5	40	40.6	101.5
20	40	44.5	111.3
44	40	40.0	100.0

(a) Results of duplicate analysis

C. Conclusion: Solutions of dimethylvinyl chloride in corn oil at concentrations of 20 and 40 mg/ml were stable after 44 days' storage at 25° C.

APPENDIX J

METHODS OF ANALYSIS OF DOSE MIXTURES

APPENDIX J. METHODS OF ANALYSIS

I. Study Laboratory

A. Procedure:

1. **Preparation of standard solutions:** An internal standard solution (ISTD) of 1% (v/v) *t*-butanol in methanol was prepared. A stock dimethylvinyl chloride standard solution was prepared by weighing approximately 2.50 g (1.25 g after 3/81) of dimethylvinyl chloride into a 25-ml volumetric flask, brought to final volume with undosed corn oil.

2. **Preparation of calibration standards:** A set of six calibration standards was prepared by adding 100, 200, 400, 600, 800, and 1,000 µl of the stock dimethylvinyl chloride standard solution to six 50-ml capacity centrifuge tubes. The volume of corn oil in each tube was brought to final volume of 1.00 ml with undosed corn oil.

3. **Preparation of gavage samples:** After they were thoroughly shaken, 1.00-ml (SMI pipettor) aliquots of each gavage sample were added to centrifuge tubes in duplicate.

4. **Extraction of samples:** Added to each centrifuge tube was 5.00 ml of ISTD solution. The tubes were then sealed and shaken in a shaker box for 10 minutes at 1,500 rpm. An aliquot of each methanol extract was placed in crimp cap sampler vials for gas chromatographic analysis.

B. Gas chromatographic analysis

Instrument: HP-5880A with 7672 ALS
Column: 100/120 mesh Chromosorb 102 on a 1.8 m × 2mm ID, silanized glass
Detection: Flame ionization
Detector temperature: 275° C
Injector temperature: 225° C
Column Temperature: 150° C, isothermal
Carrier gas: Nitrogen, 40 ml/min

II. Analytical Chemistry Laboratory

A. Preparation of spiked corn oil standards: Two standard solutions of dimethylvinyl chloride in methanol were prepared independently. The solutions were diluted with methanol to make four additional standards. Aliquots (20 ml) of the six standard solutions were pipetted into individual 35-ml septum vials containing 2 g of undosed corn oil to make spiked corn oil standards bracketing the specified concentration range of the referee sample. One 35-ml septum vial containing 2 g of undosed corn oil was treated with 20 ml of methanol for use as a blank. After the vials were sealed with Teflon®-lined septa, the spiked corn oil and the corn oil blank were used in the analysis procedure described below.

B. Preparation of referee sample: Three portions (~ 2 g each) of the referee corn oil sample were transferred to individually tared 35-ml septum vials and weighed to the nearest 0.001 g. Methanol (20 ml) was pipetted into each vial; then the vials were sealed and analyzed immediately by the procedure described below.

C. **Analysis procedure:** Vials containing the samples, standards, and the blank were agitated for 10 seconds on a vortex mixer and then shaken at maximum stroke for 15 minutes on a Burrell Model 75 Wrist-Action® shaker. After the extraction mixtures were centrifuged for 3 minutes, a 5-ml aliquot of the methanol layer from each vial was combined with 5 ml of internal standard solution (heptane in methanol, 1.5 mg/ml). The solutions were thoroughly mixed; then the dimethylvinyl chloride content was determined by the gas chromatographic system described below.

Instrument: Varian 3700 gas chromatograph with autosampler and Varian CDS 111-C integrator
Column: 20% SP-2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, 1.8 m × 4 mm ID, glass, silanized
Detection: Flame ionization
Detector temperature: 150° or 200° C
Inlet temperature: 100° or 150° C
Oven temperature: 50° C isothermal
Carrier gas: Nitrogen, 30 ml/min
Volume of solution injected: 3 µl

The total amount of dimethylvinyl chloride in the referee corn oil samples was computed from the linear regression equations obtained from the standard data.

D. **Quality assurance measures:** The referee corn oil sample was analyzed in triplicate, and the undosed corn oil sample was analyzed once. Individually spiked portions of undosed corn oil (six concentrations bracketing the specified concentration range of the referee sample) were prepared from two independently weighed standards and were used for obtaining standard data. Triplicate injections of each standard and sample were made into the gas chromatograph in a randomized order. All determinations were related to an internal standard incorporated into the sample solutions.

APPENDIX K

RESULTS OF ANALYSIS OF DOSE MIXTURES

TABLE K1. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE (a)

Date Mixed	Concentration (a) of Dimethylvinyl Chloride in Corn Oil for Target Concentration (mg/ml)			
	Mice		Rats	
	10	20	20	40
06/19/80			(b) 24.8	(b) 46.9
06/26/80			21.1	40.4
07/02/80			20.4	40.6
08/14/80			20.4	39.6
10/09/80			19.6	38.7
12/04/80			(b,c) 23.3	(c) 39.4
12/10/80			(b,c) 28.7	(b,c) 54.1
12/16/80			(c) 18.7	(c) 37.5
			(c) 18.6	(d) 34.5
12/23/80				(e) 35.7
12/29/80			20.7	38.3
			21.3	39.8
01/13/81			19.2	(d) 46.2
			21.4	42.5
01/19/81				(e) 42.7
01/29/81			21.6	41.5
03/12/81	9.4	20.2		
03/26/81	10.5	20.9	20.6	41.9
05/21/81	10.9	22.1	22.0	43.3
07/16/81	10.5	21.2	20.8	41.6
09/10/81	9.4	19.3	19.6	37.1
11/05/81	10.8	20.6	21.1	40.2
12/30/81	10.3	22.1	20.6	39.9
02/25/82	(f) 19.4	(f) 41.2	(f) 10.7	(f) 21.0
03/01/82	(d,e) 11.6	(d,e) 23.6	(e) 22.5	(e) 43.6
03/03/82	(g) 11.7	(g) 22.1		
03/05/82	10.7			
04/22/82	(b) 8.8	20.6	19.5	39.9
06/17/82	(d) 12.3	21.8		
06/21/82	(e) 9.7			
08/12/82	(d) 11.6	(d) 22.7		
08/17/82	(e) 9.5	(e) 19.4		
10/07/82	10.8	(d) 23.9		
10/13/82		(e) 22.0		
12/02/82	(d) 13.2	(d) 23.0		
12/09/82	(e) 10.3	(e) 10.3		
12/14/82	10.1			
12/23/82	9.4	19.0		
01/17/83	(h) 10.5	(e) 20.5		
01/27/83	9.9	20.0		
Mean (mg/ml)	10.5	21.2	21.1	41.1
Standard deviation	1.13	1.43	2.26	4.09
Coefficient of variation (percent)	10.8	6.7	10.7	10.0
Range (mg/ml)	8.8-13.2	19.0-23.9	18.6-28.7	34.5-54.1
Number of samples	16	14	21	21

(a) The data presented are the mean of duplicate analysis.
(b) Out of specifications; used in the study.
(c) Used for 3 days only
(d) Out of specifications; not used in studies.
(e) Remix; not included in mean.
(f) Probable labeling error; not used in study or included in the mean.
(g) Remix out of specifications; not used in study or included in the mean.
(h) Remix for referee analysis; not used in studies.

TABLE K2. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF DIMETHYLVINYL CHLORIDE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration	
		Study Laboratory (a)	Referee Laboratory (b)
08/14/80	40	39.6	37.4
03/12/81	10	9.4	9.4
11/05/81	20	20.6	19.4
06/21/82	10	9.7	9.9
12/02/82	20	23.0	17.5
01/17/83	10	10.5	9.7

(a) Results of duplicate analysis
(b) Results of triplicate analysis

APPENDIX L

SENTINEL ANIMAL PROGRAM

APPENDIX L. SENTINEL ANIMAL PROGRAM

I. Methods

Rodents used in the Carcinogenesis Program of the National Toxicology Program are produced in optimally clean facilities to eliminate potential pathogens that may affect study results. The Sentinel Animal Program is part of the periodic monitoring of animal health that occurs during the toxicologic evaluation of chemical compounds. Under this program, the disease state of the rodents is monitored via viral serology on sera from extra (sentinel) animals in the study rooms. These animals are untreated, and these animals and the study animals are both subject to identical environmental conditions. The sentinel animals come from the same production source and weanling groups as the animals used for the studies of chemical compounds.

Fifteen $B6C3F_1$ mice and 15 F344/N rats of each sex are selected at the time of randomization and allocation of the animals to the various study groups. Five animals of each designated sentinel group are killed at 6, 12, and 18 months on study. Data from animals surviving 24 months are collected from 5/50 randomly selected vehicle control animals of each sex and species. The blood from each animal is collected and clotted, and the serum is separated. The serum is cooled on ice and shipped to Microbiological Associates' Comprehensive Animal Diagnostic Service for determination of the viral antibody titers. The following tests are performed:

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai MHV (mouse hepatitis virus)	MHV (mouse hepatitis virus) (12 mo restart)
Rats	PVM KRV (Kilham rat virus) H-1 (Toolan's H-1 virus)	RCV (rat coronavirus) Sendai	

II. Results

No positive serologic reactions were seen in rats or mice at any of the intervals tested.

APPENDIX M

INGREDIENTS, NUTRIENT COMPOSITION, AND CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Pelleted Diet: April 1980 to January 1983

(Manufactured by Zeigler Bros., Inc., Gardners, PA)

TABLE M1. INGREDIENTS OF NIH 07 RAT AND MOUSE RATION (a)

Ingredients (b)	Percent by Weight
Ground #2 yellow shelled corn	24.50
Ground hard winter wheat	23.00
Soybean meal (49% protein)	12.00
Fish meal (60% protein)	10.00
Wheat middlings	10.00
Dried skim milk	5.00
Alfalfa meal (dehydrated, 17% protein)	4.00
Corn gluten meal (60% protein)	3.00
Soy oil	2.50
Brewer's dried yeast	2.00
Dry molasses	1.50
Dicalcium phosphate	1.25
Ground limestone	0.50
Salt	0.50
Premixes (vitamin and mineral)	0.25

(a) NIH, 1978; NCI, 1976
(b) Ingredients should be ground to pass through a U.S. Standard Screen No. 16 before being mixed.

TABLE M2. VITAMINS AND MINERALS IN NIH 07 RAT AND MOUSE RATION (a)

	Amount	Source
Vitamins		
A	5,500,000 IU	Stabilized vitamin A palmitate or acetate
D_3	4,600,000 IU	D-activated animal sterol
K_3	2.8 g	Menadione activity
d-α-Tocopheryl acetate	20,000 IU	
Choline	560.0 g	Choline chloride
Folic acid	2.2 g	
Niacin	30.0 g	
d-Pantothenic acid	18.0 g	*d*-Calcium pantothenate
Riboflavin	3.4 g	
Thiamine	10.0 g	Thiamine mononitrate
B_{12}	4,000 µg	
Pyridoxine	1.7 g	Pyridoxine hydrochloride
Biotin	140.0 mg	*d*-Biotin
Minerals		
Iron	120.0 g	Iron sulfate
Manganese	60.0 g	Manganous oxide
Zinc	16.0 g	Zinc oxide
Copper	4.0 g	Copper sulfate
Iodine	1.4 g	Calcium iodate
Cobalt	0.4 g	Cobalt carbonate

(a) Per ton (2,000 lb) of finished product

TABLE M3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION (a)

Nutrient	Mean	Range	No. of Samples
Crude protein (percent by weight)	23.95 ± 0.83	22.7-26.1	33
Crude fat (percent by weight)	4.94 ± 0.43	4.1-5.7	33
Crude fiber (percent by weight)	3.28 ± 0.44	1.4-4.3	33
Ash (percent by weight)	6.57 ± 0.47	5.8-7.4	33
Essential Amino Acids (percent of total diet)			
Arginine	1.260	1.21-1.31	2
Cystine	0.395	0.39-0.40	2
Glycine	1.175	1.15-1.20	2
Histidine	0.553	0.530-0.576	2
Isoleucine	0.908	0.881-0.934	2
Leucine	1.905	1.85-1.96	2
Lysine	1.250	1.20-1.30	2
Methionine	0.310	0.306-0.314	2
Phenylalanine	0.967	0.960-0.974	2
Threonine	0.834	0.827-0.840	2
Tryptophan	0.175	0.171-0.178	2
Tyrosine	0.587	0.566-0.607	2
Valine	1.085	1.05-1.12	2
Essential Fatty Acids (percent of total diet)			
Linoleic	2.37		1
Linolenic	0.308		1
Arachidonic	0.008		1
Vitamins			
Vitamin A (IU/kg)	10,633 ± 2,948	7,200-17,000	33
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	16.2 ± 4.0	7.3-27.0	(b) 32
Riboflavin (ppm)	6.9	6.1-7.4	2
Niacin (ppm)	75	65-85	2
Pantothenic acid (ppm)	30.2	29.8-30.5	2
Pyridoxine (ppm)	7.2	5.6-8.8	2
Folic acid (ppm)	2.1	1.8-2.4	2
Biotin (ppm)	0.24	0.21-0.27	2
Vitamin B_{12} (ppb)	12.8	10.6-15.0	2
Choline (ppm)	3,315	3,200-3,430	2
Minerals			
Calcium (percent)	1.29 ± 0.19	0.81-1.69	33
Phosphorus (percent)	0.99 ± 0.07	0.82-1.1	33
Potassium (percent)	0.809	0.772-0.846	2
Chloride (percent)	0.557	0.479-0.635	2
Sodium (percent)	0.304	0.258-0.349	2
Magnesium (percent)	0.172	0.166-0.177	2
Sulfur (percent)	0.278	0.270-0.285	2
Iron (ppm)	418	409-426	2
Manganese (ppm)	90.8	86.0-95.5	2
Zinc (ppm)	55.1	54.2-56.0	2
Copper (ppm)	12.68	9.65-15.70	2
Iodine (ppm)	2.58	1.52-3.64	2
Chromium (ppm)	1.86	1.79-1.93	2
Cobalt (ppm)	0.57	0.49-0.65	2

(a) One or two batches of feed analyzed for nutrients reported in this table were manufactured in January and/or April 1983.
(b) One batch (7/22/81) not analyzed for thiamine

TABLE M4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminant	Mean ± Standard Deviation	Range	No. of Samples
Arsenic (ppm)	0.41 ± 0.20	<0.05-1.06	33
Cadmium (ppm)	0.11 ± 0.06	<0.01-0.40	33
Lead (ppm)	0.97 ± 0.66	0.42-2.75	33
Mercury (ppm) (a)	< 0.05		
Selenium (ppm)	0.29 ± 0.08	0.10-0.52	33
Aflatoxins (ppb) (a,b)	<10	<5.0-<10.0	33
Nitrate nitrogen (ppm) (c)	8.11 ± 4.16	<1.0-17.0	33
Nitrite nitrogen (ppm) (c)	2.0 ± 1.49	<0.1-6.9	33
BHA (ppm) (d,e)	5.2 ± 4.88	<0.5-17.0	33
BHT (ppm) (d)	3.10 ± 2.34	<1.0-12.0	33
Aerobic plate count (CFU/g)	43,267 ± 31,305	4,900-120,000	33
Coliform (MPN/g) (f)	43.4 ± 91.0	<3-460	31
Coliform (MPN/g) (g)	108.3 ± 270.5	<3-1,100	33
E. coli (MPN/g) (h)	<3		33
Total nitrosamines (ppb) (i,j)	5.66 ± 5.23	0.8-18.8	30
Total nitrosamines (ppb) (k,j)	22.07 ± 56.93	0.8-279.5	33
N-Nitrosodimethylamine (ppb) (l,j)	4.95 ± 5.10	0.8-16.0	30
N-Nitrosodimethylamine (ppb) (m,j)	21.2 ± 32.0	0.8-278	33
N-Nitrosopyrrolidine (ppb) (n)	1.30 ± 0.73	<0.5-3.5	31
Pesticides (ppm)			
α-BHC (a,o)	<0.01		33
β-BHC (a)	<0.02		33
γ-BHC-Lindane (a)	<0.01		33
δ-BHC (a)	<0.01		33
Heptachlor (a)	<0.01		33
Aldrin (a)	<0.01		33
Heptachlor epoxide (a)	<0.01		33
DDE (a)	<0.01		33
DDD (a)	<0.01		33
DDT (a)	<0.01		33
HCB (a)	<0.01		33
Mirex (a)	<0.01		33
Methoxychlor (a,p)	<0.05	0.09; 8/26/81	33
Dieldrin (a)	<0.01		33
Endrin (a)	<0.01		33
Telodrin (a)	<0.01		33
Chlordane (a,q)	<0.05		23
Toxaphene (a)	<0.1		33
Estimated PCB's (a)	<0.2		33
Ronnel (a)	<0.01		33
Ethion (a)	<0.02		33
Trithion (a)	<0.05		33
Diazinon (a,p)	<0.1	0.2; 4/27/81	33
Methyl parathion (a)	<0.02		33
Ethyl parathion (a)	<0.02		33
Malathion (r)	0.09 ± 0.06	<0.05-0.27	33
Endosulfan I (s)	<0.01		14
Endosulfan II (s)	<0.01		14
Endosulfan sulfate (s)	<0.03		14

TABLE M4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION (Continued)

(a) All values were less than the detection limit, given in the table as the mean.
(b) The detection limit was reduced from 10 ppb to 5 ppb after 7/81.
(c) Source of contamination: Alfalfa, grains, and fish meal
(d) Source of contamination: Soy oil and fish meal
(e) Three batches contained more than 0.5 ppm.
(f) Mean, standard deviation, and range exclude two very high values of 1,100 obtained for batches produced on 5/29/80 and 12/16/80.
(g) Includes the high values listed in footnote (f)
(h) All values were less than 3 MPN/g (MPN = most probable number).
(i) Mean, standard deviation, and range exclude three very high values in the range of 117.6-279.5 ppb obtained for the batches produced on 1/26/81, 2/23/81, and on 4/27/81.
(j) All values were corrected for percent recovery.
(k) Mean, standard deviation, and range include the very high values given in footnote (i).
(l) Mean, standard deviation, and range exclude three very high values in the range of 115.0-278.0 ppb for batches produced on 1/26/81, 2/23/81, and 4/27/81.
(m) Mean, standard deviation, and range include the very high values given in footnote (l).
(n) The values were not detectable in batches produced on 3/24/82 and 6/24/82.
(o) BHC = hexachlorocyclohexane or benzene hexachloride.
(p) There was one observation above the detection limit; the value and date it was obtained are given under the range.
(q) Ten batches (4/1/80-12/16/80) were not analyzed for chlordane.
(r) Sixteen batches contained more than 0.05 ppm.
(s) Nineteen batches (4/1/80-11/25/81) were not analyzed for endosulfan I, endosulfan II, or endosulfan sulfate.

APPENDIX N

RESULTS OF NTP STUDIES OF THE METABOLISM AND ELIMINATION OF DIMETHYLVINYL CHLORIDE IN RATS AND MICE

TABLE N1. ELIMINATION OF ^{14}C-DIMETHYLVINYL CHLORIDE-DERIVED RADIOACTIVITY BY VARIOUS ROUTES (a)

Route	Rats	Mice
Urine	(b) 35 ± 5	49 ± 9
Feces	4.2 ± 2.3	8.7 ± 3.7
Expired carbon dioxide	26 ± 1	26 ± 1
Expired dimethylvinyl chloride	35 ± 5	5.0 ± 0.7

(a) Male F344 rats (200-250 g) were given 150 mg/kg of ^{14}C-dimethylvinyl chloride (51 μCi/kg) by gavage in corn oil (5 ml) and placed in glass metabolism cages that allow separate collection of urine, feces, and expired air. Expired air was passed first through an ethanol-filled trap or an activated carbon trap to retain expired organic compounds and then through two consecutive ethanolamine traps to retain expired carbon dioxide. Elution of the activated carbon traps followed by high-pressure liquid chromatography of the eluate allowed verification that the expired ^{14}C-labeled organic compound was dimethylvinyl chloride. An aliquot of urine was counted without further processing; feces were oxidized in a tissue oxidizer and counted. Male B6C3F$_1$ mice (25-30 g) were given 150 mg/kg of ^{14}C-dimethylvinyl chloride (150 μCi/kg) by gavage in corn oil (10 ml) and placed in similar glass metabolism cages as described above. Urine, feces, expired carbon dioxide, and expired dimethylvinyl chloride were assayed as described above.
(b) Values given are percentages of the administered dose eliminated by a given route in the 24 hours after administration of the compound. Values are the mean for three animals ± SD.

TABLE N2. TISSUE DISTRIBUTION OF ^{14}C-DIMETHYLVINYL CHLORIDE-DERIVED RADIOACTIVITY (a)

	Tissue Concentration of Radioactivity (μmol/g tissue)				
	Rats				Mice
	1D (b)	2D	4D	4D-4R	1D
Blood	(c) 0.11 ± 0.01	0.19 ± 0.03	0.26 ± 0.03	0.13 ± 0.01	--
Liver	0.45 ± 0.04	0.80 ± 0.08	1.3 ± 0.1	0.61 ± 0.19	0.43 ± 0.09
Kidney	0.44 ± 0.02	0.75 ± 0.08	1.1 ± 0.2	0.39 ± 0.04	0.61 ± 0.24
Forestomach	0.17 ± 0.01	0.31 ± 0.03	0.44 ± 0.04	0.19 ± 0.01	0.42 ± 0.10
Glandular stomach	0.17 ± 0.01	0.36 ± 0.05	0.54 ± 0.08	0.23 ± 0.01	0.18 ± 0.06
Small intestine	0.37 ± 0.02	0.70 ± 0.10	0.92 ± 0.18	0.17 ± 0.02	--
Large intestine	0.39 ± 0.02	0.59 ± 0.05	0.85 ± 0.20	0.21 ± 0.04	--
Brain	0.096 ± 0.00	0.26 ± 0.02	0.45 ± 0.09	0.21 ± 0.05	--
Testes	0.10 ± 0.01	0.22 ± 0.01	0.35 ± 0.11	0.16 ± 0.01	0.12 ± 0.06
Lungs	0.19 ± 0.01	0.32 ± 0.03	0.46 ± 0.06	0.22 ± 0.03	0.12 ± 0.04
Heart	0.12 ± 0.00	0.22 ± 0.02	0.37 ± 0.08	0.17 ± 0.01	0.087 ± 0.005
Thymus	0.39 ± 0.06	0.82 ± 0.03	0.98 ± 0.09	0.30 ± 0.06	0.35 ± 0.09

(a) Male F344 rats (200-250g) were given 150 mg/kg of ^{14}C-dimethylvinyl chloride (51 μCi/kg) by gavage in corn oil (5 ml) and placed in glass metabolism cages that allow separate collection of urine, feces, and expired air. Male B6C3F$_1$ mice (25-30 g) were given 150 mg/kg of ^{14}C-dimethylvinyl chloride (150 μCi/kg) by gavage in corn oil (10 ml) and placed in glass metabolism cages as described above. The animals were killed 24 hours after the last dose and tissues collected. Samples of tissue were oxidized in a tissue oxidizer to determine radioactivity present.
(b) D = one daily administration of 150 mg/kg; R = 1 day of recovery, e.g., 4D-4R = four successive daily doses of 150 mg/kg followed by 4 days' recovery.
(c) Values given are the mean for three animals ± SD.

TABLE N3. SPECTRAL CHARACTERISTICS OF THE MAJOR DIMETHYLVINYL CHLORIDE URINARY METABOLITE

NMR Spectrum (a)			
Signal	Chemical Shift (ppm)	Appearance	Coupling Constant (Hz)
1	1.76	Singlet	--
2	2.00	Singlet	--
3	3.32	Doublet of doublets	15 and 7
4	3.41	Doublet of doublets	15 and 4.4
5	3.95	Doublet of doublets	7 and 4.4
6	7.46	Singlet	--

Mass Spectrum (b)	
Parent ion ($+H^+$) at m/e	206.052136
Calculated for $C_7H_{11}NO_4S$	206.048708

(a) Obtained in D_2O solution using a General Electric QE-300 NMR spectrometer
(b) Obtained using a V.G. Model ZAB-4F mass spectrometer in the fast atom bombardment mode

APPENDIX O

SUMMARY OF NTP STUDIES OF THE IMMUNOTOXICITY OF DIMETHYLVINYL CHLORIDE IN MICE

TABLE O1. RESULTS OF IMMUNOTOXICOLOGIC PROBE STUDIES WITH DIMETHYVINYL CHLORIDE (a)

Assay System	Effects of Dimethylvinyl Chloride		Statistically Significant	
1. Host Resistance to:	**Resistance to Infectious Challenge**			
	Primary	Secondary	Primary	Secondary
Influenza A2/Taiwan	Decreased	Decreased	Yes	No
B16-F10 tumor	No effect		--	
PYB6 tumor	No effect		--	
Listeria monocytogenes	Decreased	No effect	Yes	
Streptococcus zooepidemicus	No effect	No effect	No	No
HSV-1	Decreased	No effect	Yes	No
HSV-2	Decreased	No effect	Yes	No
2. Immune Function/Macrophage (MØ):				
Delayed hypersensitivity	Decreased		Yes	
Mitogenic responses	Decreased		Yes	
Mixed lymphocyte culture	No effect		--	
MØ cytostasis	Decreased		Yes	
MØ phagocytosis	Increased		Yes	
MØ pulmonary bactericidal activity	Increased		Yes	
Natural killer cell function	No effect		No	
Anti-SRBC plaque-forming cell response:				
Day 4 post-SRBC (IgM)	Decreased		Yes	
Day 5 post-SRBC (IgM)	Decreased		Yes	
Day 5 post-SRBC (IgG)	No effect		No	

(a) Data from these studies are included in report numbers IITRI 983 and 984 as part of an NTP contract (NO1-ES-5000) with Illinois Institute of Technology Research Institute, Chicago, Illinois.

APPENDIX P

DATA AUDIT SUMMARY

APPENDIX P. DATA AUDIT SUMMARY

The experimental data and tables of the NTP Technical Report on the toxicology and carcinogenesis studies of dimethylvinyl chloride in F344/N rats and B6C3F$_1$ mice were examined for completeness, consistency, and accuracy and for procedures consistent with Good Laboratory Practice requirements. The audit was conducted October 1-5, 1984, by Argus Research Laboratories, Inc., under contract to the NTP. The following personnel were involved in the audit: J. Goeke, Ph.D.; J. Hills, B.A.; A. Hoberman, Ph.D.; E. Feussner, V.D.M.; P. Ference, B.S.; D. Willett, B.S.; D. Copeland, D.V.M.; G. Knutsen, D.V.M., M.S.; C. Veigle, H.T. The 2-year studies in rats and mice were conducted between June 1980 and March 1983 at Litton Bionetics, Inc., Kensington, Maryland.

The full report of the audit is on file at NIEHS, Research Triangle Park, North Carolina. The audit included, but was not limited to, a review of the records of the inlife portion of the studies for 10% of the animals; 100% of the clinical observation records for animals observed to have masses during the last 6 months of the studies; 100% of the records for study material administration; 10% of the dose calculations; 100% of all other chemistry data. All Individual Animal Data Records were examined for correspondence between necropsy observations and histologic findings. An audit of randomly selected (10%) wet tissue bags was conducted to verify animal identification and to examine residual tissues for untrimmed lesions. A complete slide/block match for both sexes of both species in the vehicle control and high dose groups was performed.

Examples of the most substantive discrepancies observed during the audit are as follows. Persistent clinical signs such as "ruptured eyeball" and "loss of tail-distal" were sometimes reported intermittently after the initial observation. Some masses that were adequately described at one observation time were not subsequently noted, and there was no notation that the mass was no longer identifiable or observed. The chemical dispensing log was incomplete regarding the source of dimethylvinyl chloride used to prepare dosing solutions between 12/16/80 and 12/24/80. Inconsistencies in gross/microscopic pathology comparisons were observed, and untrimmed lesions were found in stored wet tissues. For example, a papilloma of the forestomach in 1 rat and untrimmed lesions in 7/45 mice were observed--three fibrotic or atrophied seminal vesicles, one mesenteric nodule, one small liver focus, one forestomach area of papillomas (which was partially sampled), and one granulomatous penis. These lesions were found either through lack of correlation between a gross necropsy observation and a histopathologic description or during examination of wet tissue bags.

These discrepancies were either resolved or were not considered to influence the final interpretation of these studies. Thus, the data examined during this audit are considered adequate to support the conclusions presented in this Technical Report.

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