NATIONAL TOXICOLOGY PROGRAM
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No. 303

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 4-VINYLCYCLOHEXENE

(CAS NO. 100-40-3)

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

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 4-VINYLCYCLOHEXENE

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IN F344/N RATS AND B6C3F$_1$ MICE

(GAVAGE STUDIES)

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

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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. 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).

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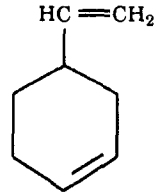

4-VINYLCYCLOHEXENE

(4-ETHENYLCYCLOHEXENE)

CAS NO. 100-40-3

C_8H_{12} Molecular weight 108.20

ABSTRACT

Toxicology and carcinogenesis studies of 4-vinylcyclohexene (greater than 98% pure), a dimer of 1,3-butadiene present in the off-gases from tire curing, were conducted by administering the chemical in corn oil by gavage 5 days per week at doses of 0, 200, or 400 mg/kg body weight to groups of 50 F344/N rats and B6C3F$_1$ mice of each sex for 103 weeks. Doses selected for the 2-year studies were based on survival, body weight gains, and histopathologic effects observed during the 14-day and 13-week studies.

All rats and most mice in the 14-day studies died when administered doses greater than or equal to 1,250 mg/kg, although no compound-related gross or histopathologic effects were observed. Final body weights were reduced in the 13-week studies in male rats receiving doses greater than or equal to 400 mg/kg of 4-vinylcyclohexene, in female rats receiving 800 mg/kg, and in female mice receiving 600 mg/kg. Extensive mortality was observed only in mice dosed at 1,200 mg/kg. Compound-related histopathologic effects in the 13-week studies included hyaline droplet degeneration of the proximal convoluted tubules of the kidney in dosed male rats, the severity of which was dose related, and a reduction in the number of primary follicles and mature graafian follicles in the ovaries of female mice receiving 1,200 mg/kg of 4-vinylcyclohexene. No compound-related gross or histopathologic effects were evident in dosed female rats or male mice in the 13-week studies.

Many dosed rats died early in the 2-year studies (male: vehicle control, 17/50; low dose, 37/50; high dose, 45/50; female: vehicle control, 10/50; low dose, 22/50; high dose, 36/50; $P<0.001$ for all groups except low dose female rats, for which $P=0.022$). The poor survival of dosed male and female rats reduced the sensitivity of the studies for detecting the possible carcinogenic effects of 4-vinylcyclohexene. Mean body weights of dosed rats were comparable to those of their respective vehicle controls, except for high dose males late in the study. Survival of high dose mice of each sex was lower ($P<0.001$) than that of the vehicle controls, whereas survival of low dose mice of each sex was comparable to that of the vehicle controls. Mean body weights of high dose mice of each sex were generally lower than those of the vehicle controls throughout most of the 2-year studies.

Administration of 4-vinylcyclohexene to F344/N rats by gavage for 2 years was associated with a slightly increased incidence of epithelial hyperplasia of the forestomach (1/50; 3/50; 5/47) and squamous cell papillomas or carcinomas (combined) of the skin in high dose males (0/50; 1/50; 4/50). Low dose female rats, whose survival was more similar to that of the vehicle controls, had a marginally

increased incidence of adenomas or squamous cell carcinomas (combined) of the clitoral gland (1/50; 5/50; 0/49).

In $B6C3F_1$ mice, administration of 4-vinylcyclohexene for 2 years by gavage was associated with mild, acute inflammatory lesions and epithelial hyperplasia of the forestomach, especially in males (0/47; 7/50; 7/46), and with an increased incidence of a number of other nonneoplastic lesions, including lung congestion in high dose males and females, splenic red pulp atrophy in high dose males, congestion of the adrenal gland in high dose females, and cytologic alteration of the adrenal cortex in low dose and high dose females.

The incidences of uncommon ovarian neoplasms were markedly increased ($P < 0.01$) in both groups of dosed female mice (mixed tumor, benign: 0/49; 25/48, 52%; 11/47, 23%; granulosa cell tumor: 1/49, 2%; 9/48, 19%; 11/47, 23%; granulosa cell tumor or carcinoma [combined]: 1/49, 2%; 10/48, 21%; 13/47, 28%). In addition, a slight increase in the incidence of adrenal gland adenomas in high dose females was observed (0/50; 3/49, 6%; 4/48, 8%). The extensive mortality seen in the high dose male mice confounded interpretation of the increased incidences of malignant lymphomas and alveolar/bronchiolar adenomas or carcinomas (combined) of the lung seen in these animals surviving to the end of the study (malignant lymphomas: 3/37, 8%; 5/39, 13%; 4/7, 57%; alveolar/bronchiolar adenomas or carcinomas [combined]: 3/37, 8%; 9/39, 23%; 3/7, 43%).

4-Vinylcyclohexene was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 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. However, several of its metabolites, including 4-vinylcyclohexene diepoxide, have been shown to be mutagenic in Salmonella and/or induce chromosomal damage in vitro.

An audit of the experimental data was conducted for these 2-year carcinogenesis studies on 4-vinylcyclohexene. No data discrepancies were found that influenced the final interpretations.

4-Vinylcyclohexene was administered by gavage in corn oil to F344/N rats and $B6C3F_1$ mice of each sex at doses of 200 or 400 mg/kg for 103 weeks. Under these conditions, the 2-year gavage studies of 4-vinylcyclohexene in male and female rats and male mice were considered *inadequate studies of carcinogenicity** because of extensive and early mortality at the high dose or at both doses and the lack of conclusive evidence of a carcinogenic effect. There was *clear evidence of carcinogenicity* of 4-vinylcyclohexene for female mice, as shown by markedly increased incidences of uncommon ovarian neoplasms at both doses. In addition, the increased incidence of adrenal gland adenomas in high dose female mice may have been related to the administration of 4-vinylcyclohexene.

*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 pages 13 and 14.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of 4-Vinylcyclohexene is based on the 14-day and 13-week studies that began in January 1979 and ended in April 1980 and on the 2-year studies that began in November 1980 and ended in November 1982 at Litton Bionetics, Inc.

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The members of the Peer Review Panel who evaluated the draft Technical Report on 4-vinylcyclohexene on March 29, 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 4-VINYLCYCLOHEXENE

On March 29, 1985, the draft Technical Report on the toxicology and carcinogenesis studies of 4-vinylcyclohexene received peer review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting began at 9:00 a.m. in the Conference Center, Building 101, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.

Dr. Purchase, a principal reviewer, agreed with the conclusion presented for male rats (inadequate study) but not with those for female rats or male and female mice (equivocal, equivocal, and clear evidence of carcinogenicity, respectively). He said the studies in female rats and male mice were compromised because of the poor health of the animals and the insufficient number of animals for statistical analysis due to high and early mortality. Thus, Dr. Purchase preferred an interpretation of inadequate studies of carcinogenicity for female rats and male mice. He proposed a conclusion for female mice of some evidence of carcinogenicity based on increased incidences of ovarian neoplasms at both doses; high mortality at the high dose may have had some confounding influence. Dr. J. Collins, NTP, replied that the studies in female rats and male and female mice were considered appropriate for interpretation of carcinogenicity based on adequate survival in the low dose groups. In low dose mice, survival after 2 years was equal to or greater than that in the concurrent vehicle control group. He stated that the substantial increases in ovarian tumors in female mice, at the highest incidences ever seen in any single NCI or NTP study, supported a categorization of clear evidence of carcinogenicity.

As a second principal reviewer, Dr. Turnbull said that a more detailed rationale should be given as to why the gavage rather than inhalation route was used. He had general comments on cage placement and on whether there are more gavage errors in high dose animals than in low dose or vehicle control groups. Dr. Collins said that the gavage route was chosen primarily because of a lack of adequate inhalation facilities at the time the studies were initiated and because gavage studies were more common then.

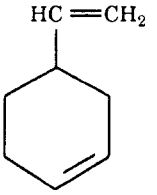
As a third principal reviewer, Dr. Perera said that the study in female rats should be considered an inadequate study of carcinogenicity. Her major concern was that some of the positive findings in rats would be considered not biologically significant or would be minimized because of the poor survival. In her opinion, the increased incidences of skin tumors in high dose male rats and of benign and malignant tumors of the clitoral gland and anterior pituitary gland in low dose female rats, along with the appearance of a rare transitional cell carcinoma of the urinary bladder, should be noted and emphasized. Dr. Collins said that because this study was considered inadequate, there was only modest discussion of tumors in male rats. However, if reexamination determined that the skin tumors were detected on visual examination, more discussion could be warranted. Dr. Hooper noted that the significantly increased incidence of skin tumors in male rats at the high dose should support a designation of equivocal evidence of carcinogenicity. Dr. W. Kluwe, NIEHS/NTP, replied that when a study is considered inadequate, a level of evidence is not given. Dr. Perera said that the possibility of false negative results as a result of low survival should be discussed along with the already discussed problem of possible false positives.

In further discussion, Dr. Swenberg stated that the NTP should have terminated the studies during the 1st year after the early mortality in high dose animals; the causes of death should have been more closely monitored, and then new studies should have been started with more appropriate doses. Dr. Kotelchuck also felt that the poor survival in female rats made this an inadequate study.

Dr. Hooper moved that the studies in both male and female rats be considered inadequate studies of carcinogenicity. Dr Perera seconded the motion and asked that the tumor types with increased incidences be mentioned. The Panel agreed to mention the increases in tumors in the abstract but not in the conclusion. The amended motion was approved unanimously. Dr. Purchase then moved that the conclusion for male mice be an inadequate study of carcinogenicity. Dr. Kociba seconded the motion, and it was approved unanimously by the Panel. Dr. Purchase moved that the conclusion for female mice be some evidence of carcinogenicity. Dr. Kotelchuck seconded the motion. In discussion preceding the vote, Dr. J. Haseman, NTP, pointed out that in the low dose group, there was a sizable increase in ovarian tumors with neither mortality nor body weight loss. Dr. Swenberg said that the study of the high dose group was also acceptable, since more than 50% of the animals were alive at week 78. In addition, these tumors are uncommon, and both malignant and benign tumors were induced. Dr. Kotelchuck suggested that the lack of a dose response weighed against the strongest category of evidence. The motion for some evidence of carcinogenicity in female mice was defeated by seven negative votes to three affirmative votes (Dr. Kociba, Dr. Kotelchuck, and Dr. Purchase). Dr. Hooper moved that the conclusion in female mice (clear evidence of carcinogenicity) be accepted as written. Dr. Swenberg seconded the motion, and it was approved by seven affirmative votes; there were two negative votes (Dr. Kociba and Dr. Kotelchuck) and one abstention (Dr. Purchase).

I. INTRODUCTION

I. INTRODUCTION



4-VINYLCYCLOHEXENE

(4-ETHENYLCYCLOHEXENE)

CAS NO. 100-40-3

C_8H_{12} Molecular weight 108.20

General

4-Vinylcyclohexene, a colorless liquid, is a dimer of 1,3-butadiene. It is used primarily as an intermediate in the production of 4-epoxyethyl-1,2-epoxycyclohexane (vinylcyclohexene diepoxide), which itself is used as a reactive diluent in the manufacture of epoxy resins (IARC, 1976). 4-Vinylcyclohexene is also present in gases discharged during the production of synthetic rubber, especially as a result of the process of curing rubber in tire manufacturing. It has a boiling point of 128.9° C, a density at 20° C of 0.83, a refractive index at 20° C of 1.46, and a vapor pressure of 25.8 mm mercury at 38° C (Sandmeyer, 1981).

Although a threshold limit value for 4-vinylcyclohexene has not yet been established (IARC, 1982; ACGIH, 1983), it has been suggested that the vapor concentration of this substance be kept below 100 ppm in any workroom environment (Sandmeyer, 1981). 4-Vinylcyclohexene is produced commercially by the dimerization of 1,3-butadiene (IARC, 1976), a process that also occurs during rubber curing (Rappaport and Fraser, 1976); the quantity of 4-vinylcyclohexene produced in the United States in 1977 ranged between 1.2×10^6 and 12.1×10^6 pounds (5.4×10^8 and 54.9×10^8 g) (USEPA, 1980); more current production figures are not available (USITC, 1983).

Animal Toxicity

A single-dose oral LD_{50} value of 2.6 g/kg has been reported for Carworth-Wistar rats (Smyth et al., 1969). Inhalation studies demonstrated that exposure of rats for 15 minutes to air saturated with 4-vinylcyclohexene vapor was lethal, whereas exposure at a concentration of 8,000 ppm (35,440 mg/m^3) for 4 hours was lethal to 4/6 rats. LC_{50} values of 6,095 ppm (27,000 mg/m^3) in rats and 10,610 ppm (47,000 mg/m^3) in mice have been reported (IARC, 1976), whereas administration of 226 ppm (1,000 mg/m^3) by inhalation to rats and mice for 6 hours per day over 4 months was reported to inhibit weight gain and to cause leukocytosis, leukopenia, and impairment of hemodynamics (Bykov, 1968).

Application of a 1:1 mixture of 4-vinylcyclohexene (45 mg) and benzene in 0.1 ml doses to the skin of 30 Swiss mice 3 days per week for 54 weeks resulted in one squamous cell carcinoma (Van Duuren et al., 1963). However, even this limited effect was subsequently attributed to contamination with small amounts of vinylcyclohexene hydroperoxide (Van Duuren, 1965). The hydroperoxide derivative, a known carcinogen (Van Duuren et al., 1963), is readily generated by autoxidation when 4-vinylcyclohexene comes in contact with oxygen; the addition of inhibitors of peroxide formation is therefore needed to prevent contamination with this derivative. (The samples of 4-vinylcyclohexene used in these NTP studies contained 100 ppm butylated hydroxytoluene [BHT] or 50 ppm *tert*-butylcatechol for this purpose.) Because of the inconclusive results of the previous in vivo studies (Van Duuren et al., 1963; Van Duuren, 1965) conducted before the present NTP studies, it had been concluded that the carcinogenic status of

4-vinylcyclohexene was undefined (IARC, 1976, 1982; NIOSH, 1980).

Metabolism

4-Vinylcyclohexene is metabolized in vitro by liver microsomal enzymes. The major metabolic products are 4-vinyl-1,2-epoxycyclohexane and 4-epoxyethyl-1,2-dihydroxycyclohexane, with trace amounts (less than 0.001%) of vinylcyclohexene diepoxide also being produced (Gervasi et al., 1980; Watabe et al., 1980, 1981). Intraperitoneal administration of 4-vinylcyclohexene to male Swiss mice at a dose of 500 mg/kg induced the activities of a number of xenobiotic metabolizing enzymes in the liver (Giannarini et al., 1981), including those which generate vinylcyclohexene diepoxide (e.g., NADPH-cytochrome c reductase). This finding is important because of the well-established carcinogenicity of this diepoxide derivative. Dermal or intraperitoneal administration of 4-vinylcyclohexene diepoxide causes squamous cell sarcomas and carcinomas or peritoneal sarcomas, respectively (Van Duuren et al., 1963, 1967; IARC, 1976; ACGIH, 1983). Data on the pharmacokinetics and tissue distribution of 4-vinylcyclohexene were not located in the literature.

Mutagenicity

4-Vinylcyclohexene was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 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 of Haworth et al. (1983) (Appendix G). Although no additional information regarding the genetic toxicology of this compound was found in the literature, several recognized metabolites of 4-vinylcyclohexene, including 4-vinylcyclohexene diepoxide, 4-vinyl-1,2-epoxycyclohexane, and 4-epoxyethyl-1,2-dihydroxycyclohexane, were mutagenic in Salmonella and/or produced chromosomal damage in vitro (Murray and Cummins, 1979; Simmon and Baden, 1980; Watabe et al., 1980; Turchi et al., 1981; E. Zeiger, NTP, unpublished data).

Human Exposure

Concentrations of 4-vinylcyclohexene at its site of manufacture in Russia were reported to average 271-542 $\times$ 10^3 ppb (1.2-2.4 $\times$ 10^6 mg/m^3), with maximum concentrations of 677 $\times$ 10^3 ppb (3.0 $\times$ 10^6 mg/m^3) being measured (Bykov, 1968). In contrast, Fraser and Rappaport (1976), using a simulated laboratory model of tire curing, reported the presence of 4-vinylcyclohexene at concentrations of 71-92 ppb (310-410 mg/m^3). In subsequent studies involving the actual sampling of the discharged off-gases to which rubber workers are exposed during the tire-curing process, these investigators measured concentrations of 4-vinylcyclohexene of up to 118 ppb (520 mg/m^3) (Rappaport and Fraser, 1977). Although it is not clear if this compound has any relationship to the elevated levels of cancer mortality characteristic of rubber workers (Mancuso et al., 1968; Mancuso, 1976; IARC, 1982; Wang et al., 1984), workers exposed to 4-vinylcyclohexene at much higher concentrations than those detected by Rappaport and Fraser (1977) have been reported to suffer from keratitis, rhinitis, headache, hypotonia, leukopenia, neutrophilia, lymphocytosis, and impairment of pigment and carbohydrate metabolism (Bykov, 1968). Furthermore, there is additional potential for worker exposure given the use of 4-vinylcyclohexene as an intermediate for the production of its diepoxide, which itself is used in the manufacture of epoxy resins (IARC, 1976).

Study Rationale

4-Vinylcyclohexene was selected for study in order to characterize and evaluate its toxicologic potential, including carcinogenic activity, because of the potential for worker exposure, the carcinogenic activity of closely related derivatives, and the inconclusive results of previous carcinogenicity studies (Van Duuren et al., 1963; Van Duuren, 1965). Although administration of 4-vinylcyclohexene by inhalation would probably have best simulated the principal route of human exposure, the original decision to test by gavage was based primarily on limitations in available inhalation testing facilities.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 4-VINYLCYCLOHEXENE

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

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 4-VINYLCYCLOHEXENE

4-Vinylcyclohexene was obtained in two lots (Table 1). Lot no. C592777, which was reported by the supplier (Chemical Samples Company) to contain 100 ppm (0.01%) butylated hydroxytoluene (BHT) as an inhibitor of peroxide formation, was used for the 14-day studies, 13-week studies, and the first 44 weeks of the 2-year studies. Lot no. A061181 was obtained from Aldrich Chemical Company in 28 containers, the contents of which were combined, mixed, and used for the remainder of the 2-year studies. Lot no. A061181 was reported by Aldrich to contain 50 ppm (0.005%) *tert*-butylcatechol as an inhibitor of peroxide formation.

Purity, identity, and stability analyses were conducted at Midwest Research Institute (Appendix H). Both lots were identified as 4-vinylcyclohexene by spectroscopy. Infrared and nuclear magnetic resonance spectra were consistent with those expected for the structure of 4-vinylcyclohexene and with literature data; ultraviolet/visible spectra were consistent with its structure.

Cumulative data for lot no. C592777 indicated a purity of greater than 99%. Results of the elemental analysis for both carbon and hydrogen agreed with theoretical values. Water content by Karl Fischer titration was 0.012%. Gas chromatography by the two systems used indicated impurities with combined areas of 0.22% and 0.15%, respectively, relative to that of the major peak.

Cumulative data for lot no. A061181 indicated a purity slightly less than that of lot no. C592777 but still greater than 98%. Elemental analysis values for carbon and hydrogen agreed with theoretical values. Water content by Karl Fischer titration was 0.07%. Gas chromatography by the two systems used indicated impurities with combined areas of 0.69% and 1.1%, respectively, relative to the major peak.

The bulk chemical was stable when stored for 2 weeks at −20° to 25° C (Appendix H). The study laboratory stored several portions at −20° C as reference samples, and the remainder was stored at room temperature. The study and reference samples were analyzed periodically at the study laboratory by infrared spectroscopy and gas chromatography; no notable deterioration of the study chemical occurred over the course of the studies.

TABLE 1. IDENTITY AND SOURCE OF LOTS USED IN THE GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Lot Numbers	C592777	C592777	C592777, A061181
Date of Initial Use of Each Lot	1/8/79	N/A	10/5/81
Supplier	Chemical Samples Co. (Columbus, OH)	Same as the 14-d studies	Lot no. C592777--Chemical Samples Co. (Columbus, OH); lot no. A061181--Aldrich Chemical Co. (Milwaukee, WI)

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

4-Vinylcyclohexene and corn oil were mixed to give the desired concentrations (Table 2). 4-Vinylcyclohexene (5.2% w/v) in corn oil was found to be stable when stored at room temperature for 7 days (Appendix I). In the 2-year studies, 4-vinylcyclohexene/corn oil mixtures were stored at room temperature for no longer than 7 days. Formulations of 4-vinylcyclohexene in corn oil were analyzed periodically by the study and referee laboratories to confirm chemical content. The analytical method included a methanolic extraction as a purification step and a gas chromatographic assay as the quantitation step (Appendix J). Because 32/34 samples analyzed were within ± 10% of the target concentration, it is estimated that dose mixtures were prepared within specifications approximately 94% of the time during the 2-year studies (Table 3; Appendix K, Table K1).

TABLE 2. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
Preparation	4-Vinylcyclohexene was pipetted into a graduated cylinder, diluted with corn oil, and thoroughly mixed by inversion	A known quantity of 4-vinylcyclohexene was diluted with corn oil	Same as the 14-d studies
Maximum Storage Time	7 d	7 d	7 d
Storage Conditions	Room temperature	Room temperature	Room temperature

TABLE 3. SUMMARY OF RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

	Determined Concentration for Target Concentration of	
	60.1 mg/ml	120.1 mg/ml
Mean (mg/ml)	59.3	117.5
Standard deviation	3.54	4.58
Coefficient of variation (percent)	6.0	3.9
Range (mg/ml)	49.7-66.2	110.0-126.9
Number of samples	17	17

II. MATERIALS AND METHODS

FOURTEEN-DAY STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories (Portage, Michigan) and were held for 20 days (mice) or 27 days (rats) before the studies began. Groups of five rats and five mice of each sex were administered 0, 300, 600, 1,250, 2,500, or 5,000 mg/kg 4-vinylcyclohexene in corn oil by gavage for 14 consecutive days.

Animals were housed five per cage and received water and feed ad libitum. Details of animal maintenance are presented in Table 4. The rats and mice were observed twice per day for mortality and once per day for clinical signs and were weighed on days 0 and 14. A necropsy was performed on all animals; only stomachs, previously identified as the target organ, were examined microscopically.

THIRTEEN-WEEK STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of 4-vinylcyclohexene and to determine the doses to be used in the 2-year studies. Four- to five-week-old male and female F344/N rats and 5- to 6-week-old male and female B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and were observed for 17 days before the studies began. Rats and mice were housed five per cage in polycarbonate cages. Diets consisting of NIH 07 Rat and Mouse Ration pellets (Appendix M) and water (acidified with hydrochloric acid to pH 2.5 for bacterial control, a procedure no longer used in the Program) were available ad libitum.

Groups of 10 rats of each sex received 0, 50, 100, 200, 400, or 800 mg/kg 4-vinylcyclohexene in corn oil by gavage, 5 days per week for 13 weeks. Groups of 10 mice of each sex received 0, 75, 150, 300, 600, or 1,200 mg/kg on the same schedule. Further experimental details are summarized in Table 4. Animals were observed two times per day; moribund animals were killed. Animal weights and detailed clinical observations were recorded once per week. Survivors were killed at the end of the 13-week studies. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Tissues and groups examined are listed in Table 4.

TWO-YEAR STUDIES

These studies were conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of 4-vinylcyclohexene.

Study Design

Groups of 50 rats and 50 mice of each sex received 0, 200, or 400 mg/kg 4-vinylcyclohexene in corn oil by gavage, 5 days per week for 103 weeks. Further experimental details are summarized in Table 4.

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 this study were produced under strict barrier conditions at Charles River Breeding Laboratories (Kingston, New York) 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. Animals were shipped to the study laboratory at 4-5 weeks of age. The animals were quarantined at the study facility for 3 weeks. Thereafter, a complete necropsy with gross pathologic examination was performed on five animals of each sex and species to assess their health status. The rodents were placed on study at 7-8 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.

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups	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	0, 300, 600, 1,250, 2,500, or 5,000 mg/kg 4-vinylcyclohexene in corn oil by gavage; dose vol--5.81 ml/kg	Rats--0, 50, 100, 200, 400, or 800 mg/kg 4-vinylcyclohexene in corn oil by gavage; mice--0, 75, 150, 300, 600, or 1,200 mg/kg 4-vinylcyclohexene in corn oil by gavage; dose vol--3.33 ml/kg	0, 200, or 400 mg/kg 4-vinylcyclohexene in corn oil by gavage; dose vol--3.33 ml/kg
Date of First Dose	Rats--1/9/79; mice--1/8/79	1/21/80	Rats--11/17/80; mice--11/10/80
Date of Last Dose	Rats--1/22/79; mice--1/21/79	Rats--4/22/80; mice--4/18/80	Rats--11/5/82; mice--10/29/82
Duration of Dosing	14 consecutive days	5d/wk for 13 wk	5d/wk for 103 wk
Type and Frequency of Observation	Observed 2 × d for mortality and 1 × d for clinical signs; weighed on days 0 and 14	Observed 2 × d; weighed 1 × wk	Observed 2 × d; observed 1 × wk for clinical signs and palpated 1 × 4 wk; weighed 1 × wk for 13 wk and 1 × mo thereafter
Necropsy and Histologic Examination	Necropsy performed on all animals; stomachs examined microscopically	Necropsy performed on all animals; histologic examination performed on all animals in the vehicle control and 800 mg/kg groups of rats, as well as the kidneys and stomachs of all male rats and the stomachs of all female rats, on vehicle control and 1,200 mg/kg groups of mice, and on all animals dying before the end of the studies. Tissues examined include: gross lesions and tissue masses, mandibular lymph nodes, salivary glands, sternebrae (including marrow), thyroid gland, parathyroids, small intestine, colon, liver, gallbladder (mice), prostate/testes or ovaries/uterus, lungs and mainstem bronchi, skin, heart, esophagus, stomach, brain, thymus, pancreas, spleen, kidneys, adrenal glands, urinary bladder, pituitary gland, trachea, eyes, mammary gland, blood smear, and spinal cord (if neurologic signs present)	Necropsy performed on all but two animals (one missing, one pregnant); tissues examined microscopically include: gross lesions and tissue masses, regional lymph nodes, parathyroids, colon, prostate/testes or ovaries/uterus, lung and mainstem bronchi, stomach, brain, spinal cord (if neurologic signs present), blood smear (as required by pathologist), sternebrae (including marrow), liver, heart, thymus, pancreas, kidneys, urinary bladder, eyes (if grossly abnormal), mandibular and mesenteric lymph nodes, salivary glands, thyroid gland, small intestine, esophagus, mammary gland, trachea, adrenal glands, pituitary gland, and gallbladder (mice)
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species	Rats--F344/N; mice--B6C3F$_1$	Same as 14-d studies	Same as 14-d studies
Animal Source	Charles River Breeding Laboratories (Portage, MI)	Same as the 14-d studies	Charles River Breeding Laboratories (Kingston, NY)

TABLE 4. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE (Continued)

	Fourteen-Day Studies	Thirteen-Week Studies	Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Study Laboratory	Litton Bionetics, Inc.	Litton Bionetics, Inc.	Litton Bionetics, Inc.
Method of Animal Identification	Rats--ear notch; mice--ear punch and cage cards	Rats--ear tags and cage cards; mice--toe clip, ear tags, and cage cards	Same as 13-wk studies
Time Held Before Study	Rats--27 d; mice--20 d	17 d	19 d
Age When Placed on Study	Rats--7 wk; mice--8 wk	Rats--7 wk; mice--8 wk	Rats--7 wk; mice--8 wk
Age When Killed	Rats--9 wk; mice--10 wk	Rats--20 wk; mice--21 wk	Rats--111-112 wk; mice--112 wk
Necropsy Dates	Rats--1/23/79; mice--1/22/79	Rats--4/23/80-4/24/80; mice--4/21/80-4/22/80	Rats--11/15/82-11/17/82; mice--11/8/82-11/10/82
Method of Animal Distribution	Assigned to cages, then to groups according to a series of computer-generated random numbers	Same as the 14-d studies	Same as the 14-d studies
Feed	Lab Chow Checkers® (Ralston Purina, St. Louis, MO); available ad libitum	NIH 07 Rat and Mouse Ration (Zeigler Bros., Gardners, PA); available ad libitum	Same as 13-wk studies
Bedding	AB-SORB-DRI® hardwood chips (Williams Feed and Bedding, Gaithersburg, MD)	Same as the 14-d studies	AB-SORB-DRI® hardwood chips (Willams Feed and Bedding, Gaithersburg, MD), then Sani-Chips® (P.J. Murphy Forest Products Corp., Rochelle Park, NJ)
Water	Tap water acidified to pH 2.5 with HCl; available ad libitum	Same as the 14-d studies	Same as the 14-d studies
Cages	Polycarbonate (Lab Products, Inc., Garfield, NJ, or Rochelle Park, NJ, and Hazleton Systems, Aberdeen, MD)	Same as the 14-d studies	Same as the 14-d studies
Cage Filters	Nonwoven filter paper (Snow Filtration Co., Cincinnati, OH)	Same as the 14-d studies	Nonwoven polyester filter sheets (Snow Filtration Co., Cincinnati, OH)
Animals per Cage	5	5	5
Other Chemicals on Study in the Same Room	None	None	None
Animal Room Environment	N/A	Temp--22°-24° C; hum--30%-70%; fluorescent light 12h/d; 15 room air changes/h	Temp--22°-24° C (min 21° C, max 29° C); hum--generally 30%-70% but not controlled; fluorescent light 12 h/d; 12-15 room air changes/h

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

Rats and mice were housed five per cage in polycarbonate cages. Diets and water (acidified with hydrochloric acid to pH 2.5 for bacterial control) were available ad libitum. Details of animal maintenance are summarized in Table 4.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded once per week. Body weights by cage were recorded once per week for the first 13 weeks of the study and once per month thereafter. Mean body weights were calculated for each group. Moribund animals were killed, as were animals that survived to the end of the study. A necropsy was performed on all animals, including those found dead unless they were excessively autolyzed or cannibalized. 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 in each group.

Examinations for grossly visible lesions were performed on major tissues or organs. 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 4.

When the pathology examination was completed, the slides, individual animal data records, and summary tables were sent to an independent quality assurance laboratory. 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 assurance pathologist. Slides of all target tissues and those about which the original and quality assurance pathologists disagreed were submitted to the Chairperson of the Pathology Working Group (PWG) for evaluation. Representative coded slides selected by the Chairperson were reviewed by PWG pathologists, who reached a consensus and compared their findings with the original and quality assurance diagnoses. When diagnostic differences were found, the PWG sent the appropriate slides and comments to the original pathologist for review. 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 evaluations, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Nonneoplastic lesions are not examined routinely by the quality assurance pathologist or the PWG. Certain nonneoplastic findings are reviewed by the quality assurance pathologist and the PWG if they are considered part of the toxic response to a chemical or if they are deemed of special interest.

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 using these procedures were carried out to determine the time point at which significant differences in the survival curves were first detected. 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 are 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.

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 study 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 in these studies.

III. RESULTS

RATS

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III. RESULTS: RATS

FOURTEEN-DAY STUDIES

All the rats that received 1,250, 2,500, or 5,000 mg/kg 4-vinylcyclohexene died before the end of the studies (Table 5). Before these animals died, they were inactive, wet in the perianal region, and had tremors, soft stools, and an unsteady gait. Animals that survived to the end of the studies appeared normal, although male, but not female, vehicle control rats lost weight during the study. The death of one male rat in the 300 mg/kg group on day 3 was judged not to be compound related. With the exception of the weight loss seen in the vehicle control male rats, all surviving rats were similar in body weight to other animals of the same sex, regardless of dose received. No compound-related gross changes were noted at necropsy. Histologic examination was limited to the stomach, since it was predesignated as the target organ; no microscopic lesions were detected in this organ.

Based on the mortality observed in these studies at 4-vinylcyclohexene doses of 1,250 mg/kg or higher, doses of 0, 50, 100, 200, 400, and 800 mg/kg were selected for the 13-week studies.

TABLE 5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	237 ± 17	184 ± 6	−53 ± 18	--
300	(d) 4/5	225 ± 17	221 ± 10	+10 ± 3	120.1
600	5/5	219 ± 6	215 ± 9	−4 ± 5	116.8
1,250	(e) 0/5	195 ± 22	(f)	(f)	(f)
2,500	(g) 0/5	215 ± 8	(f)	(f)	(f)
5,000	(g) 0/5	199 ± 3	(f)	(f)	(f)
FEMALE					
0	5/5	152 ± 6	153 ± 6	+1 ± 1	--
300	5/5	158 ± 5	157 ± 5	−1 ± 1	102.6
600	5/5	157 ± 2	154 ± 3	−3 ± 1	100.7
1,250	(h) 0/5	133 ± 4	(f)	(f)	(f)
2,500	(g) 0/5	153 ± 3	(f)	(f)	(f)
5,000	(i) 0/5	157 ± 6	(f)	(f)	(f)

(a) Number surviving/number in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Death judged accidental
(e) Day of death: 4, 7, 8, 14, 14
(f) No data are reported due to the 100% mortality in this group.
(g) Day of death: all 2
(h) Day of death: all 4
(i) Day of death: 1, 2, 2, 2, 2

THIRTEEN-WEEK STUDIES

One male rat that received 400 mg/kg and one female rat that received 800 mg/kg 4-vinylcyclohexene died before the end of the studies (Table 6). Body weight gain was reduced in a dose-related fashion for male rats, and final mean body weights relative to those of the vehicle controls were 13% lower for high dose males and 6% lower for high dose females. The final mean body weight of male rats that received 400 mg/kg was 7% lower than that of the vehicle controls.

Hyaline droplet degeneration of the proximal convoluted tubule of the kidney was observed in dosed males but not in dosed females or the vehicle controls (Table 7). The lesion consisted of accumulations of brightly eosinophilic granules and globules in the cytoplasm of affected epithelial cells. The severity of the lesion was considered to be minimal for all groups except the 800 mg/kg males, in that only in this group did it appear to be of a degree that might reduce longevity or be life threatening in a 2-year study. Inflammation in the submucosa of the nonglandular portion of the stomach was seen in one male and three females in the 800 mg/kg groups; this acute lesion consisted of focal infiltration of neutrophils and diffuse edema in the gastric submucosa. No other histopathologic abnormalities were observed which were considered to be compound related.

Dose Selection Rationale: Based on the considerable depression in the body weights of male rats receiving 800 mg/kg 4-vinylcyclohexene, as well as the appearance at this dose of kidney lesions of a severity judged to be sufficient to promote earlier spontaneous kidney pathologic effects, doses selected for male rats in the 2-year studies were 200 and 400 mg/kg 4-vinylcyclohexene, to be administered in corn oil by gavage, 5 days per week. For the sake of consistency, the same doses were also selected for female rats. These doses appeared reasonable at the time, especially for the female rats in which no severe histopathologic lesions and only marginal body weight depression were seen at the high dose (800 mg/kg) in the 13-week study.

TABLE 6. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	163 ± 6	360 ± 9	+197 ± 8	--
50	10/10	163 ± 4	363 ± 6	+200 ± 6	101
100	10/10	157 ± 6	347 ± 7	+190 ± 6	96
200	10/10	161 ± 6	349 ± 10	+188 ± 7	97
400	(d) 9/10	158 ± 7	336 ± 11	+178 ± 7	93
800	10/10	162 ± 6	315 ± 7	+153 ± 6	87
FEMALE					
0	10/10	131 ± 4	210 ± 3	+ 79 ± 4	--
50	10/10	127 ± 3	213 ± 5	+ 86 ± 6	101
100	10/10	121 ± 5	202 ± 2	+ 81 ± 4	96
200	10/10	123 ± 5	203 ± 4	+ 80 ± 4	97
400	10/10	121 ± 6	208 ± 3	+ 87 ± 6	99
800	(e) 9/10	124 ± 4	197 ± 4	+ 72 ± 4	94

(a) Number surviving/number in group
(b) Initial mean group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 12
(e) Week of death: 2

TABLE 7. NUMBER OF RATS WITH COMPOUND-RELATED LESIONS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE (a)

	Vehicle Control	50 mg/kg	100 mg/kg	200 mg/kg	400 mg/kg	800 mg/kg
MALE						
Kidneys						
Hyaline droplet degeneration	0	3	10	10	(b)9	10
Stomach						
Inflammation	0	0	0	0	0	1
FEMALE						
Kidneys						
Hyaline droplet degeneration	0	0	0	0	0	0
Stomach						
Inflammation	0	0	0	0	0	3

(a) Ten animals were examined in each group.
(b) The nonaffected rat in this group died before the end of the study, and the kidneys were not optimally preserved.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

The initial mean body weights relative to vehicle controls were 93% and 109% for low dose and high dose male rats and 113% and 114% for low dose and high dose female rats (Table 8). These differences indicate that the animal distribution technique used (see Table 4) did not result in optimal randomization by weight. Mean body weights of high dose male rats were essentially the same as those of the vehicle controls until approximately week 72 of the study, after which they were between 5%-14% lower than those of the vehicle controls (Figure 1). The reason for this late weight loss in high dose males is unknown. Mean body weights of dosed and vehicle control female rats were comparable throughout the study.

TABLE 8. MEAN BODY WEIGHTS AND SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

Weeks on Study	Vehicle Control		200 mg/kg			400 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	118	50	110	93	50	129	109	50
1	151	49	148	98	50	161	107	49
2	188	49	183	97	50	192	102	48
3	164	49	161	98	50	174	106	48
4	217	49	208	96	50	223	103	48
5	240	49	237	99	49	247	103	43
6	240	49	233	97	49	239	100	42
7	266	49	264	99	49	273	103	42
8	275	49	278	101	49	282	103	40
9	294	49	290	99	49	297	101	40
10	310	49	304	98	49	308	99	40
11	314	49	312	99	49	318	101	40
12	321	49	319	99	49	320	100	39
13	329	49	326	99	49	331	101	39
16	348	49	347	100	49	352	101	38
20	375	49	373	99	49	377	101	35
24	395	49	397	101	48	399	101	35
28	409	49	412	101	48	409	100	35
32	424	49	423	100	47	418	99	35
36	442	48	442	100	47	435	98	35
40	449	47	455	101	45	447	100	34
44	453	47	450	99	42	442	98	34
48	461	46	467	101	42	454	98	32
52	468	45	474	101	41	459	98	32
56	469	44	477	102	38	460	98	30
60	476	44	483	101	37	462	97	29
64	474	43	482	102	37	455	96	29
68	472	42	478	101	36	457	97	26
72	481	40	466	97	36	458	95	25
76	482	40	480	100	36	456	95	25
80	485	39	471	97	34	445	92	22
84	481	37	468	97	31	436	91	21
88	477	36	467	98	26	415	87	15
92	471	36	464	99	22	406	86	12
96	465	35	457	98	19	404	87	9
100	450	34	444	99	15	407	90	6
FEMALE								
0	98	50	111	113	50	112	114	50
1	120	50	124	103	48	127	106	47
2	136	50	137	101	48	141	104	45
3	138	50	141	102	47	144	104	42
4	158	50	157	99	46	154	97	42
5	165	50	165	100	46	165	100	39
6	167	50	162	97	46	164	98	39
7	176	50	175	99	46	176	100	39
8	176	50	178	101	46	177	101	39
9	182	50	181	99	46	183	101	38
10	187	50	187	100	46	187	100	38
11	190	50	187	98	45	186	98	38
12	193	50	190	98	45	188	97	37
13	194	50	192	99	45	190	98	36
16	202	50	198	98	45	200	99	32
20	208	50	206	99	45	208	100	31
24	214	50	212	99	45	215	100	31
28	221	50	216	98	45	217	98	30
32	226	50	223	99	45	227	100	27
36	235	50	231	98	45	233	99	26
40	240	50	237	99	45	240	100	24
44	245	49	242	99	45	242	99	24
48	248	49	244	98	45	248	100	22
52	252	49	248	98	45	245	97	21
56	257	49	253	98	43	247	96	20
60	266	49	261	98	43	253	95	20
64	269	49	262	97	42	257	96	20
68	272	48	271	100	42	263	97	19
72	274	47	276	101	42	270	99	19
76	285	47	285	100	42	282	99	19
80	296	47	292	99	42	292	99	19
84	301	47	299	99	41	298	99	19
88	306	47	294	96	38	299	98	19
92	305	44	296	97	36	298	98	16
96	307	42	300	98	34	300	98	13
100	311	41	307	99	31	309	99	13

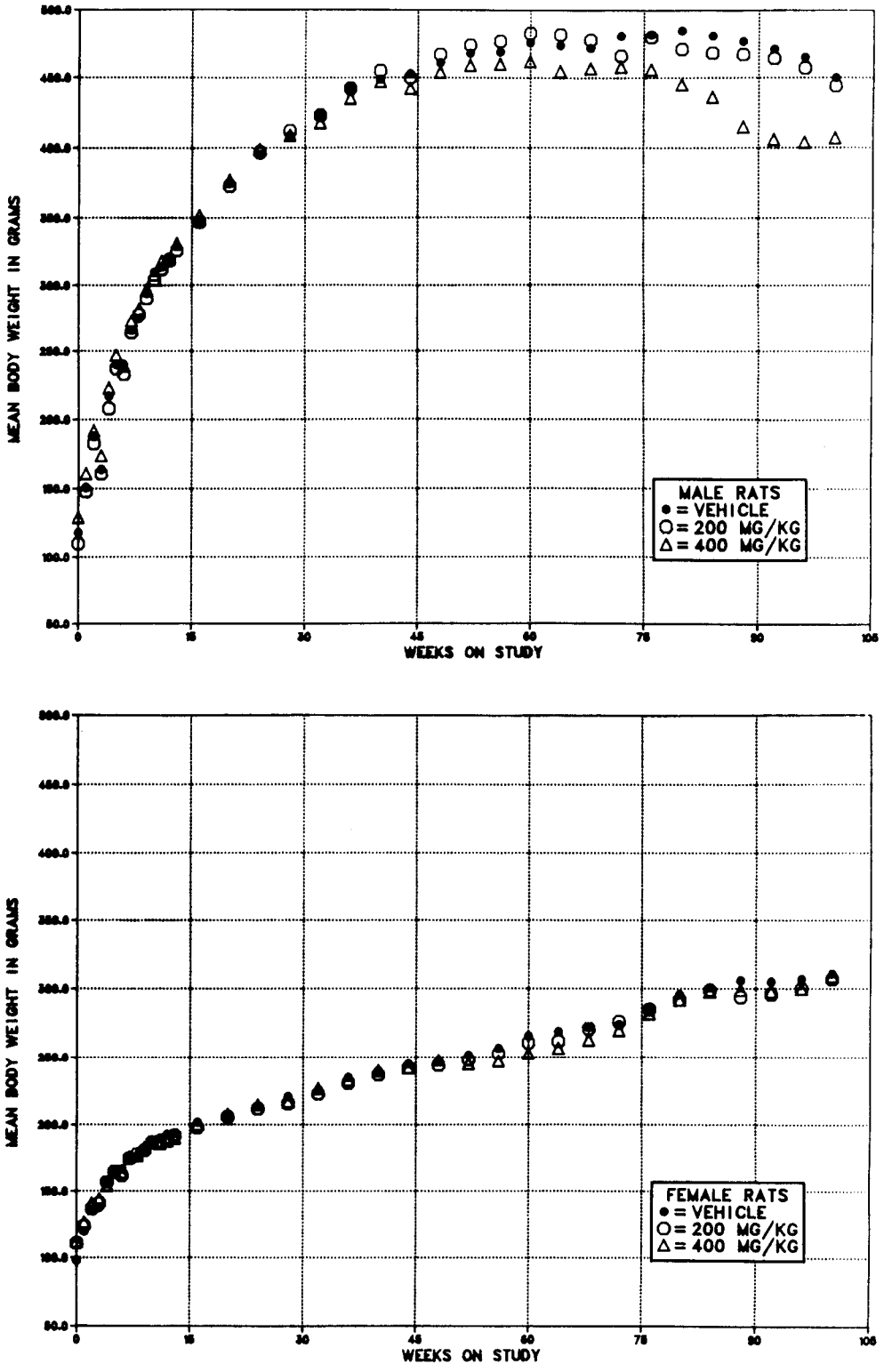

FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED 4-VINYLCYCLOHEXENE IN CORN OIL BY GAVAGE FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats receiving 4-vinylcyclohexene 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 high dose group of male rats was significantly lower than that of the vehicle controls after week 5; the survival of the low dose group was significantly lower after week 88 (Table 9). In addition, the survival of the high dose group was significantly lower than that of the low dose group ($P=0.019$) at the end of the study. In female rats, the survival of the high dose group was significantly reduced after week 3 when compared with that of the vehicle controls. The survival of the low dose group was significantly reduced only after week 102. As with male rats, the survival of the high dose females was significantly lower than that of the low dose group ($P<0.001$). Neither gross observations nor histopathologic evaluations revealed a specific cause of death in any of the dosed rat groups. There is no obvious explanation for the large number of deaths in the high dose (400 mg/kg) rat groups by week 13 of the 2-year studies, especially in light of the excellent survival of rats (38/40) receiving 400 or 800 mg/kg in the 13-week studies. Although termination of the 2-year rat studies was considered because of the observed mortality, the absence of an obvious cause of death and uncertainties as to whether carcinogenic effects would be observed led to the decision to continue these studies as planned.

TABLE 9. SURVIVAL OF RATS IN THE TWO-YEAR GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

	Vehicle Control	200 mg/kg	400 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	16	37	42
Accidentally killed	1	0	3
Killed at termination	32	13	5
Died during termination period	1	0	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)	10	21	35
Accidentally killed	0	1	1
Animals missing	0	0	1
Killed at termination	40	28	13
Survival P values (c)	<0.001	0.022	<0.001

(a) Terminal-kill period: weeks 104-105
(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.

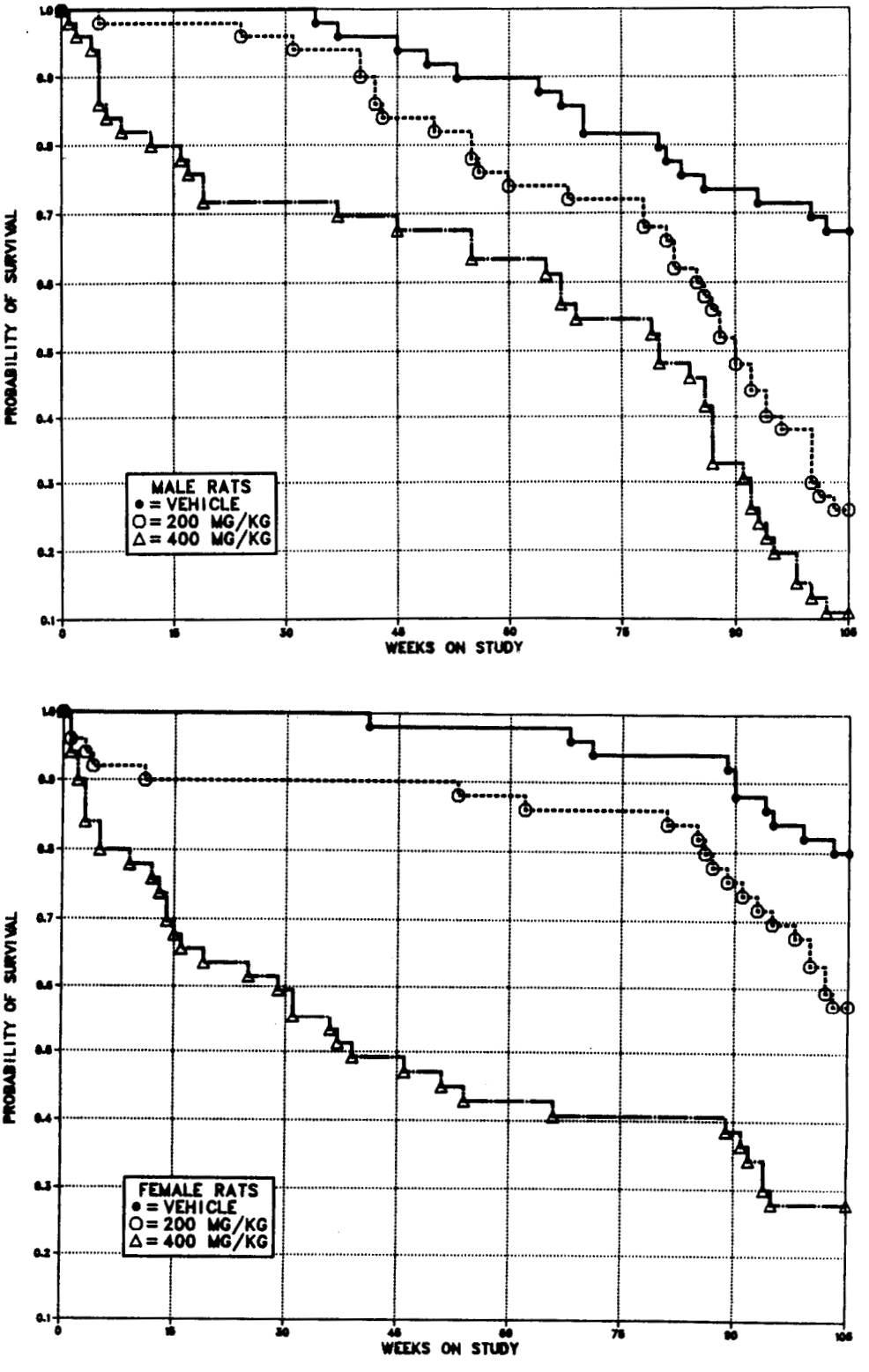

FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED 4-VINYLCYCLOHEXENE IN CORN OIL BY GAVAGE FOR TWO YEARS

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 skin, urinary bladder, pituitary gland, preputial gland, clitoral gland, adrenal gland, testis, hematopoietic system, forestomach, and eye. 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). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

The statistical analyses and interpretation of the tumor incidence data for dosed male rats and high dose female rats were complicated by the marked reduction in survival in these groups compared with that of the vehicle controls. In this situation, the incidental tumor test has reduced sensitivity, since there is relatively little overlapping of survival in dosed and vehicle control groups.

Skin: Squamous cell papillomas and squamous cell papillomas or carcinomas (combined) in male rats occurred with significant positive trends, and the incidences in the high dose group were significantly greater than those in the vehicle controls by the life table test (Table 10). These skin lesions were first detected during clinical observations between weeks 60 and 88, with an average of 23 weeks between time of detection and death of the animal. Based on this information, the life table test using the time of tumor observation appears to be most appropriate for the statistical analysis of these lesions.

Urinary Bladder: A transitional cell papilloma was observed in 1/47 high dose female rats, and a transitional cell carcinoma was observed in 1/49 low dose female rats. These tumors are uncommon in F344/N rats, occurring with a historical incidence of 3/1,084 (0.3%) in corn oil vehicle control female rats. Transitional cell neoplasms were not observed in any other male or female rat group.

TABLE 10. ANALYSIS OF SKIN TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (a)

	Vehicle Control	200 mg/kg	400 mg/kg
Squamous Cell Papilloma			
Overall Rates	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates	0.0%	3.6%	31.9%
Terminal Rates	0/33 (0%)	0/13 (0%)	1/5 (20%)
Life Table Tests (b)	P=0.004	P=0.450	P=0.006
Life Table Tests (c)	P=0.025	P=0.465	P=0.055
Incidental Tumor Tests	P=0.052	P=0.718	P=0.102
Squamous Cell Papilloma or Carcinoma (d)			
Overall Rates	0/50 (0%)	1/50 (2%)	4/50 (8%)
Adjusted Rates	0 %	3.6%	37.5%
Terminal Rates	0/33 (0%)	0/13 (0%)	1/5 (20%)
Life Table Tests (b)	P<0.001	P=0.450	P=0.001
Life Table Tests (c)	P=0.006	P=0.465	P=0.014
Incidental Tumor Tests	P=0.024	P=0.718	P=0.070

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) Analysis using time of death
(c) Analysis using time of tumor observation
(d) Historical incidence at study laboratory (mean): 2/150 (1.3%); historical incidence in NTP studies: 21/1,094 (1.9%)

Anterior Pituitary Gland: The incidences of adenomas and of adenomas or carcinomas (combined) in low dose female rats were significantly greater than those in the vehicle controls by the life table test; however, no corresponding increase was seen in the high dose group (Table 11).

Preputial Gland: Adenomas or carcinomas (combined) in male rats occurred with a significant positive trend by the life table test, although the incidence in the high dose group was not significantly greater than that in the vehicle controls (Table 12).

Clitoral Gland: The incidence of adenomas or squamous cell carcinomas (combined) in low dose female rats was significantly greater than that in the vehicle controls by both the life table and incidental tumor tests (Table 12). No clitoral gland tumors were evident in any of the high dose female rats.

Other Neoplastic Lesions: The incidences of two other neoplasms in low dose and high dose groups were significant by life table analysis because of the earlier appearance of these tumors, despite the fact that overall tumor incidences were actually lower than vehicle control rates. These two neoplasms in male rats were adrenal gland pheochromocytomas (vehicle control, 17/50; low dose, 16/50; high dose, 8/50) and interstitial cell tumors of the testis (vehicle control, 35/50; low dose, 30/50; high dose, 29/50). Since these tumors are not generally considered to be life threatening, life table analyses are probably not appropriate for these particular neoplasms in the present study. The apparent significance of the altered incidences of these tumors is considered to be an artifact caused by the shortened survival of the dosed male rats.

The incidence of mononuclear cell leukemia in high dose male rats was also significantly ($P<0.001$) decreased as measured by the incidental tumor test (vehicle control, 14/50; low dose, 8/50; high dose, 1/50). Again, the apparent effect on the occurrence of this common tumor of F344/N rats was judged to be an artifact of the shortened survival of these dosed animals. In addition, the apparent significant decrease in the incidence of mesotheliomas in high dose male rats ($P=0.042$ by the incidental tumor test) appears to be an artifact that reflects not only the shortened survival of these animals but also the greater than expected incidence of this uncommon tumor in the vehicle controls, (3/50, 6%, vs an historical incidence of 31/1,146, 3%) (Appendix F, Table F2).

TABLE 11. ANALYSIS OF ANTERIOR PITUITARY GLAND TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE

	Vehicle Control	200 mg/kg	400 mg/kg
Adenoma			
Overall Rates	19/50 (38%)	23/48 (48%)	7/44 (16%)
Adjusted Rates	44.9%	65.0%	39.9%
Terminal Rates	17/40 (43%)	15/27 (56%)	3/13 (23%)
Life Table Tests	P=0.212	P=0.022	P=0.512
Incidental Tumor Tests	P=0.522	P=0.095	P=0.444N
Carcinoma			
Overall Rates	0/50 (0%)	1/48 (2%)	0/44 (0%)
Adenoma or Carcinoma (a)			
Overall Rates	19/50 (38%)	24/48 (50%)	7/44 (16%)
Adjusted Rates	44.9%	66.0%	39.9%
Terminal Rates	17/40 (43%)	15/27 (56%)	3/13 (23%)
Life Table Tests	P=0.195	P=0.014	P=0.512
Incidental Tumor Tests	P=0.516	P=0.073	P=0.444N

(a) Historical incidence at study laboratory (mean ± SD): 69/149 (46.3% ± 8.0%); historical incidence in NTP studies: 451/1,092 (41.3% ± 9.3%)

TABLE 12. ANALYSIS OF PREPUTIAL/CLITORAL GLAND TUMORS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

	Vehicle Control	200 mg/kg	400 mg/kg
MALE			
Preputial Gland: Adenoma or Carcinoma			
Overall Rates	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates	2.4%	5.3%	20.9%
Terminal Rates	0/33 (0%)	0/13 (0%)	0/5 (0%)
Life Table Tests	P=0.038	P=0.675	P=0.082
Incidental Tumor Tests	P=0.411	P=0.600N	P=0.637
FEMALE			
Clitoral Gland: Adenoma			
Overall Rates	1/50 (2%)	4/50 (8%)	0/49 (0%)
Adjusted Rates	2.5%	14.3%	0.0%
Terminal Rates	1/40 (3%)	4/28 (14%)	0/13 (0%)
Life Table Tests	P=0.459	P=0.088	P=0.723N
Incidental Tumor Tests	P=0.459	P=0.088	P=0.723N
Clitoral Gland: Adenoma or Squamous Cell Carcinoma (a)			
Overall Rates	1/50 (2%)	5/50 (10%)	0/49 (0%)
Adjusted Rates	2.5%	17.9%	0 0%
Terminal Rates	1/40 (3%)	5/28 (18%)	0/13 (0%)
Life Table Tests	P=0.387	P=0.040	P=0.723N
Incidental Tumor Tests	P=0.387	P=0.040	P=0.723N

(a) Historical incidence at study laboratory (mean): 4/150 (2.7%); range: 1/50-2/50; historical incidence in NTP studies: 24/1,147 (2.1%); range: 0/52-3/48

Forestomach: Epithelial hyperplasia of the forestomach was observed at greater incidences in dosed groups than in the vehicle controls (male: vehicle control, 1/50; low dose, 3/50; high dose, 5/47; female: vehicle control, 0/49; low dose, 2/50; high dose, 2/48). For male rats that survived beyond week 93, this late-appearing lesion occurred at a significantly increased rate ($P<0.01$ by the Fisher exact test) in the high dose group relative to the vehicle controls (vehicle control, 1/35, 3%; low dose, 3/22, 14%; high dose, 4/11, 36%).

Cataracts and Retinal Atrophy: The dose-related decrease in incidences of ocular pathologic effects in male rats (cataracts: vehicle control, 11/50; low dose, 4/50; high dose, 2/50; retinal atrophy: vehicle control, 9/50; low dose, 5/50; high dose, 2/50) probably reflects the placement of cages in racks and the absence of cage rotation, resulting in differences in light exposure among groups. Presumably, this arrangement also accounts for the increased incidences of these lesions in dosed female rats (cataracts: vehicle control, 0/50; low dose, 5/50; high dose, 4/49; retinal atrophy: vehicle control, 0/50; low dose, 5/50; high dose, 5/49). This explanation cannot be verified in the present studies because information indicating the precise placement of cages for the various rat groups is unavailable, but similar observations have been made in other NTP studies conducted before cages were routinely rotated in which differences in ocular pathologic effects were related to specific cage placement relative to the light source.

FOURTEEN-DAY STUDIES

All the mice that received 2,500 or 5,000 mg/kg and 3/5 males that received 1,250 mg/kg 4-vinylcyclohexene died before the end of the studies (Table 13). Tremors and inactivity were observed in the animals that died. Both vehicle control groups and all dosed groups, except the 300 mg/kg group of females, lost weight (4.0%-11.5%) during the studies. No compound-related gross changes were noted at necropsy. Histologic examination was limited to the stomach, as it was previously identified as the target organ; no microscopic lesions were detected in this organ.

Based on the mortality observed in these studies at 4-vinylcyclohexene doses of 1,250 mg/kg or higher, doses of 0, 75, 150, 300, 600, and 1,200 mg/kg were selected for the 13-week studies.

THIRTEEN-WEEK STUDIES

Nine of 10 male and 5/10 female mice that received 1,200 mg/kg and 2/10 female mice that received 300 mg/kg 4-vinylcyclohexene died before the end of the studies (Table 14). All other deaths and one of the deaths in the female 1,200 mg/kg group were considered to be due to gavage error based on tissue injury in the trachea and/or suppurative inflammation in the mediastinum. The sole surviving male receiving 1,200 mg/kg weighed 6% less than the vehicle controls, and females receiving 600 mg/kg weighed 5% less than the vehicle controls. The final body weights of the other dosed groups were not markedly different from those of the vehicle controls.

Mild, acute inflammation of the stomach was seen in the 1,200 mg/kg groups in three males that died before the end of the study and in one female that lived to the end of the study. In addition, histologic reexamination of the ovaries of the high dose female mice revealed that in all 10 animals, whether they died before or at the end of the study, there was a reduction in the number of primary follicles and mature graafian follicles (the ovaries of female mice receiving lower doses were not similarly examined). No other compound-related clinical signs or histopathologic effects were observed in mice that died or were killed (moribund) during the studies or in mice killed at the end of the studies.

TABLE 13. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	26.0 ± 0.9	24.4 ± 0.7	−1.6 ± 0.4	--
300	5/5	25.2 ± 1.0	23.6 ± 0.6	−1.6 ± 0.5	96.7
600	5/5	25.8 ± 1.0	24.0 ± 0.5	−1.8 ± 0.5	98.4
1,250	(d) 2/5	26.0 ± 0.9	22.5 ± 1.5	−2.0 ± 1	92.2
2,500	(e) 0/5	25.2 ± 0.8	(f)	(f)	(f)
5,000	(g) 0/5	25.2 ± 1.1	(f)	(f)	(f)
FEMALE					
0	5/5	19.4 ± 0.2	18.0 ± 0.3	−1.4 ± 0.2	--
300	5/5	18.8 ± 0.4	19.4 ± 0.2	+0.6 ± 0.6	107.8
600	5/5	19.6 ± 0.4	18.2 ± 0.4	−1.4 ± 0.2	101.1
1,250	5/5	18.6 ± 0.7	17.2 ± 0.5	−1.4 ± 0.2	95.5
2,500	(e) 0/5	19.2 ± 0.8	(f)	(f)	(f)
5,000	(g) 0/5	18.8 ± 0.7	(f)	(f)	(f)

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

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	26.3 ± 0.5	32.4 ± 0.5	+6.1 ± 0.3	--
75	10/10	25.6 ± 0.9	33.2 ± 0.8	+7.6 ± 1.0	102.5
150	10/10	26.7 ± 0.7	33.6 ± 1.1	+6.9 ± 0.8	103.7
300	10/10	25.7 ± 0.9	32.5 ± 1.0	+6.8 ± 0.5	100.3
600	10/10	25.4 ± 0.9	31.6 ± 0.9	+6.2 ± 0.6	97.5
1,200	(d) 1/10	26.2 ± 0.6	30.4	+3.3	93.8
FEMALE					
0	10/10	19.5 ± 0.5	24.6 ± 0.6	+5.1 ± 0.4	--
75	10/10	18.9 ± 0.5	24.9 ± 0.7	+6.0 ± 0.4	101.2
150	(e) 9/10	18.8 ± 0.4	25.4 ± 0.6	+6.4 ± 0.5	103.3
300	(f) 8/10	19.1 ± 0.5	24.8 ± 0.6	+5.7 ± 0.6	100.8
600	(e) 8/10	18.8 ± 0.3	23.3 ± 0.4	+4.6 ± 0.2	94.7
1,200	(g) 5/10	19.1 ± 0.5	24.2 ± 0.8	+5.1 ± 0.6	98.4

(a) Number surviving/number in group
(b) Initial group body weight ± standard error of the mean. Subsequent calculations are based on those animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Week of death: 1, 1, 2, 4, 4, 4, 9, 9, 9
(e) Death judged accidental
(f) Week of death: 12, 12
(g) Week of death: 9, 9, 10, 12, 12 (death at week 10 judged accidental)

Dose Selection Rationale: Based on the high mortality observed in female mice receiving 1,200 mg/kg 4-vinylcyclohexene, as well as the marginal depression of final body weights in animals receiving 600 mg/kg, doses of 150 and 300 mg/kg 4-vinylcyclohexene, to be administered in corn oil by gavage, 5 days per week, were originally recommended for the female mice in the 2-year study. For consistency, doses of 150 and 300 mg/kg were recommended for mice of each sex. This recommendation was subsequently modified, and doses of 200 and 400 mg/kg 4-vinylcyclohexene were chosen for the 2-year studies to avoid preparing different doses for mice and rats. These doses appeared reasonable at the time, especially for the male mice, because toxic effects (high mortality) were seen only at the high dose (1,200 mg/kg) in the 13-week study.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice were lower than those of the vehicle controls between weeks 8 and 76, and those of low dose male mice were decreased relative to the vehicle controls between weeks 28 and 60; however, final mean body weights of dosed male mice were comparable to those of the vehicle controls (Table 15 and Figure 3). Mean body weights of high dose female mice were slightly lower than those of the vehicle controls after week 20, whereas the mean body weights of the low dose female mice were generally greater than or comparable to those of the vehicle controls.

TABLE 15. MEAN BODY WEIGHTS AND SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

Weeks on Study	Vehicle Control		200 mg/kg			400 mg/kg		
	Av. Wt. (grams)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors	Av. Wt. (grams)	Wt. (percent of controls)	No. of Survivors
MALE								
0	24.2	50	24.3	100	50	23.7	98	50
1	24.8	50	24.3	98	50	24.7	100	50
2	25.7	48	25.6	100	50	25.0	97	50
3	26.9	48	26.5	99	50	26.4	98	50
4	28.1	48	28.2	100	49	27.6	98	50
5	28.6	48	28.1	98	49	27.7	97	50
6	29.4	48	28.6	97	49	28.2	96	50
7	30.3	48	29.0	96	49	28.5	94	50
8	31.0	48	29.8	96	49	29.3	95	50
9	31.6	44	30.2	96	49	29.8	94	48
10	31.9	44	30.9	97	49	30.2	95	48
11	32.8	44	31.5	96	49	30.8	94	48
12	32.9	44	31.5	96	49	30.9	94	48
13	32.6	44	31.6	97	49	30.4	93	48
16	33.8	44	32.9	97	49	31.8	94	48
20	35.4	44	34.1	96	49	32.9	93	47
24	35.8	44	34.4	96	49	33.0	92	47
28	37.6	44	35.8	95	49	34.2	91	47
32	39.0	44	36.2	93	49	35.2	90	35
36	40.7	44	38.9	96	49	37.4	92	35
40	42.1	44	39.5	94	49	37.5	89	35
44	42.0	44	40.1	95	49	37.5	89	35
48	42.7	44	41.0	96	49	38.3	90	35
52	43.9	44	41.0	93	49	38.1	87	33
56	43.5	44	40.8	94	49	38.3	88	32
60	42.7	44	40.2	94	49	37.9	89	32
64	42.4	43	40.8	96	47	38.6	91	32
68	42.0	43	40.7	97	47	38.2	91	31
72	42.1	43	40.6	96	47	38.7	92	31
76	42.3	43	40.5	96	47	39.0	92	18
80	43.6	43	41.9	96	46	41.3	95	18
84	43.7	43	42.7	98	45	41.6	95	17
88	43.8	42	43.2	99	45	42.0	96	17
92	43.4	42	42.3	97	44	42.0	97	8
96	43.4	41	42.1	97	44	42.4	98	8
100	42.8	38	41.5	97	41	42.8	100	8
FEMALE								
0	19.4	50	19.8	102	50	19.4	100	50
1	20.2	50	20.1	100	50	20.0	99	49
2	20.6	50	20.6	100	50	20.9	101	49
3	21.6	50	21.6	100	50	21.1	98	49
4	22.5	50	22.3	99	50	21.8	97	48
5	22.5	50	22.3	99	50	21.9	97	48
6	22.9	50	22.5	98	50	22.2	97	48
7	22.4	50	23.1	103	50	22.7	101	48
8	23.7	50	23.3	98	50	22.6	95	48
9	23.8	50	23.9	100	50	23.3	98	48
10	24.3	50	24.0	99	50	23.3	96	48
11	24.4	50	24.4	100	50	23.8	98	48
12	24.9	50	24.1	97	50	23.9	96	48
13	24.8	50	24.0	97	50	23.7	96	48
16	25.8	50	25.2	98	50	24.4	95	48
20	27.0	50	25.8	96	50	25.3	94	47
24	27.4	50	26.3	96	50	25.3	92	47
28	28.0	49	27.1	97	50	26.4	94	47
32	30.2	49	28.7	95	50	28.2	93	40
36	31.7	49	30.5	96	50	30.1	95	40
40	33.7	49	32.9	98	50	31.3	93	40
44	33.6	49	33.2	99	49	31.3	93	40
48	33.3	49	34.4	103	49	32.7	98	40
52	35.6	49	35.9	101	49	32.7	92	40
56	34.4	48	35.7	104	49	32.6	95	38
60	34.3	48	36.4	106	48	32.9	96	37
64	34.6	48	37.2	108	48	32.7	95	37
68	34.6	48	37.3	108	48	32.8	95	37
72	34.7	48	36.9	106	48	32.6	94	37
76	35.2	48	37.4	106	48	32.7	93	36
80	37.2	48	38.7	104	48	34.7	93	36
84	37.5	48	38.5	103	47	34.7	93	35
88	38.0	47	39.6	104	47	35.9	94	34
92	39.0	43	39.7	102	44	35.9	92	20
96	39.1	42	39.2	100	44	35.8	92	18
100	39.9	41	37.3	93	41	35.1	88	17

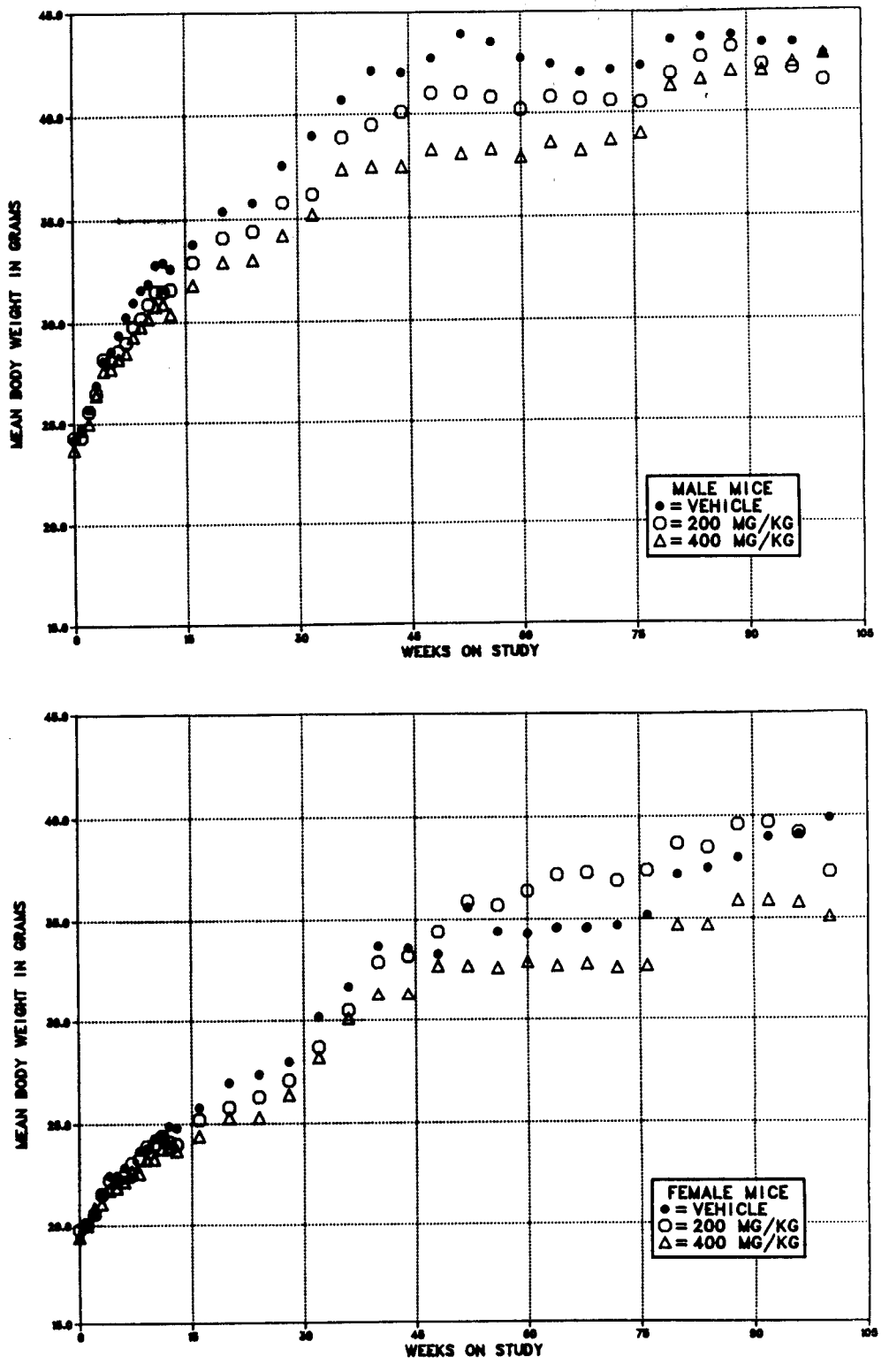

FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED 4-VINYLCYCLOHEXENE IN CORN OIL BY GAVAGE FOR TWO YEARS

III. RESULTS: MICE

Survival

Estimates of the probabilities of survival for male and female mice receiving 4-vinylcyclohexene 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 high dose group of male mice was significantly lower than that of the vehicle controls after week 29; the survival of the female high dose group was significantly reduced after week 32 (Table 16). The survival of both high dose groups was significantly lower than that of their respective low dose groups ($P<0.001$), whereas the survival of the low dose groups was comparable to that of the vehicle controls. Neither gross observations nor histopathologic evaluations revealed a specific cause of death in any of the dosed mouse groups.

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 ovary, lung, hematopoietic system, adrenal gland, forestomach, and liver. 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). Historical incidences of tumors in corn oil vehicle control animals are listed in Appendix F.

TABLE 16. SURVIVAL OF MICE IN THE TWO-YEAR GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

	Vehicle Control	200 mg/kg	400 mg/kg
MALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	9	11	41
Accidentally killed	4	0	2
Killed at termination	37	39	7
Survival P values (c)	<0.001	0.938	<0.001
FEMALE (a)			
Animals initially in study	50	50	50
Nonaccidental deaths before termination (b)	10	11	31
Animals missing	0	0	1
Withdrawn, pregnant	0	0	1
Killed at termination	40	39	17
Survival P values (c)	<0.001	0.846	<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.

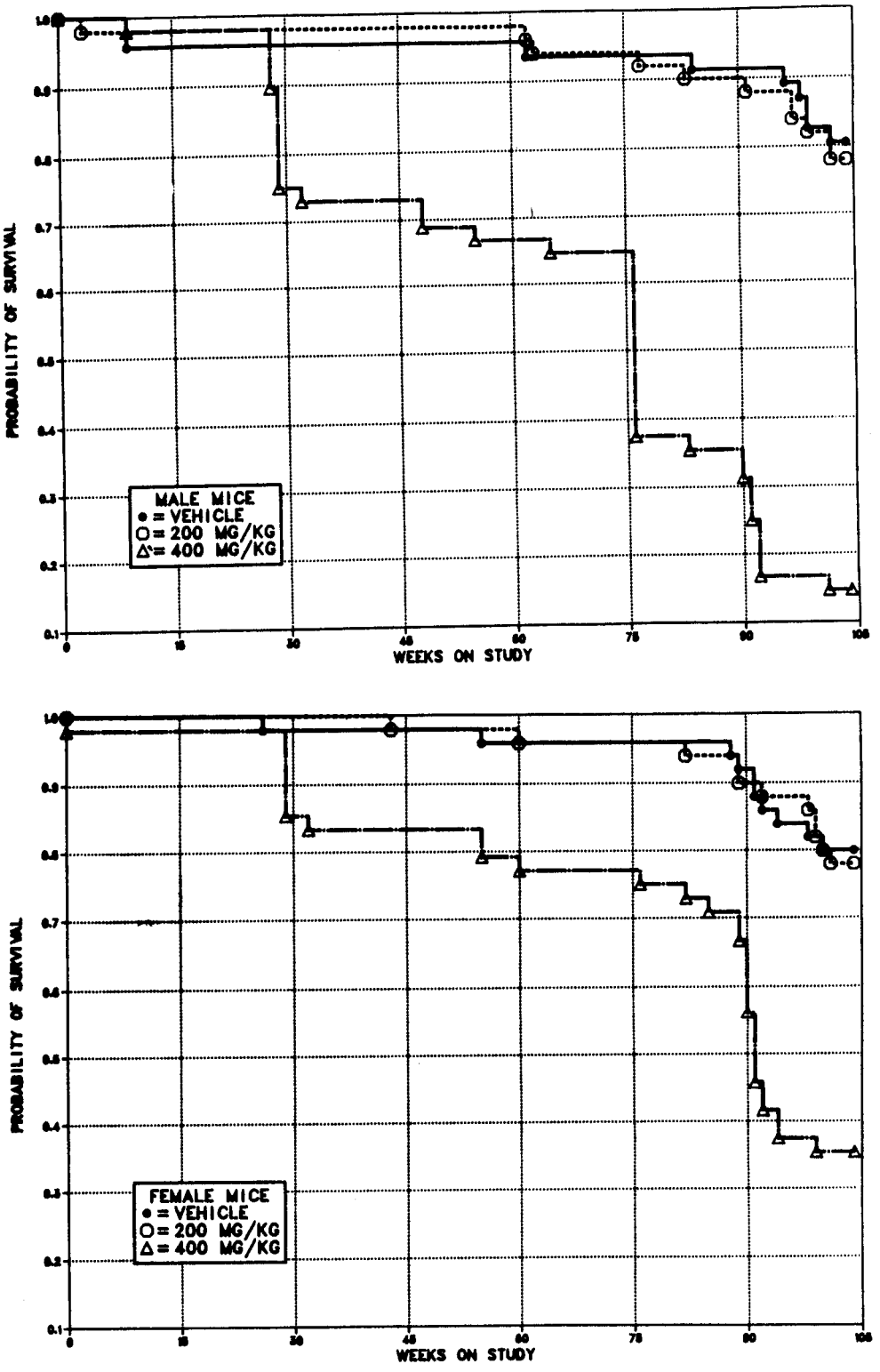

FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED 4-VINYLCYCLOHEXENE IN CORN OIL BY GAVAGE FOR TWO YEARS

Ovary: Mixed benign tumors, granulosa cell tumors, and granulosa cell tumors or carcinomas (combined) occurred in female mice with significant positive trends, and the incidences in both dosed groups were significantly greater than those in the vehicle controls (Table 17). Many ovarian neoplasms were not observed grossly. When observed at necropsy, the neoplasms were usually described as yellow or tan nodules, either solitary or multiple, up to 1 cm in diameter. The ovaries of a few animals were completely replaced by large, red cystic masses measuring as much as 1.5 cm in diameter.

The ovarian neoplasms of many mice were bilateral and were of the same or different histopathologic types. Tubular cell hyperplasia and granulosa cell hyperplasia were also observed at increased incidences in dosed mice (Table 18).

Pathologic descriptions of major ovarian neoplasms and related lesions are as follows:

Mixed tumors, benign are noninvasive, nonmetastasizing neoplasms composed of mixtures of proliferating germinal epithelial cells and granulosa cells.

Granulosa cell neoplasms are proliferations of granulosa cells in patterns that can be described as follicular, trabecular, tubular, solid, or adenomatous, although a single pattern generally predominates in an individual tumor. The majority of the tumors observed in mice in these studies were characterized by follicular or solid patterns. The few that were characterized by the trabecular pattern could be distinguished from mixed tumors by the fact that the tubules were lined with granulosa cells. The cells of the granulosa cell tumors were morphologically similar to those present in granulosa cell *hyperplasia*, although in some animals they were slightly larger than normal granulosa cells and had scant, clear cytoplasm. Those neoplasms designated "granulosa cell carcinoma" had replaced the entire ovary and were described grossly as cystic and hemorrhagic, and all had metastasized to the lungs. (The granulosa cell lesions are a continuum of hyperplastic to benign and malignant neoplastic proliferations, a distinction that is sometimes difficult to make.)

Tubular adenomas are an advanced degree of tubular cell hyperplasia and are part of a continuum of proliferative lesions originating in the germinal epithelium on the outer surface of the ovary; this distinction between neoplastic and nonneoplastic lesions is not always clear. These hyperplastic cells invade the underlying stroma of the ovary-forming tubules and cleft-like spaces lined by cuboidal or low columnar epithelium. The cells of the hyperplastic and neoplastic lesions in the mice of this study had small round nuclei with moderately condensed chromatin and small amounts of amphophilic cytoplasm (stainable with either acidic or basic dyes). The term "tubular adenoma" designated those neoplasms in which the entire ovary was replaced by proliferating tubules.

Luteomas are proliferations of large polyhedral cells with abundant eosinophilic cytoplasm that frequently exhibits a foamy appearance because of lipid droplets.

Papillary adenomas are proliferations of cuboidal or columnar epithelium, which form frond-like projections, the cores of which resemble normal stroma. When forming mucin in cyst-like spaces, these neoplasms are designated as cystadenomas.

TABLE 17. ANALYSIS OF OVARIAN TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (a)

	Vehicle Control	200 mg/kg	400 mg/kg
Mixed Tumor, Benign (b)			
Overall Rates	0/49 (0%)	25/48 (52%)	11/47 (23%)
Adjusted Rates	0 0%	64.1%	43.3%
Terminal Rates	0/39 (0%)	24/38 (63%)	4/16 (25%)
Life Table Tests	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests	P<0.001	P<0.001	P<0.001
Granulosa Cell Tumor			
Overall Rates	1/49 (2%)	9/48 (19%)	11/47 (23%)
Adjusted Rates	2.6%	23.7%	47.3%
Terminal Rates	1/39 (3%)	9/38 (24%)	6/16 (38%)
Life Table Tests	P<0.001	P=0.008	P<0.001
Incidental Tumor Tests	P<0 001	P=0.008	P<0.001
Granulosa Cell Tumor or Carcinoma (c)			
Overall Rates	1/49 (2%)	10/48 (21%)	13/47 (28%)
Adjusted Rates	2.6%	25.5%	54.9%
Terminal Rates	1/39 (3%)	9/38 (24%)	7/16 (44%)
Life Table Tests	P<0.001	P=0.005	P<0.001
Incidental Tumor Tests	P<0 001	P=0.006	P<0.001

(a) The statistical analyses used are discussed in Chapter II (Statistical Methods) and Appendix E (footnotes).
(b) This tumor has not been observed in 1,028 vehicle controls in NTP studies.
(c) One granulosa cell carcinoma and two granulosa cell tumors have been observed among 1,028 vehicle control animals in NTP studies; none of these was observed at the study laboratory.

TABLE 18. NUMBER OF FEMALE MICE WITH OVARIAN LESIONS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE

Lesion	Vehicle Control	200 mg/kg	400 mg/kg
Number of mice examined	49	48	47
Mixed tumor, benign	0	25	11
Tubular adenoma	0	2	1
Tubular cell hyperplasia	1	10	13
Granulosa cell tumor	1	9	11
Granulosa cell carcinoma	0	1	2
Granulosa cell hyperplasia	0	5	1
Luteoma	0	2	0
Papillary adenoma	1	1	0
Papillary cystadenoma	0	0	1
Papillary hyperplasia	0	0	2
Teratoma	1	0	0
Stromal hyperplasia	1	0	0

Lung: Congestion was observed at increased incidences in high dose mice (male: vehicle control, 2/49, 4%; low dose, 2/50, 4%; high dose, 36/50, 72%; female: vehicle control, 0/50; low dose, 1/49, 2%; high dose, 19/48, 40%). In male mice, alveolar/bronchiolar adenomas occurred with a significant positive trend, and the incidence in the high dose group was significantly greater than that in the vehicle controls by the life table test (Table 19). The incidences of adenomas or carcinomas (combined) in dosed female mice were not increased: vehicle control, 6/50 (12%); low dose, 1/49 (2%); high dose, 4/48 (8%).

Hematopoietic System: Atrophy of the splenic red pulp was observed at increased incidence in high dose male mice (vehicle control, 0/49; low dose, 0/49; high dose, 10/46, 22%). Lymphomas in male mice occurred with a significant positive trend (Table 20). Although the overall incidence in the high dose group was similar to that in the vehicle controls, pairwise comparisons incorporating survival adjustments indicated a significantly greater occurrence of lymphomas in high dose males (terminal rates: vehicle control, 3/37, 8%; low dose, 5/39, 13%; high dose, 4/7, 57%).

TABLE 19. ANALYSIS OF LUNG TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE

	Vehicle Control	200 mg/kg	400 mg/kg
Hyperplasia			
Overall Rates	0/49 (0%)	2/50 (4%)	0/50 (0%)
Alveolar/Bronchiolar Adenoma			
Overall Rates	1/49 (2%)	4/50 (8%)	3/50 (6%)
Adjusted Rates	2.7%	9.7%	30.9%
Terminal Rates	1/37 (3%)	3/39 (8%)	2/7 (29%)
Life Table Tests	P=0.014	P=0.199	P=0.021
Incidental Tumor Tests	P=0.095	P=0.236	P=0.051
Alveolar/Bronchiolar Carcinoma			
Overall Rates	3/49 (6%)	7/50 (14%)	1/50 (2%)
Adjusted Rates	7.8%	17.3%	14.3%
Terminal Rates	2/37 (5%)	6/39 (15%)	1/7 (14%)
Life Table Tests	P=0.234	P=0.185	P=0.579
Incidental Tumor Tests	P=0.229	P=0.177	P=0.579
Alveolar/Bronchiolar Adenoma or Carcinoma (a)			
Overall Rates	4/49 (8%)	11/50 (22%)	4/50 (8%)
Adjusted Rates	10.4%	26.5%	44.7%
Terminal Rates	3/37 (8%)	9/39 (23%)	3/7 (43%)
Life Table Tests	P=0.011	P=0.062	P=0.030
Incidental Tumor Tests	P=0.047	P=0.068	P=0.065

(a) Historical incidence at study laboratory (mean ± SD): 14/150 (9.3% ± 5.0%); historical incidence in NTP studies: 155/1,082 (14.3% ± 6.3%)

TABLE 20. ANALYSIS OF HEMATOPOIETIC SYSTEM TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE

	Vehicle Control	200 mg/kg	400 mg/kg
Lymphoma, All Malignant (a)			
Overall Rates	4/50 (8%)	7/50 (14%)	5/50 (10%)
Adjusted Rates	10.5%	16.7%	62.5%
Terminal Rates	3/37 (8%)	5/39 (13%)	4/7 (57%)
Life Table Tests	P=0.007	P=0.301	P=0.002
Incidental Tumor Tests	P=0.013	P=0.340	P=0.001

(a) Historical incidence at study laboratory (mean ± SD): 19/150 (12.7% ± 1.1%); historical incidence in NTP studies: 126/1,090 (11.6% ± 5.6%)

Adrenal Gland: The incidences of cytologic alteration of the adrenal cortex (subcapsular cell hyperplasia, Type B cells) and of congestion of the adrenal gland were increased in dosed female mice (cytologic alteration: vehicle control, 0/50; low dose, 24/49, 49%; high dose, 14/48, 29%; congestion: vehicle control, 0/50; low dose, 0/49; high dose, 8/48, 17%). In female mice, capsular adenomas occurred with a significant positive trend, and the incidence in the high dose group was greater than that in the vehicle controls by the life table test (Table 21). However, it is not clear that the occurrence of these neoplasms is related to compound administration, primarily because the criteria for diagnosis of benign adrenal gland tumors are controversial.

In the present studies, adrenal capsular adenoma refers to a focal collection of type A cells as described by Dunn (1979). Type A cells are fusiform lipid-free cells that appear to arise beneath the adrenal capsule. Cytologic alteration of the adrenal cortex refers to the proliferation of type B cells (polygonal cells containing highly vacuolated cytoplasm) in association with type A cells. The adrenal gland lesions seen in female mice in the present study consisted of clusters of B-cell nests, each nest surrounded by one or two layers of type A spindle cells. The B-cells had abundant clear or vacuolated, sometimes faintly granular, pale, eosinophilic cytoplasm and round, central or slightly eccentrically located vesicular nuclei. These clusters occurred either focally or multifocally in the subcapsular area of the adrenal gland and extended downward into the cortex. In several animals, this proliferation was quite extensive, causing bulging of the capsule and extending down to the medulla. Although the diagnosis was somewhat controversial, the PWG generally considered this proliferation to be severe hyperplasia of the B-cells. Most female mice also had mild diffuse subcapsular type A proliferation that was considered to be within the normal range for aged female mice and was not diagnosed.

TABLE 21. ANALYSIS OF CORTICAL OR CAPSULAR ADRENAL GLAND LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE

	Vehicle Control	200 mg/kg	400 mg/kg
Hyperplasia			
Overall Rates	0/50 (0%)	4/49 (8%)	2/48 (4%)
Adenoma (a)			
Overall Rates	0/50 (0%)	3/49 (6%)	4/48 (8%)
Adjusted Rates	0 0%	7.7%	18.3%
Terminal Rates	0/40 (0%)	3/39 (8%)	2/17 (12%)
Life Table Tests	P=0.005	P=0.117	P=0.011
Incidental Tumor Tests	P=0.027	P=0.117	P=0.056

(a) Historical incidence (includes adrenal adenoma and adrenal cortical adenoma) at study laboratory (mean ± SD): 0/139; historical incidence in NTP studies: 7/1,056 (0.7% ± 1.2%)

Forestomach: Ulcers, mild inflammation, and epithelial hyperplasia were observed at increased incidences in dosed mice of each sex, especially in males (Table 22). The inflammation of the forestomach was generally not observed grossly; microscopic analysis revealed focal or multifocal acute inflammation with erosions of the squamous epithelium and accumulations of polymorphonuclear leukocytes in the submucosa.

Liver: The incidence of centrilobular congestion was increased in high dose male mice (vehicle control, 0/49; low dose, 0/50; high dose, 7/50, 14%); congestion was not observed in any of the female mice.

TABLE 22. NUMBER OF MICE WITH LESIONS OF THE FORESTOMACH IN THE TWO-YEAR GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

Lesion	Vehicle Control	200 mg/kg	400 mg/kg
MALE			
Number of mice examined	47	50	46
Ulcer	0	3	7
Inflammation	0	7	16
Epithelial hyperplasia	0	7	7
Hyperkeratosis	0	0	1
Papilloma	2	0	0
FEMALE			
Number of mice examined	49	49	45
Ulcer	0	0	4
Inflammation	1	2	10
Epithelial hyperplasia	1	3	4
Papilloma	0	2	0

IV. DISCUSSION AND CONCLUSIONS

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4-Vinylcyclohexene was studied for toxic and carcinogenic potential in male and female F344/N rats and B6C3F$_1$ mice that received the compound by oral administration in corn oil. The doses in the 14-day studies were 0 (vehicle control), 300, 600, 1,250, 2,500, or 5,000 mg/kg administered by gavage for 14 consecutive days. In the 13-week studies, the doses were 0 (vehicle control), 50, 100, 200, 400, or 800 mg/kg per day for rats and 0 (vehicle control), 75, 150, 300, 600, or 1,200 mg/kg per day for mice, 5 days per week (gavage). The doses for the 2-year studies, based on survival, body weight gains, and histopathologic effects observed during the 14-day and 13-week studies, were 0 (vehicle control), 200, or 400 mg/kg per day, administered 5 days per week (gavage) for 103 weeks to rats and mice of each sex.

Since many animals died in the 14-day and 13-week studies at doses higher than or equal to 1,200 mg/kg, a relatively cautious approach was attempted in selecting doses for the 2-year studies. Nevertheless, in the 2-year studies, survival of low dose and high dose rats and high dose mice was significantly decreased, including the unexpected deaths within 13 weeks at or below doses that were not lethal in the 13-week studies. Twenty-five of 100 high dose rats were dead by week 13 of the 2-year studies, although only 2/40 rats receiving 400 or 800 mg/kg 4-vinylcyclohexene in the 13-week studies died before the terminal kill. In addition, the major nonneoplastic lesion identified in male rats in the 13-week study, hyaline droplet degeneration of the proximal convoluted tubule of the kidney, was not observed in male rats either dying early or killed at 2 years, and neither gross observations nor histopathologic evaluations revealed a specific cause of death in the dosed rat groups. Similarly, no consistent histopathologic lesions were observed in mice dying before the end of the 2-year studies; thus, the cause of these early deaths is also undetermined.

A slightly greater incidence of epithelial hyperplasia was noted in the forestomachs of dosed rats as compared with that in the vehicle controls. Nonneoplastic effects observed in dosed mice included mild, acute inflammatory lesions of the forestomach, especially in males, lung congestion in high dose males and females, splenic red pulp atrophy in high dose males, and congestion or cytologic alteration of the adrenal cortex in females. However, it is doubtful that these usually nonlethal effects were related to the observed decreased survival.

The increased mortality of dosed animals affected the interpretation of the increased incidences of various neoplastic lesions, especially in rats. Because of the marked decrease in survival observed in both dosed male and female rats, the biologic significance of the altered incidences of several neoplasms is uncertain. These neoplasms include squamous cell papillomas or carcinomas (combined) of the skin in high dose males, pheochromocytomas of the adrenal gland and interstitial cell tumors of the testis in low dose and high dose males, and adenomas or carcinomas (combined) of the anterior pituitary gland and of the clitoral gland in low dose females. It is most likely that the apparent significance of some of these generally nonlethal neoplasms reflects the earlier detection of these tumors in dosed rats dying of unrelated (and undefined) causes, rather than shorter tumor latency or increased tumor frequency. Conversely, the poor survival of dosed rats may have artifactually reduced the incidences of some late-developing neoplasms in these studies.

One animal in each dosed female rat group developed a urinary bladder neoplasm (a transitional cell carcinoma in a low dose female and an adenocarcinoma in a high dose female); although the significance of this finding is unclear, these are uncommon tumors in untreated or corn oil vehicle control F344/N female rats (Haseman et al., 1984). In summary, because of the severe mortality unrelated to neoplasia that occurred at both doses, the present 2-year gavage studies of 4-vinylcyclohexene in F344/N rats are considered inadequate for determining the presence or absence of a carcinogenic response.

In B6C3F$_1$ mice, administration of 4-vinylcyclohexene for 2 years resulted in a significant increase in the incidence of uncommon ovarian neoplasms in both groups of dosed females (Table 23). This effect was statistically significant ($P < 0.01$) whether the results were analyzed by survival-adjusted or unadjusted analyses; thus,

TABLE 23. INCIDENCE OF OVARIAN LESIONS IN FEMALE B6C3F$_1$ MICE IN THE PRESENT STUDY AND IN VEHICLE CONTROL GROUPS IN NTP STUDIES OF 104 WEEKS

Tumor Type	4-Vinylcyclohexene			Historical Controls	
	Vehicle Control	200 mg/kg	400 mg/kg	Same Laboratory	All Laboratories
Tubular cell or granulosa cell hyperplasia	1/49 (2%)	(a) 15/48 (31%)	(a) 14/47 (30%)		
Mixed tumor, benign	0/49 (0%)	(a) 25/48 (52%)	(a) 11/47 (23%)	0/141 (0%)	0/1,028 (0%)
Granulosa cell tumor	1/49 (2%)	(a) 9/48 (19%)	(a) 11/47 (23%)	0/141 (0%)	2/1,028 (0.2%)
Granulosa cell tumor or carcinoma	1/49 (2%)	(a) 10/48 (21%)	(a) 13/47 (28%)	0/141 (0%)	3/1,028 (0.3%)

(a) Significant ($P<0.01$) relative to vehicle control

compound-related effects on survival, which were seen only in high dose mice, did not influence the interpretation of the results in females. Several types of histologically distinct ovarian neoplasms were seen at increased incidences, including granulosa cell tumors, granulosa cell tumors or carcinomas (combined), and those classified as "mixed tumor, benign." Dosed female mice also had increased incidences of tubular cell or granulosa cell hyperplasia.

Adrenal gland adenomas in female mice occurred with a significant positive trend by the life table test, and the incidences at both doses substantially exceeded that of the historical vehicle controls (see Table 21). However, it is unclear whether the increased occurrence of this lesion is a direct effect of compound administration or is secondary to the ovarian effects. Studies have demonstrated the induction by ovariectomy of similar adrenal gland lesions in which type A cells proliferate, followed by type B cells (Dunn, 1979). This process continues until nodular masses of type A and type B cells fill the cortex. Since these subcapsular changes are found spontaneously in aged female mice as ovarian function is decreasing, the proliferation of type A and type B cells in the adrenal cortex of dosed female mice in the present study may have been secondary to the effect of 4-vinylcyclohexene on the ovary.

The early deaths of most high dose male mice complicated interpretation of the increased incidences of malignant lymphomas and alveolar/bronchiolar adenomas or carcinomas (combined) in the few survivors. Low dose mice, whose survival was similar to that of the vehicle controls, did not demonstrate significantly increased incidences of any neoplastic lesions. These considerations lead to the conclusion that, as in the case of the F344/N rats, the 2-year study in male B6C3F$_1$ mice was inadequate for determining the presence or absence of a carcinogenic response.

Long-term administration of 4-vinylcyclohexene to B6C3F$_1$ mice increased the incidences of a variety of nonneoplastic lesions, including ulcers, inflammation, and epithelial hyperplasia of the forestomach in males and females, cytologic alteration of the adrenal cortex in high dose and low dose females, congestion of the lung in high dose males and females and of the adrenal gland in high dose females, and splenic red pulp atrophy in high dose males. However, it is unlikely that these nonneoplastic lesions contributed to the large number of deaths in high dose mice of each sex in these studies, since these lesions are generally considered to be nonlethal.

Several in vivo and in vitro studies support the hypothesis that 4-vinylcyclohexene may be metabolized in vivo to yield mutagenic/carcinogenic derivatives. The NTP found that 4-vinylcyclohexene was not mutagenic in *Salmonella typhimurium* strains TA100, TA1535, TA1537, or TA98 in the presence or absence of Aroclor 1254-induced male Sprague-Dawley rat or male Syrian hamster liver S9 (Appendix G). In contrast,

IV. DISCUSSION AND CONCLUSIONS

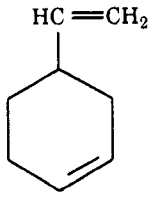
a number of metabolites of 4-vinylcyclohexene, especially its diepoxide, have been shown to be highly mutagenic. (Figure 5 presents the structural relationships between 4-vinylcyclohexene and some of its derivatives.) 4-Vinylcyclohexene diepoxide was mutagenic in *Salmonella typhimurium* strains TA100 and TA1535 both in the presence and absence of S9 (Murray and Cummins, 1979; El-Tantawy and Hammock, 1980; Simmon and Baden, 1980; Frantz and Sinsheimer, 1981; Turchi et al., 1981; Watabe et al., 1981); it was also mutagenic in *Klebsiella pneumoniae* (Voogd et al., 1981). In Salmonella, this compound is a direct-acting, base-pair substitution mutagen. In addition, the diepoxide was mutagenic at the HGPRT locus in V79 Chinese hamster lung cells and induced chromosomal abnormalities (anaphase bridges) in these cells (Turchi et al., 1981). Turchi and coworkers also compared the genetic effects of the diepoxide with a number of other epoxide derivatives of 4-vinylcyclohexene, including 4-vinyl-1,2-epoxycyclohexane and 4-epoxyethyl-1,2-dihydroxycyclohexane, and found that the diepoxide was most active. These investigators concluded that the degree of genotoxicity was directly related to the alkylating properties of the epoxides. Recent studies have confirmed the mutagenicity of 4-vinylcyclohexene diepoxide in several strains of Salmonella in the presence and absence of S9, as well as its S9-independent ability to induce sister-chromatid exchanges and chromosomal aberrations in Chinese hamster ovary cells (E. Zeiger, NTP, unpublished data).

4-Vinylcyclohexene diepoxide has also been shown to be carcinogenic in long-term dermal studies in Swiss-Millerton mice (Van Duuren et al., 1963, 1967), and a threshold limit value of 10 ppm has been established (ACGIH, 1983). Furthermore, the current NTP 2-year dermal studies of 4-vinylcyclohexene diepoxide in $B6C3F_1$ mice indicate the induction of papillomas and squamous cell carcinomas of the skin by week 65; a variety of neoplastic and nonneoplastic ovarian lesions were also observed in dosed female mice (R. Chhabra, NTP, unpublished data).

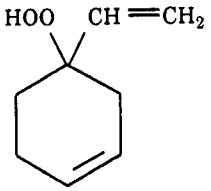
Theoretically, mutagenic metabolites of 4-vinylcyclohexene could be hydrolyzed to diols or conjugated with reduced glutathione. Consistent with the latter pathway, both the diepoxide of 4-vinylcyclohexene and 4-vinyl-1,2-epoxycyclohexane have been shown to be substrates for glutathione S-transferase (Boyland and Williams, 1965; Hayakawa et al., 1975). Furthermore, intraperitoneal administration of 500 mg/kg 4-vinylcyclohexene or its monoxide to male Swiss mice induced a number of hepatic xenobiotic biotransforming enzymes involved in the metabolism of these compounds, including cytochromes P-450 and b_5, NADPH-cytochrome c reductase, aminopyrine-*N*-demethylase, and epoxide hydrolase (Giannarini et al., 1981). (Note that NADPH-cytochrome c reductase is involved in the conversion of 4-vinylcyclohexene to its mutagenic/carcinogenic diepoxide derivative.) Intraperitoneal administration of 4-vinylcyclohexene rapidly depleted hepatic reduced glutathione. Thus, 4-vinylcyclohexene is probably converted to mono- and diepoxide derivatives, which in turn are detoxified to the respective glycols by epoxide hydrolase and glutathione (Figure 6). As expected, the epoxide derivatives of 4-vinylcyclohexene are mutagenic, whereas the glycol derivatives are not (Turchi et al., 1981).

The induction of uncommon ovarian neoplasms in female mice may indicate that hormonal influences are involved in the carcinogenic response to 4-vinylcyclohexene. It is of particular interest that long-term inhalation testing of 1,3-butadiene, from which 4-vinylcyclohexene forms via dimerization (Rappaport and Fraser, 1976), also has revealed the induction of high incidences of ovarian neoplasms in $B6C3F_1$ mice, especially granulosa cell tumors (NTP, 1984; Huff et al., 1985).

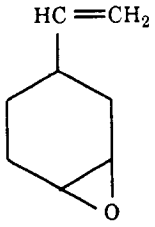
The inhalation route of exposure would appear to be most appropriate for further safety assessment studies of 4-vinylcyclohexene. In addition, pharmacokinetic studies may contribute to an understanding of the mechanism(s) responsible for the targeting of the ovary in female mice by this compound. It should be noted that the doses used in the present gavage studies, converted to inhaled concentrations according to the procedure of Alarie (1982), correspond to exposure concentrations of approximately 300-400 ppm, similar to the suggested vapor concentration limit for 4-vinylcyclohexene in the workplace



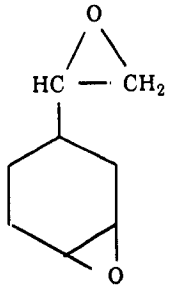
4-Vinylcyclohexene



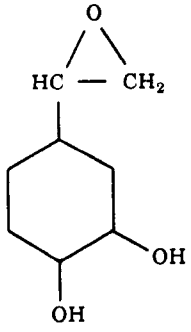
4-Vinylcyclohexene hydroperoxide



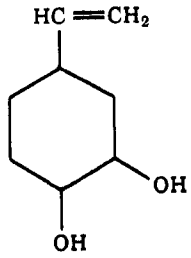
4-Vinyl-1,2-epoxycyclohexane
(4-Vinylcyclohexene monoxide,
4-Vinylcyclohexene-1,2-epoxide)



4-Vinylcyclohexene diepoxide
(4-Epoxyethyl-1,2-epoxycyclohexane)



4-Epoxyethyl-1,2-dihydroxycyclohexane
(4-Vinylcyclohexene-7,8-epoxide-1,2-diol)



4-Vinylcyclohexene-1,2-glycol

FIGURE 5. STRUCTURAL RELATIONSHIP BETWEEN 4-VINYLCYCLOHEXENE AND ITS MAJOR DERIVATIVES

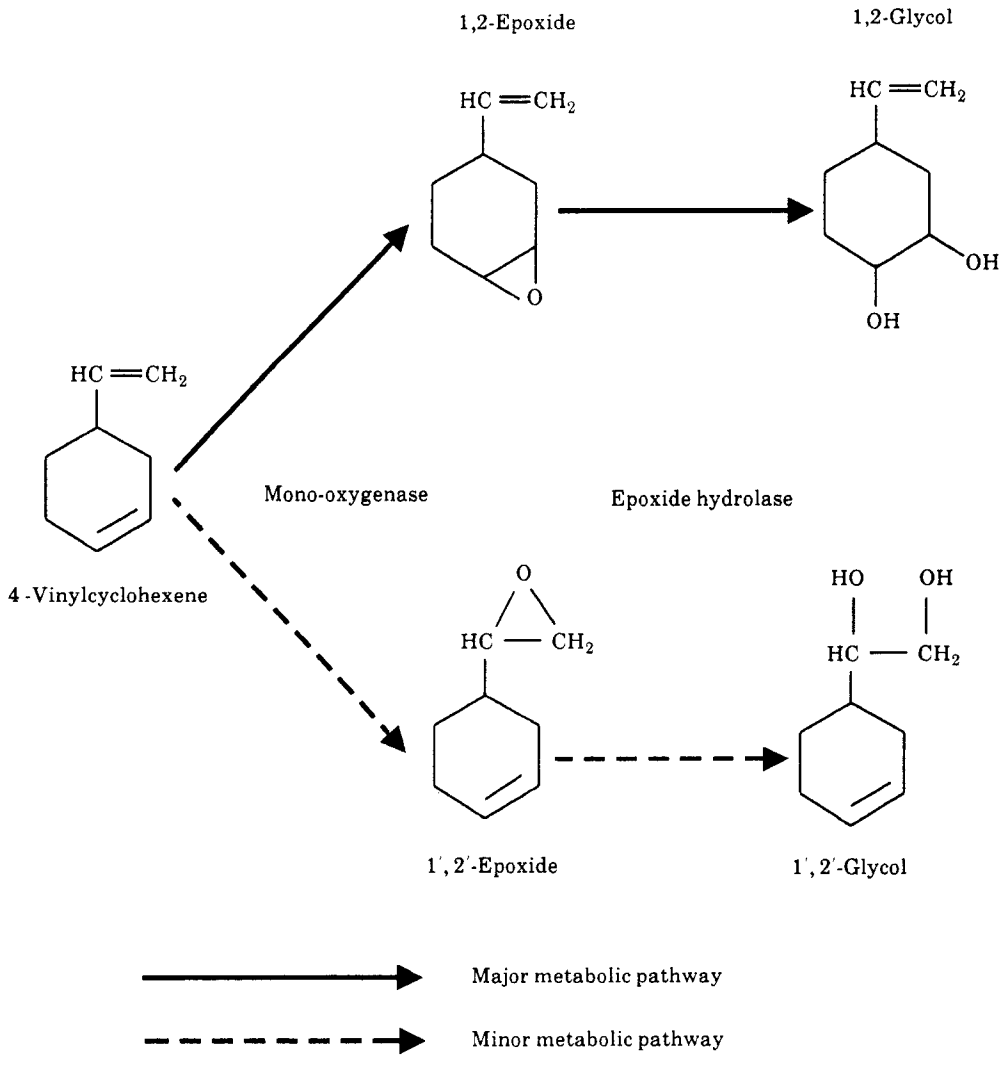


FIGURE 6. METABOLIC OXIDATION OF 4-VINYLCYCLOHEXENE TO GLYCOLS VIA EPOXIDE INTERMEDIATES BY LIVER MICROSOMAL ENZYMES

(Watabe et al., 1981)

environment of 100 ppm (Sandmeyer, 1981). For comparison, the reported LC_{50} values of 4-vinylcyclohexene are 6,095 ppm in rats and 10,610 ppm in mice (IARC, 1976).

Conclusions: 4-Vinylcyclohexene was administered by gavage in corn oil to F344/N rats and B6C3F$_1$ mice of each sex at doses of 200 or 400 mg/kg for 103 weeks. Under these conditions, the 2-year gavage studies of 4-vinylcyclohexene in male and female rats and male mice were considered *inadequate studies of carcinogenicity** because of extensive and early mortality at the high dose or at both doses and the lack of conclusive evidence of a carcinogenic effect. There was *clear evidence of carcinogenicity* of 4-vinylcyclohexene for female mice, as shown by markedly increased incidences of uncommon ovarian neoplasms at both doses. In addition, the increased incidence of adrenal gland adenomas in high dose female mice may have been related to the administration of 4-vinylcyclohexene.

*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 pages 13 and 14.

V. REFERENCES

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1. Alarie, Y. (1982) Inhalation and toxic responses of lung. Mid-America Toxicology Course Study Guide (Kansas City, KA). Washington, DC: American Board of Toxicology, pp. 395-396.

2. American Conference of Governmental Industrial Hygienists (ACGIH) (1983) TLVs: Threshold limit values for chemical substances and physical agents in the work environment with intended changes for 1983-84. Cincinnati, OH: ACGIH.

3. Armitage, P. (1971) Statistical Methods in Medical Research. New York: John Wiley & Sons, Inc., pp. 362-365.

4. Berenblum, I., Ed. (1969) Carcinogenicity Testing: A Report of the Panel on Carcinogenicity of the Cancer Research Commission of UICC, Vol. 2. Geneva: International Union Against Cancer.

5. Boorman, G.; Montgomery, C., Jr.; Hardisty, J.; Eustis, S.; Wolfe, M.; McConnell, E. (1985) Quality assurance in pathology for rodent toxicology and carcinogenicity tests. Milman H.; Weisburger E., Eds.: Handbook of Carcinogen Testing. Park Ridge, NJ: Noyes Publications, pp. 345-357.

6. Boyland, E.; Williams, K. (1965) An enzyme catalysing the conjugation of epoxides with glutathione. Biochem. J. 94:190-197.

7. Bykov, L. (1968) Maximum permissible concentration of vinylcyclohexene in the air of industrial buildings. Proceedings of a Conference on the Toxicology and Hygiene of Petrochemical Industrial Products. Moscow, pp. 32-34.

8. Chemical Rubber Company (CRC) Handbook of Chemistry and Physics, 53rd ed. (1972) Cleveland, OH: Chemical Rubber Company Press, p. C-259.

9. Cox, D. (1972) Regression models and life tables. J. R. Stat. Soc. B34:187-220.

10. Dunn, T. (1979) Tumours of the adrenal gland. Pathology of Tumours in Laboratory Animals, Volume II, Tumours of the Mouse, IARC Scientific Publication No. 23. Lyon, France, pp. 475-486.

11. El-Tantawy, M.; Hammock, B. (1980) The effect of hepatic microsomal and cytosolic subcellular fractions on the mutagenic activity of epoxide-containing compounds in the Salmonella assay. Mutat. Res. 79:59-71.

12. Frantz, S.; Sinsheimer, J. (1981) Bacterial mutagenicity and toxicity of cycloaliphatic epoxides. Mutat. Res. 90:67-78.

13. Fraser, D.; Rappaport, S. (1976) Health aspects of the curing of synthetic rubbers. Environ. Health Perspect. 17:45-53.

14. Gart, J.; Chu, K.; Tarone, R. (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity. J. Natl. Cancer Inst. 62:957-974.

15. Gervasi, P.; Abbondandolo, A.; Citti, L.; Turchi, G. (1980) Microsomal 4-vinylcyclohexene monooxygenase and mutagenic activity of metabolic intermediates. Gut, I., Ed.: Proceedings of the International Conference on Industrial and Environmental Xenobiotics: Biotransformation and Pharmacokinetics. Berlin: Springer-Verlag, pp. 205-210.

16. Giannarini, C.; Citti, L.; Gervasi, P.; Turchi, G. (1981) Effects of 4-vinylcyclohexene and its main oxirane metabolite on mouse enzymes and glutathione levels. Toxicol. Lett. 8:115-121.

17. Haseman, J. (1984) Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environ. Health Perspect. 58:385-392.

18. Haseman, J.; Huff, J.; Boorman, G. (1984) Use of historical control data in carcinogenicity studies in rodents. Toxicol. Pathol. 12:126-135.

19. Haworth, S.; Lawlor, T.; Mortelmans, K.; Speck, W.; Zeiger, E. (1983) *Salmonella* mutagenicity test results for 250 chemicals. Environ. Mutagen. 5 (Suppl. 1):3-142.

20. Hayakawa, T.; Udenfriend, S.; Yagi, H.; Jerina, D. (1975) Substrates and inhibitors of hepatic glutathione S-epoxide transferase. Arch. Biochem. Biophys. 170:438-451.

21. Huff, J.; Melnick, R.; Solleveld, H.; Haseman, J.; Powers, M. (1985) Multiple organ carcinogenicity of 1,3-butadiene in B6C3F$_1$ mice after 60 weeks of inhalation exposure. Science 227:548-549.

22. International Agency for Research on Cancer (IARC) (1976) Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general considerations on volatile anaesthetics. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 11. Lyon, France, pp. 141-145, 277-281.

23. International Agency for Research on Cancer (IARC) (1982) The rubber industry. Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 28. Lyon, France.

24. Kaplan, E.; Meier, P. (1958) Nonparametric estimation of incomplete observations. J. Am. Stat. Assoc. 53:457-481.

25. Linhart, M.; Cooper, J.; Martin, R.; Page, N.; Peters, J. (1974) Carcinogenesis bioassay data system. Comp. Biomed. Res. 7:230-248.

26. Mancuso, T. (1976) Problems and perspectives in epidemiological study of occupational health hazards in the rubber industry. Environ. Health Perspect. 17:21-30.

27. Mancuso, T.; Ciocci, A.; El-Attar, A. (1968) An epidemiological approach to the rubber industry. A study based on departmental experience. J. Occup. Med. 10:213-232.

28. Mantel, N.; Haenszel, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719-748.

29. Maronpot, R.; Boorman, G. (1982) Interpretation of rodent hepatocellular proliferative alterations and hepatocellular tumors in chemical safety assessment. Toxicol. Pathol. 10:71-80.

30. McConnell, E.; Solleveld, H.; Swenberg, J.; Boorman, G. (1986) Guidelines for combining neoplasms for evaluation of rodent carcinogenesis studies. J. Natl. Cancer Inst. (in press).

31. Murray, M.; Cummins, J. (1979) Mutagenic activity of epoxy embedding reagents employed in electron microscopy. Environ. Mutagen. 1:307-313.

32. National Cancer Institute (NCI) (1976) Guidelines for Carcinogen Bioassay in Small Rodents. NCI Carcinogenesis Technical Report Series No. 1, February.

33. National Institute for Occupational Safety and Health (NIOSH) (1980) Registry of Toxic Effects of Chemical Substances, Vol. II. Cincinnati, OH: NIOSH, p. 569.

34. National Institutes of Health (NIH) (1978) NIH Specification NIH-11-133f, November 1.

35. National Toxicology Program (NTP) (1984) Toxicology and Carcinogenesis Studies of 1,3-Butadiene in B6C3F$_1$ Mice (NTP Technical Report No. 288). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. 111 p.

36. Rappaport, S.; Fraser, D. (1976) Gas chromatographic-mass spectrophotometric identification of volatiles released from a rubber stock during simulated vulcanization. Anal. Chem. 48:476-481.

37. Rappaport, S.; Fraser, D. (1977) Air sampling and analysis in a rubber vulcanization area. Am. Ind. Hyg. Assoc. J. 38:205-210.

38. Sadtler Research Laboratories, Sadtler Standard Spectra. IR No. 6321; NMR No. 9681 M. Philadelphia, PA.

39. Sandmeyer, E. (1981) Alicyclic hydrocarbons. Clayton G.; Clayton, F., Eds.: Patty's Industrial Hygiene and Toxicology, Vol. 2B: Toxicology, 3rd rev. ed. New York: John Wiley & Sons, Inc., pp. 3221-3251.

40. Simmon, V.; Baden, J. (1980) Mutagenic activity of vinyl compounds and derived epoxides. Mutat. Res. 78:227-231.

41. Smyth, Jr., H.; Carpenter, C.; Weil, C.; Pozzani, U.; Striegel, J.; Nycum, J. (1969) Range-finding toxicity data: List VII. Am. Ind. Hyg. Assoc. J. 30:470-476.

42. Tarone, R. (1975) Tests for trend in life table analysis. Biometrika 62:679-682.

V. REFERENCES

43. Turchi, G.; Bonatti, S.; Citti, L.; Gervasi, P.; Abbondandolo, A.; Presciuttini, S. (1981) Alkylating properties and genetic activity of 4-vinylcyclohexene metabolites and structurally related epoxides. Mutat. Res. 83:419-430.

44. U.S. Environmental Protection Agency (USEPA) (1980) TSCA Inventory. Toxic Substances Control Act. Washington, DC: USEPA, Office of Pesticides and Toxic Substances, Chemical Information Division, Chemicals in Commerce Information System.

45. U.S. International Trade Commission (USITC) (1983) Synthetic Organic Chemicals, United States Production and Sales 1982. USITC Publication No. 1422, Washington, DC: Government Printing Office.

46. Van Duuren, B. (1965) Carcinogenic epoxides, lactones, and hydroperoxides. Wogan, G., Ed.: Mycotoxins in Foodstuffs. Cambridge, MA: MIT Press, pp. 275-285.

47. Van Duuren, B.; Nelson, N.; Orris, L.; Palmes, E.; Schmitt, F. (1963) Carcinogenicity of epoxides, lactones, and peroxy compounds. J. Natl. Cancer Inst. 31:41-55.

48. Van Duuren, B.; Langseth, L.; Goldschmidt, B.; Orris, L. (1967) Carcinogenicity of epoxides, lactones, and peroxy compounds. VI. Structure and carcinogenic activity. J. Natl. Cancer Inst. 39:1217-1228.

49. Voogd, C.; van der Stel, J.; Jacobs, J. (1981) The mutagenic action of aliphatic epoxides. Mutat. Res. 89:269-282.

50. Wang, H.; You, X.; Qu, Y.; Wang, W.; Wang, D.; Long, Y.; Ni, J. (1984) Investigation of cancer epidemiology and study of carcinogenic agents in the Shanghai rubber industry. Cancer Res. 44:3101-3105.

51. Watabe, T.; Hiratsuka, A.; Isobe, M.; Ozawa, N. (1980) Metabolism of *d*-limonene by hepatic microsomes to non-mutagenic epoxides toward *Salmonella typhimurium*. Biochem. Pharmacol. 29:1068-1071.

52. Watabe, T.; Hiratsuka, A.; Ozawa, N.; Isobe, M. (1981) A comparative study on the metabolism of *d*-limonene and 4-vinylcyclohex-1-ene by hepatic microsomes. Xenobiotica 11:333-344.

APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE

	CONTROL (VEH)	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		1 (2%)	3 (6%)
Squamous cell carcinoma			1 (2%)
Basal cell tumor	2 (4%)	2 (4%)	
Keratoacanthoma		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
Fibroma	1 (2%)	2 (4%)	
Fibrosarcoma		1 (2%)	
Neurofibroma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(50)
Alveolar/bronchiolar carcinoma		1 (2%)	
Sarcoma, NOS, metastatic			1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Leukemia, mononuclear cell	14 (28%)	7 (14%)	1 (2%)
#Spleen	(50)	(49)	(46)
Leiomyoma	1 (2%)		
Leukemia, mononuclear cell		1 (2%)	
CIRCULATORY SYSTEM			
#Heart	(50)	(49)	(50)
Sarcoma, NOS, metastatic			1 (2%)
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(49)	(50)
Adenoma, NOS	1 (2%)		
#Liver	(50)	(50)	(50)
Neoplastic nodule		1 (2%)	
Hepatocellular carcinoma	1 (2%)		
#Pancreas	(50)	(50)	(46)
Adenoma, NOS			1 (2%)
#Jejunum	(47)	(48)	(40)
Adenocarcinoma, NOS		1 (2%)	
#Colon	(48)	(49)	(44)
Sarcoma, NOS, metastatic			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Tubular cell adenoma	1 (2%)		1 (2%)
Sarcoma, NOS, metastatic			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(49)	(45)
Adenoma, NOS	15 (30%)	11 (22%)	7 (16%)
#Adrenal	(50)	(50)	(50)
Pheochromocytoma	15 (30%)	14 (28%)	8 (16%)
#Adrenal medulla	(50)	(50)	(50)
Pheochromocytoma	2 (4%)	2 (4%)	
#Thyroid	(48)	(50)	(46)
Follicular cell adenoma		1 (2%)	
C-cell adenoma	4 (8%)	5 (10%)	
#Pancreatic islets	(50)	(50)	(46)
Islet cell carcinoma	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Fibroadenoma		1 (2%)	
*Preputial gland	(50)	(50)	(50)
Carcinoma, NOS	1 (2%)	1 (2%)	1 (2%)
Adenoma, NOS			2 (4%)
#Testis	(50)	(50)	(50)
Interstitial cell tumor	35 (70%)	30 (60%)	29 (58%)
NERVOUS SYSTEM			
#Brain	(50)	(49)	(50)
Glioma, NOS		1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
*Eye/iris	(50)	(50)	(50)
Leiomyoma			1 (2%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(50)
Paraganglioma, NOS	1 (2%)		
*Tunica vaginalis	(50)	(50)	(50)
Mesothelioma, NOS	2 (4%)		
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Mesothelioma, NOS	1 (2%)		
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	9	23	32
Moribund sacrifice	8	14	10
Terminal sacrifice	32	13	5
Dosing accident			3
Accidentally killed, NOS	1		

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	44	37	31
Total primary tumors	98	87	56
Total animals with benign tumors	38	36	31
Total benign tumors	77	71	52
Total animals with malignant tumors	17	13	3
Total malignant tumors	17	15	4
Total animals with secondary tumors##			1
Total secondary tumors			4
Total animals with tumors uncertain-- benign or malignant	4	1	
Total uncertain tumors	4	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 4-VINYLCYCLOHEXENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(49)
Squamous cell papilloma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(49)
Undifferentiated carcinoma		1 (2%)	
Fibroma	1 (2%)		
Neurofibrosarcoma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(50)	(48)
Neoplasm, NOS, metastatic	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(49)
Leukemia, mononuclear cell	7 (14%)	13 (26%)	5 (10%)
#Spleen	(49)	(49)	(47)
Leukemia, mononuclear cell	1 (2%)		
#Mandibular lym,ph node	(49)	(48)	(46)
Neoplasm, NOS, unclear primary or metas	1 (2%)		
#Liver	(49)	(50)	(48)
Leukemia, mononuclear cell	1 (2%)		
CIRCULATORY SYSTEM			
None			
DIGESTIVE SYSTEM			
*Tongue	(50)	(50)	(49)
Squamous cell papilloma			1 (2%)
#Liver	(49)	(50)	(48)
Neoplastic nodule	1 (2%)	2 (4%)	
#Pancreas	(49)	(49)	(49)
Sarcoma, NOS, unclear primary or metas			1 (2%)
URINARY SYSTEM			
#Urinary bladder	(50)	(49)	(47)
Transitional cell papilloma			1 (2%)
Transitional cell carcinoma		1 (2%)	
Adenocarcinoma, NOS, invasive			1 (2%)
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(48)	(44)
Carcinoma, NOS		1 (2%)	
Adenoma, NOS	19 (38%)	23 (48%)	7 (16%)
#Adrenal	(50)	(49)	(49)
Pheochromocytoma	3 (6%)	3 (6%)	1 (2%)

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM (Continued)			
#Thyroid	(49)	(50)	(47)
Follicular cell carcinoma		1 (2%)	
C-cell adenoma	3 (6%)	4 (8%)	
C-cell carcinoma	2 (4%)		
#Pancreatic islets	(49)	(49)	(49)
Islet cell adenoma	2 (4%)		
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(49)
Carcinoma, NOS		1 (2%)	
Fibroadenoma	7 (14%)	9 (18%)	4 (8%)
*Clitoral gland	(50)	(50)	(49)
Squamous cell carcinoma		1 (2%)	
Adenoma, NOS	1 (2%)	4 (8%)	
#Uterus	(49)	(49)	(47)
Adenoma, NOS		2 (4%)	
Adenocarcinoma, NOS	1 (2%)		1 (2%)
Leiomyosarcoma	2 (4%)		
Endometrial stromal polyp	8 (16%)	9 (18%)	5 (11%)
NERVOUS SYSTEM			
#Brain	(50)	(50)	(49)
Carcinoma, NOS, invasive		1 (2%)	
Glioma, NOS	1 (2%)	1 (2%)	1 (2%)
SPECIAL SENSE ORGANS			
None			
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(50)	(49)
Undiff. carcinoma, metastatic		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(49)
Adenocarcinoma, NOS, metastatic			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	4	10	30
Moribund sacrifice	6	11	5
Terminal sacrifice	40	28	13
Dosing accident		1	1
Animal missing			1

TABLE A2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
Total animals with primary tumors**	38	37	18
Total primary tumors	62	77	27
Total animals with benign tumors	33	33	16
Total benign tumors	45	54	19
Total animals with malignant tumors	13	20	7
Total malignant tumors	15	21	7
Total animals with secondary tumors##	1	2	1
Total secondary tumors	1	2	2
Total animals with tumors uncertain--benign or malignant	1	2	
Total uncertain tumors	1	2	
Total animals with tumors uncertain--primary or metastatic	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 A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE: VEHICLE CONTROL

ANIMAL NUMBER	0028	0040	0161	0446	0334	0338	0051	0126	0008	0144	0499	0077	0044	0399	0422	0477	0302	0023	0055	0066	0099	0110	0111	0133
WEEKS ON STUDY	0001	0034	0037	0045	0049	0053	0064	0067	0070	0070	0080	0081	0083	0086	0093	0100	0102	0104	0104	0104	0104	0104	0104	0104
INTEGUMENTARY SYSTEM																								
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell tumor											X													
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyoma																			X					
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																				X				
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																								
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	−	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
Large intestine	+	+	−	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																								
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																X		X					X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																X	X	X			X	X	X	
Thyroid	−	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma														X				X						
Parathyroid	−	+	+	+	+	+	+	−	+	−	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																								
REPRODUCTIVE SYSTEM																								
Mammary gland	+	+	N	+	+	+	+	N	+	+	+	+	+	N	+	+	+	+	+	N	+	+	N	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor											X	X		X	X	X	X	X		X	X	X	X	X
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
Carcinoma, NOS									X															
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
BODY CAVITIES																								
Peritoneum	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Paraganglioma, NOS								X																
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
Mesothelioma, NOS												X												
Leukemia, mononuclear cell					X		X				X		X	X		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 A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	015	017	018	019	020	021	022	023	024	025	026	027	029	031	032	033	035	036	037	041	043	044	045	048	050	TOTAL
WEEKS ON STUDY	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Basal cell tumor					X																					2
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma												X														1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyoma																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma			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	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma			X																							1
Urinary bladder	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS		X				X		X		X	X		X	X			X			X		X	X	X		15
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma			X				X	X	X	X			X	X	X							X	X		X	17
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C-cell adenoma								X										X								4
Parathyroid	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	–	+	–	+	+	+	41
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell carcinoma								X																		1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	+	+	N	N	N	+	+	+	N	+	N	+	N	+	+	N	+	+	+	+	*50
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	35
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
Carcinoma, NOS																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
BODY CAVITIES																										
Peritoneum	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
Paraganglioma, NOS																										1
Tunica vaginalis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Mesothelioma, NOS				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
Mesothelioma, NOS																										1
Leukemia, mononuclear cell		X										X					X		X			X	X		X	14

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE: LOW DOSE

ANIMAL NUMBER	00209	00247	00313	00410	00448	00417	00442	00402	00430	00501	00528	00539	00505	00607	00645	00747	00825	00840	00849	00933	00932	00935	00918	00936	00922
WEEKS ON STUDY	00 5	02 4	03 1	04 0	04 0	04 2	04 2	04 3	.5 0	05 5	05 5	05 6	06 0	06 8	07 8	07 8	08 1	08 2	08 2	08 5	08 6	08 7	08 8	08 8	09 0
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																								X	
Basal cell tumor																				X					
Keratoacanthoma																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																									
Fibroma																			X						
Fibrosarcoma												X													
Neurofibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar carcinoma																			X						
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
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	N
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Large intestine	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																			X			X	X	X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular-cell adenoma																									
C-cell adenoma																		X		X					
Parathyroid	+	+	+	+	+	+	+	+	–	–	+	–	+	+	+	+	+	+	–	+	+	+	–	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell carcinoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	N	+	+	+	+	+	N	+	+	+
Fibroadenoma																								X	
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor														X	X	X	X	X		X	X	X			X
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
Carcinoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS																									
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								

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

ANIMAL NUMBER	029	008	031	004	026	013	012	020	024	041	046	043	006	011	014	015	016	019	021	023	034	037	038	044	050	TOTAL
WEEKS ON STUDY	090	092	092	094	094	096	100	100	100	100	101	103	104	104	104	104	104	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Basal cell tumor												X														2
Keratoacanthoma		X																								1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																	X									1
Fibroma															X											2
Fibrosarcoma																										1
Neurofibroma									X																	1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell																				X						1
Lymph nodes	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	–	+	–	+	+	+	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
DIGESTIVE SYSTEM																										
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
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma, NOS																	X									1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS			X		X						X			X	X			X								11
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma	X	X			X		X			X	X		X	X				X	X	X	X	X	X	X	X	16
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular-cell adenoma												X														1
C-cell adenoma											X	X			X											5
Parathyroid	+	+	+	–	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	–	+	+	40
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islet cell carcinoma													X													1
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Fibroadenoma																										1
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	30
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Glioma, NOS																					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
Leukemia, mononuclear cell					X	X	X					X					X		X							7

* Animals Necropsied

TABLE A3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE: HIGH DOSE

ANIMAL NUMBER	0 3 5	0 1 4	0 2 1	0 0 8	0 4 4	0 4 5	0 4 9	0 3 1	0 2 8	0 3 0	0 4 6	0 3 6	0 1 9	0 0 4	0 4 1	0 4 8	0 2 7	0 3 3	0 1 1	0 1 8	0 3 4	0 3 2	0 1 5	0 2 6	0 4 3
WEEKS ON STUDY	0 0 1	0 0 2	0 0 4	0 0 5	0 0 5	0 0 5	0 0 5	0 0 6	0 0 8	0 0 8	0 1 2	0 1 6	0 1 7	0 1 9	0 1 9	0 3 7	0 4 5	0 4 7	0 5 5	0 5 5	0 5 7	0 6 5	0 6 7	0 6 7	0 6 9
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Squamous cell carcinoma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																									
Trachea	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Spleen	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	–	+	–	+	+	+	+	+	–	+	+	+	+	–	–	+	+	+	+	–	+	–	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																									
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	N
Pancreas	+	–	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Adenoma, NOS																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+
Stomach	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Small intestine	–	–	+	–	+	–	–	–	+	+	–	+	+	–	+	+	–	–	+	+	+	+	+	+	+
Large intestine	+	–	+	+	+	–	–	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Sarcoma, NOS, metastatic																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Sarcoma, NOS, metastatic																									
Urinary bladder	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	–	–	–	+	+	+
Adenoma, NOS																								X	X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Parathyroid	+	+	+	–	+	+	–	+	+	–	+	–	+	+	–	–	–	+	+	+	+	+	–	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	+	+	N	+	N	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell tumor																		X	X		X		X		
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
Carcinoma, NOS																									
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS																									
SPECIAL SENSE ORGANS																									
Eye	N	N	N	N	N	N	N	N	+	N	N	N	N	+	N	N	N	N	N	N	+	N	N	N	N
Leiomyoma																									
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																									

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

ANIMAL NUMBER	020	021	022	023	012	022	006	037	047	050	051	010	041	042	009	040	038	002	029	022	039	003	005	007	013	017	TOTAL
WEEKS ON STUDY	079	080	080	084	086	086	087	087	087	087	091	092	092	093	094	095	098	098	100	102	104	104	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																											
Skin	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma			X															X								X	3
Squamous cell carcinoma														X													1
RESPIRATORY SYSTEM																											
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic				X																							1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																											
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	+	+	+	+	+	–	+	+	+	–	+	–	+	+	+	+	–	–	+	–	+	+	+	+	+	+	36
CIRCULATORY SYSTEM																											
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS, metastatic				X																							1
DIGESTIVE SYSTEM																											
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	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma, NOS																	X										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Large intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Sarcoma, NOS, metastatic				X																							1
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma																										X	1
Sarcoma, NOS, metastatic				X																							1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																											
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma, NOS				X	X								X		X									X			7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma				X						X	X						X		X					X	X	X	8
Thyroid	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Parathyroid	+	–	+	–	+	–	+	–	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+	+	–	+	34
REPRODUCTIVE SYSTEM																											
Mammary gland	+	+	+	+	+	N	+	+	N	+	+	+	+	+	+	+	N	+	+	N	+	+	+	+	+	N	*50
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	X	X	X	29
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial/clitoral 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	N	*50
Carcinoma, NOS																			X								1
Adenoma, NOS		X										X															2
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma, NOS														X													1
SPECIAL SENSE ORGANS																											
Eye	N	N	N	N	N	N	N	N	+	N	N	N	N	+	N	N	N	N	N	N	+	+	N	+	+		*50
Leiomyoma																					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	N	*50
Leukemia, mononuclear cell																			X								1

*Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE: VEHICLE CONTROL

ANIMAL NUMBER	00009	00039	00366	00289	00045	00056	00211	00155	00400	00200	00101	00202	00303	00606	00707	00808	00110	00111	00112	00113	00114	00116	00117	00118	00119
WEEKS ON STUDY	04 1	06 8	07 1	08 9	09 0	09 0	09 4	09 5	09 9	10 3	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 4	10 5
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma								X																	
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma				X																					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS, metastatic									X																
Trachea	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia, mononuclear cell																									
Lymph nodes	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplasm, NOS, unc prim or meta									X																
Thymus	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																		X							
Leukemia, mononuclear cell																									
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS		X				X					X			X	X	X		X			X			X	
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C-cell adenoma																					X				
C-cell carcinoma										X													X		
Parathyroid	+	+	+	–	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	–	+	+	+
Pancreatic islets	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islet cell adenoma																									
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma														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
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS								X																	
Leiomyosarcoma						X																			
Endometrial stromal polyp							X											X	X			X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, 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		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 A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	022	023	024	025	026	027	028	030	031	032	033	034	035	037	038	041	042	043	044	045	046	047	048	049	050	TOTAL
WEEKS ON STUDY	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Squamous cell papilloma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplasm, NOS, metastatic																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia, mononuclear cell																									X	1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplasm, NOS, unc prim or meta																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	47
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Neoplastic nodule																										1
Leukemia, mononuclear cell					X																					1
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	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma, NOS	X		X				X				X						X		X	X	X		X		X	19
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma						X			X									X								3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	49
C-cell adenoma									X										X							3
C-cell carcinoma																										2
Parathyroid	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	–	–	–	+		41
Pancreatic islets	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islet cell adenoma	X				X																					2
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroadenoma			X	X													X		X							7
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
Adenoma, NOS										X																1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	49
Adenocarcinoma, NOS																										1
Leiomyosarcoma						X																				2
Endometrial stromal polyp		X												X		X				X						8
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Glioma, NOS																										1
ALL OTHER SYSTEMS																										
Multiple organs NOS	N	N	N	N	N	N	N	N	N	N	N	N	X	N	N	N	N	N	N	N	N	X	N	N	N	*50
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 4-VINYLCYCLOHEXENE: LOW DOSE

ANIMAL NUMBER	02 26	04 48	01 17	01 18	01 12	02 23	01 19	03 32	03 38	04 04	04 45	01 00	04 40	03 11	00 07	04 47	01 15	02 29	03 00	02 21	02 28	02 27	00 01	00 02	00 03
WEEKS ON STUDY	00 01	00 11	00 03	00 04	01 11	05 33	05 36	06 22	08 11	08 85	08 86	08 87	08 89	09 11	09 33	09 55	09 98	10 00	10 00	10 22	10 22	10 33	10 44	10 44	10 44
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Undifferentiated carcinoma																									
Neurofibrosarcoma																		X							
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	+
Spleen	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Neoplastic nodule																			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	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell carcinoma																									
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																X									
Adenoma, NOS										X	X	X					X	X		X	X	X	X		X
Adrenal	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																		X							
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell carcinoma														X											
C-cell adenoma																									
Parathyroid	+	–	+	+	+	+	–	+	–	+	–	+	+	–	–	–	+	+	+	+	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	N	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS																									
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
Squamous cell carcinoma																									
Adenoma, NOS																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Endometrial stromal polyp														X								X			
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, NOS, invasive																X									
Glioma, NOS																									
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
Undiff. carcinoma, metastatic																									
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	X		X				X

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

ANIMAL NUMBER	0005	0006	0008	0009	0011	0013	0014	0016	0020	0022	0024	0025	0033	0034	0035	0036	0037	0039	0041	0042	0043	0044	0046	0049	0050	TOTAL
WEEKS ON STUDY	1004	1004	1004	1004	1004	1004	1004	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	1005	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Undifferentiated carcinoma																				X						1
Neurofibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	48
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thymus	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	46
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Neoplastic nodule																				X						2
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	49
Transitional cell carcinoma										X																1
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Carcinoma, NOS																										1
Adenoma, NOS		X		X						X			X	X		X	X	X		X	X	X	X	X		23
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma										X									X							3
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell carcinoma																										1
C-cell adenoma		X									X									X				X		4
Parathyroid	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	39
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Carcinoma, NOS																								X		1
Fibroadenoma	X													X			X	X					X			9
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
Adenoma, NOS	X					X													X		X					4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	49
Adenoma, NOS				X			X																			2
Endometrial stromal polyp									X	X		X			X	X				X		X				9
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	49
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, NOS, invasive																										1
Glioma, NOS																			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	N	*50
Undiff. carcinoma, metastatic																				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
Leukemia, mononuclear cell						X		X				X	X				X	X			X	X				13

* Animals Necropsied

TABLE A4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE: HIGH DOSE

ANIMAL NUMBER	005	034	050	010	021	032	035	046	013	017	049	007	001	036	022	033	012	027	047	043	024	039	040	002	030
WEEKS ON STUDY	001	001	001	002	002	003	003	003	005	005	005	009	012	013	014	014	015	016	019	025	029	031	031	036	037
RESPIRATORY SYSTEM																									
Lungs and bronchi	-	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	-	+	+	+	+	+	+	+	+	M	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	-	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	-	+	+	+	+	M	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+
Thymus	-	+	-	-	-	+	+	+	+	M	+	+	+	+	+	-	+	+	+	+	+	+	+	-	-
CIRCULATORY SYSTEM																									
Heart	-	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Oral cavity	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Squamous cell papilloma																									
Salivary gland	-	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	-	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bile duct	-	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	N	+	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Pancreas	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS, unc prim or meta	X																								
Esophagus	-	-	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	-	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	-	+	+	+	+	-	+	+	-	M	+	+	+	+	+	-	+	-	+	+	+	-	+	+	+
Large intestine	-	+	+	+	+	-	+	+	-	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional cell papilloma																									
Adenocarcinoma, NOS, invasive																									
ENDOCRINE SYSTEM																									
Pituitary	-	+	+	+	-	+	+	+	+	M	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma																									
Thyroid	-	-	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	-	-	+	+	+	-	+	+	-	M	+	+	+	-	-	-	+	+	+	-	+	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	N	N	+	N	+	+	+	+	+	M	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroadenoma																									
Uterus	-	+	-	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Endometrial stromal polyp																									
Ovary	-	+	-	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Glioma, NOS																									
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	N	N	N	N	N	N	N	N	M	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Adenocarcinoma, NOS, metastatic																									
Leukemia, mononuclear cell																									

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

ANIMAL NUMBER	01 19	02 26	04 45	02 23	04 44	00 08	02 29	01 16	02 20	00 04	04 41	03 31	00 03	00 06	00 09	01 11	01 14	01 15	01 18	02 25	02 28	03 37	03 38	04 42	04 48	TOTAL
WEEKS ON STUDY	03 39	04 45	04 46	05 51	05 54	06 66	08 89	09 91	09 92	09 94	09 94	09 95	10 44	10 44	10 44	10 55	10 55	10 55	10 55	10 55	10 55	10 55	10 55	10 55	10 55	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	47
Lymph nodes	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Thymus	+	+	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
CIRCULATORY SYSTEM																										
Heart	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
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	*49
Squamous cell papilloma									X																	1
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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	*49
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Sarcoma, NOS, unc prim or meta																										1
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Small intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+	+	+	+	+	47
Transitional cell papilloma																X										1
Adenocarcinoma, NOS, invasive																					X					1
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenoma, NOS						X		X		X		X		X									X	X		7
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma												X														1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*49
Fibroadenoma				X					X			X						X								4
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenocarcinoma, NOS																					X					1
Endometrial stromal polyp																			X	X	X	X			X	5
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Glioma, NOS																						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	*49
Adenocarcinoma, NOS, metastatic																					X					1
Leukemia, mononuclear cell										X	X	X						X		X						5

*Animals Necropsied

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MICE IN THE TWO-YEAR GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE

	CONTROL (VEH)	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)
Cystadenoma, NOS		1 (2%)	
Fibroma		1 (2%)	
Fibrosarcoma	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(50)
Fibroma			1 (2%)
RESPIRATORY SYSTEM			
#Lung	(49)	(50)	(50)
Hepatocellular carcinoma, metastatic	2 (4%)	1 (2%)	
Alveolar/bronchiolar adenoma	1 (2%)	4 (8%)	3 (6%)
Alveolar/bronchiolar carcinoma	3 (6%)	7 (14%)	1 (2%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(50)
Malignant lymphoma, lymphocytic type	1 (2%)	2 (4%)	
Malignant lymphoma, histiocytic type		2 (4%)	1 (2%)
Malignant lymphoma, mixed type	2 (4%)	3 (6%)	3 (6%)
#Spleen	(49)	(49)	(46)
Malignant lymphoma, mixed type	1 (2%)		
#Mesenteric lymph node	(31)	(44)	(38)
Malignant lymphoma, histiocytic type			1 (3%)
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(50)
Sarcoma, NOS		1 (2%)	
Hemangioma		1 (2%)	
#Liver	(49)	(50)	(50)
Hemangiosarcoma	1 (2%)	1 (2%)	
DIGESTIVE SYSTEM			
#Liver	(49)	(50)	(50)
Hepatocellular adenoma	7 (14%)	11 (22%)	3 (6%)
Hepatocellular carcinoma	11 (22%)	10 (20%)	3 (6%)
#Forestomach	(47)	(50)	(46)
Squamous cell papilloma	2 (4%)		
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Tubular cell adenoma		1 (2%)	
ENDOCRINE SYSTEM			
#Adrenal	(48)	(50)	(50)
Cortical adenoma		1 (2%)	
#Thyroid	(45)	(47)	(45)
Follicular cell adenoma		1 (2%)	1 (2%)
#Pancreatic islets	(48)	(49)	(50)
Islet cell adenoma			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Adenoma, NOS		1 (2%)	
NERVOUS SYSTEM			
None			
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(50)
Papillary adenoma	1 (2%)		
Papillary cystadenoma, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
None			
ALL OTHER SYSTEMS			
None			
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	7	6	41
Moribund sacrifice	2	5	
Terminal sacrifice	37	39	7
Dosing accident	1		
Accidentally killed, NOS	3		2
TUMOR SUMMARY			
Total animals with primary tumors**	26	33	12
Total primary tumors	32	48	18
Total animals with benign tumors	11	17	8
Total benign tumors	12	22	9
Total animals with malignant tumors	19	21	7
Total malignant tumors	20	26	9
Total animals with secondary tumors##	2	1	
Total secondary tumors	2	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 B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	50	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	48
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(48)
Trichoepithelioma	1 (2%)		
Fibrosarcoma			1 (2%)
*Subcutaneous tissue	(50)	(50)	(48)
Sarcoma, NOS	1 (2%)		
Fibrosarcoma		1 (2%)	
RESPIRATORY SYSTEM			
#Lung	(50)	(49)	(48)
Alveolar/bronchiolar adenoma	5 (10%)	1 (2%)	3 (6%)
Alveolar/bronchiolar carcinoma	1 (2%)		1 (2%)
Granulosa cell carcinoma, metastatic		1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(48)
Malignant lymphoma, NOS	1 (2%)		
Malignant lymphoma, lymphocytic type	1 (2%)	4 (8%)	5 (10%)
Malignant lymphoma, histiocytic type	3 (6%)	3 (6%)	1 (2%)
Malignant lymphoma, mixed type	10 (20%)	4 (8%)	5 (10%)
#Spleen	(50)	(48)	(47)
Malignant lymphoma, mixed type	1 (2%)	1 (2%)	
#Mesenteric lymph node	(47)	(47)	(38)
Malignant lymphoma, lymphocytic type		1 (2%)	
#Small intestine	(47)	(46)	(39)
Malignant lymphoma, lymphocytic type		1 (2%)	
#Uterus	(49)	(50)	(48)
Malignant lymphoma, histiocytic type		1 (2%)	
CIRCULATORY SYSTEM			
*Vagina	(50)	(50)	(48)
Hemangioma		1 (2%)	
#Uterus	(49)	(50)	(48)
Hemangioma	1 (2%)		1 (2%)
DIGESTIVE SYSTEM			
#Liver	(50)	(49)	(48)
Hepatocellular adenoma	1 (2%)	2 (4%)	2 (4%)
Hepatocellular carcinoma		1 (2%)	2 (4%)
#Forestomach	(49)	(49)	(45)
Squamous cell papilloma		2 (4%)	
#Jejunum	(47)	(46)	(39)
Leiomyosarcoma		1 (2%)	
URINARY SYSTEM			
#Kidney	(50)	(49)	(48)
Tubular cell adenoma		1 (2%)	

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Anterior pituitary	(49)	(49)	(44)
Adenoma, NOS	9 (18%)	7 (14%)	3 (7%)
Adenocarcinoma, NOS		1 (2%)	
#Adrenal/capsule	(50)	(49)	(48)
Adenoma, NOS		3 (6%)	4 (8%)
#Adrenal medulla	(50)	(49)	(48)
Pheochromocytoma		1 (2%)	1 (2%)
#Thyroid	(47)	(46)	(45)
Follicular cell adenoma		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(48)
Adenocarcinoma, NOS	1 (2%)	1 (2%)	1 (2%)
Adenosquamous carcinoma			1 (2%)
Mixed tumor, malignant	1 (2%)		
*Vagina	(50)	(50)	(48)
Squamous cell papilloma			1 (2%)
#Ovary	(49)	(48)	(47)
Papillary adenoma	1 (2%)	1 (2%)	
Papillary cystadenoma, NOS			1 (2%)
Luteoma		2 (4%)	
Granulosa cell tumor	1 (2%)	9 (19%)	11 (23%)
Granulosa cell carcinoma		1 (2%)	2 (4%)
Tubular adenoma		2 (4%)	1 (2%)
Mixed tumor, benign		25 (52%)	11 (23%)
Teratoma, NOS	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(49)	(48)
Adenocarcinoma, NOS, invasive		1 (2%)	
SPECIAL SENSE ORGANS			
*Harderian gland	(50)	(50)	(48)
Papillary adenoma		4 (8%)	
MUSCULOSKELETAL SYSTEM			
*Coccyx	(50)	(50)	(48)
Osteosarcoma		1 (2%)	
BODY CAVITIES			
*Abdominal cavity	(50)	(50)	(48)
Sarcoma, NOS		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(48)
Alveolar/bronchiolar carcinoma, metastatic	1 (2%)		

TABLE B2. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	50	50	50
Natural death	7	6	28
Moribund sacrifice	3	5	3
Scheduled sacrifice			1
Terminal sacrifice	40	39	17
Animal missing			1
TUMOR SUMMARY			
Total animals with primary tumors**	28	47	30
Total primary tumors	40	85	58
Total animals with benign tumors	16	33	21
Total benign tumors	18	53	28
Total animals with malignant tumors	20	21	16
Total malignant tumors	20	23	19
Total animals with secondary tumors##	1	2	2
Total secondary tumors	1	2	2
Total animals with tumors uncertain-- benign or malignant	2	9	11
Total uncertain tumors	2	9	11

* 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 4-VINYLCYCLOHEXENE: VEHICLE CONTROL

ANIMAL NUMBER	00018	00161	00211	00318	00420	00537	00623	00724	00844	00912	00902	00946	01032	01001	01003	01004	01005	01006	01007	01009	01101	01111	01131	01141	01155
WEEKS ON STUDY	00101	00101	00108	00109	00109	00109	00622	00844	00966	00988	00999	00999	01022	01044	01044	01044	01044	01044	01044	01044	01044	01044	01044	01044	01044
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma											X														
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metas										X															
Alveolar/bronchiolar adenoma																							X		
Alveolar/bronchiolar carcinoma												X													
Trachea	+	+	+	A	+	–	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	A	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																	X								
Lymph nodes	+	+	+	A	+	–	+	–	+	+	+	–	+	–	–	–	+	+	+	–	+	–	+	+	+
Thymus	+	–	+	A	+	–	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	–	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	A	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																			X				X		
Hepatocellular carcinoma							X	X	X	X							X						X		
Hemangiosarcoma																									
Bile duct	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	+	N	+	N	N	+	N	N	+	+	N	N	N	+	+	+	+	+	+	+	N	+	+
Pancreas	+	–	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	–	–	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																									
Small intestine	–	+	–	A	–	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	–	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	A	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	–	+	+	A	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	–	+	+	–	+	+
Adrenal	–	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	–	+	+	A	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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																									
Papillary cystadenoma, NOS																									
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												
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 B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	0017	0019	0022	0025	0026	0027	0028	0029	0030	0031	0033	0034	0035	0036	0038	0039	0040	0041	0042	0043	0045	0047	0048	0049	0050	TOTAL
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	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular carcinoma, metas											X															2
Alveolar/bronchiolar adenoma																										1
Alveolar/bronchiolar carcinoma																	X					X				3
Trachea	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Malignant lymphoma, mixed type																										1
Lymph nodes	+	–	–	–	–	+	+	+	+	+	+	–	+	–	–	–	+	+	–	+	+	+	+	+	–	31
Thymus	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma		X		X								X					X	X								7
Hepatocellular carcinoma										X	X		X											X		X	11
Hemangiosarcoma												X														1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Squamous cell papilloma								X		X																2
Small intestine	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Urinary bladder	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	45
ENDOCRINE SYSTEM																										
Pituitary	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Thyroid	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Parathyroid	–	+	–	+	+	–	–	–	–	–	+	–	–	+	+	–	–	+	+	–	+	+	–	+	–	24
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	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
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	1
Papillary cystadenoma, NOS									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
Malig. lymphoma, lymphocytic type																										1
Malignant lymphoma, mixed type			X																							2

* Animals Necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE: LOW DOSE

ANIMAL NUMBER	04301	00601	01801	05001	03001	02701	00901	04001	00701	03801	04701	00101	00201	00301	00401	00501	00801	01001	01101	01201	01301	01401	01501	01601	01701
WEEKS ON STUDY	00301	00602	00603	00707	00803	00901	00907	00907	00909	01002	01002	01004	01004	01004	01004	01004	01004	01004	01004	01004	01004	01004	01004	01004	01004
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma, NOS																									
Fibroma																									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma, metas																									
Alveolar/bronchiolar adenoma						X																			
Alveolar/bronchiolar carcinoma								X															X		
Trachea	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	–	+	+	+	+	–	+	+	+	+	–	–	+	+	–	+	+	+	+	+	+	+	+
Thymus	–	+	+	+	–	+	+	–	+	–	–	+	+	+	+	+	+	+	+	+	–	+	+	+	–
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS								X																	
Hemangioma																									
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma								X								X			X		X	X			X
Hepatocellular carcinoma		X		X	X		X	X		X	X														
Hemangiosarcoma																						X			
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	N	+	+	+	+	+	+	N	+	N	N	N	N	+	+	+	+	+	+	+	+	+	+	N
Pancreas	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma																									
Urinary bladder	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cortical adenoma																									X
Thyroid	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	–	–	–	–	–	–	+	+	+	–	+	–	–	–	–	+	+	–	–	+	+	+	+	+	–
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
Adenoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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			X																						
Malignant lymphoma, mixed type												X													

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

ANIMAL NUMBER	019	020	021	022	023	024	025	026	028	029	031	032	033	034	035	036	037	039	041	042	044	045	046	048	049	TOTAL
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	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Cystadenoma, NOS																					X					1
Fibroma																					X					1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma, metas																X										1
Alveolar/bronchiolar adenoma							X			X									X							4
Alveolar/bronchiolar carcinoma			X											X		X					X		X			7
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph nodes	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Thymus	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, NOS																										1
Hemangioma																					X					1
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma		X				X			X	X			X													11
Hepatocellular carcinoma					X		X									X										10
Hemangiosarcoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	N	N	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tubular cell adenoma	X																									1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	46
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cortical adenoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Follicular cell adenoma															X											1
Parathyroid	+	–	+	+	+	+	–	–	+	+	+	+	–	+	–	–	+	+	+	+	+	–	+	+	+	29
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	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	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
Adenoma, NOS													X													1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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		2
Malignant lymphoma, mixed type					X	X																				3

* Animals Necropsied

TABLE B3. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE: HIGH DOSE

ANIMAL NUMBER	01136	03619	01917	01722	02225	02541	04112	01214	01116	02020	02301	03311	04040	00101	00033	04455	01109	04902	00204	00046	00067	00079	00096	01363
WEEKS ON STUDY	00999	00999	01919	02888	02288	02288	02288	02299	02299	02299	02299	02299	02299	03232	04488	04485	05556	06565	07676	07766	07766	07766	07766	07676
INTEGUMENTARY SYSTEM																								
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibroma																								
RESPIRATORY SYSTEM																								
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																								
Alveolar/bronchiolar carcinoma																								
Trachea	+	+	+	–	–	–	–	+	+	+	+	+	–	–	+	+	+	+	+	+	–	+	–	+
HEMATOPOIETIC SYSTEM																								
Bone marrow	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	–	+	+	–	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	+	+	+	+	+	–	+	–	+	+	–	–	+	+	+	–	+	–	+	+	+	+	+
Malig. lymphoma, histiocytic type																								
Thymus	–	–	–	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+
CIRCULATORY SYSTEM																								
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																								
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																								
Hepatocellular carcinoma																			X					
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	N	+	N	N	N	N	+	N	N	N	N	+	N	+	+	+	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	–	+	–	+	+	+	+	+	–	+	–	+	+	+	+	+	+	+	+	+	+
Small intestine	–	–	+	–	+	–	–	+	–	–	–	–	–	–	+	+	+	+	+	+	+	+	+	–
Large intestine	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																								
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																								
Pituitary	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	–	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	–	+	+
Follicular cell adenoma																								
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
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																								
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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
Malig. lymphoma, histiocytic type																								
Malignant lymphoma, mixed type																								

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

ANIMAL NUMBER	0115	0118	0128	0229	0335	0337	0339	0227	0338	0446	0223	0334	0447	0005	0008	0221	0505	0332	0224	0226	0333	0422	0443	0444	0448	TOTAL
WEEKS ON STUDY	076	076	076	076	076	076	076	083	090	090	091	091	091	092	092	092	092	101	104	104	104	104	104	104	104	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibroma																		X								1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma				X															X			X				3
Alveolar/bronchiolar carcinoma																									X	1
Trachea	+	+	+	+	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Lymph nodes	+	–	+	+	+	–	+	+	–	–	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	38
Malig. lymphoma, histiocytic type																						X				1
Thymus	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma										X								X						X		3
Hepatocellular carcinoma																					X				X	3
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	N	N	N	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	N	N	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Small intestine	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	35
Large intestine	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Follicular cell adenoma																			X							1
Parathyroid	+	–	–	–	–	–	+	+	–	–	–	–	–	+	+	–	–	–	–	+	–	+	+	–	+	15
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	N	*50
Testis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Prostate	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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, histiocytic type																		X								1
Malignant lymphoma, mixed type																				X			X		X	3

*Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE: VEHICLE CONTROL

ANIMAL NUMBER	0101	0118	0140	0209	0112	0134	0144	0224	0038	0381	0101	0202	0303	0404	0505	0606	0707	0909	1011	1013	1014	1015	1016	1017	1019
WEEKS ON STUDY	0265	0555	0888	0889	0991	0991	0992	0994	0998	1100	1104	1104	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004	1004
INTEGUMENTARY SYSTEM																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trichoepithelioma	X																								
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, NOS																		X							
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																									
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	+	N	+	+	N	N	+	N	N	N	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	–	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	–	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS								X		X	X							X			X				X
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thyroid	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid	+	–	–	–	–	+	–	–	+	–	–	–	+	+	+	+	+	+	+	+	+	+	+	–	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	N	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS										X															
Mixed tumor, malignant																X									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																									
Granulosa cell tumor																							X		
Teratoma, NOS																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
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 ca, metast																									X
Malignant lymphoma, NOS																									
Malig. lymphoma, lymphocytic type			X																						
Malig. lymphoma, histiocytic type		X				X	X																		
Malignant lymphoma, mixed type				X					X		X	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 B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

ANIMAL NUMBER	020	021	022	023	025	026	027	028	030	031	032	033	035	036	037	039	041	042	043	045	046	047	048	049	050	TOTAL
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	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Trichoepithelioma																										1
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Sarcoma, NOS																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma			X																			X		X		5
Alveolar/bronchiolar carcinoma																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malignant lymphoma, mixed type																		X								1
Lymph nodes	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	47
Thymus	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular adenoma																	X									1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Large intestine	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X							X										X								9
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thyroid	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Parathyroid	+	–	+	+	+	+	+	+	–	–	+	–	+	+	–	+	+	+	+	–	+	–	+	–	–	30
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																										1
Mixed tumor, malignant																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangioma																		X								1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papillary adenoma							X																			1
Granulosa cell tumor																										1
Teratoma, NOS									X																	1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
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 ca, metast																										1
Malignant lymphoma, NOS																		X								1
Malig. lymphoma, lymphocytic type																										1
Malig. lymphoma, histiocytic type																										3
Malignant lymphoma, mixed type	X		X														X					X			X	10

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE: LOW DOSE

ANIMAL NUMBER	0048	0033	0015	0021	0038	0031	0007	0004	0027	0025	0020	0001	0002	0003	0005	0006	0008	0009	0010	0011	0012	0013	0014	0016	0017
WEEKS ON STUDY	043	060	082	089	089	092	098	099	099	100	101	104	104	104	104	104	104	104	104	104	104	104	104	104	104
INTEGUMENTARY SYSTEM																									
Subcutaneous tissue	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma				X																					
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Granulosa cell carcinoma, metas									X																
Trachea	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malignant lymphoma, mixed type																									X
Lymph nodes	–	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig. lymphoma, lymphocytic type																									
Thymus	+	+	+	+	–	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CIRCULATORY SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma												X													
Bile duct	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	+	N	N	N	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pancreas	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell papilloma																							X		
Small intestine	–	+	+	–	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																							X		
Malig. lymphoma, lymphocytic type																									
Large intestine	+	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tubular cell adenoma									X																
Urinary bladder	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS									X				X						X	X					
Adenocarcinoma, NOS											X														
Adrenal	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Pheochromocytoma																									X
Thyroid	–	+	+	–	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
Parathyroid	–	+	–	–	–	–	+	+	+	+	–	+	–	+	+	+	+	+	+	–	–	+	+	+	+
REPRODUCTIVE SYSTEM																									
Mammary gland	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS																									
Vagina	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
Hemangioma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Malig. lymphoma, histiocytic type																									
Ovary	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary adenoma																									
Luteoma																		X							
Granulosa cell tumor																						X			X
Granulosa cell carcinoma									X																
Tubular adenoma								X								X									
Mixed tumor, benign										X		X	X	X	X	X	X	X	X	X	X			X	X
NERVOUS SYSTEM																									
Brain	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS, invasive											X														
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	X									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																							X		
BODY CAVITIES																									
Peritoneum	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
Sarcoma, 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
Malig. lymphoma, lymphocytic type		X								X															
Malig. lymphoma, histiocytic type			X				X	X																	
Malignant lymphoma, mixed type											X			X							X				

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

ANIMAL NUMBER	018	019	022	023	024	026	028	029	030	032	034	035	036	037	039	040	041	042	043	044	045	046	047	049	050	TOTAL
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	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Subcutaneous tissue	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Alveolar/bronchiolar adenoma													X													1
Granulosa cell carcinoma, metas																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Malignant lymphoma, mixed type																										1
Lymph nodes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Malig. lymphoma, lymphocytic type					X																					1
Thymus	+	+	+	+	+	–	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	–	+	+	+	45
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hepatocellular adenoma												X									X					2
Hepatocellular carcinoma																										1
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Squamous cell papilloma								X																		2
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Leiomyosarcoma																										1
Malig. lymphoma, lymphocytic type										X																1
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tubular cell adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS													X						X			X				7
Adenocarcinoma, NOS																										1
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma, NOS	X											X													X	3
Pheochromocytoma																										1
Thyroid	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	46
Follicular cell adenoma																					X					1
Parathyroid	+	+	+	–	+	–	–	+	–	–	–	–	+	+	–	+	+	+	–	+	–	–	–	+	+	29
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	N	+	+	+	+	+	+	N	+	+	+	N	N	+	+	+	+	+	+	+	*50
Adenocarcinoma, NOS																					X					1
Vagina	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
Hemangioma																						X				1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Malig. lymphoma, histiocytic type																								X		1
Ovary	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Papillary adenoma																					X					1
Luteoma												X														2
Granulosa cell tumor					X				X					X			X	X	X		X					9
Granulosa cell carcinoma																										1
Tubular adenoma																										2
Mixed tumor, benign		X				X	X	X		X	X		X		X	X				X	X	X				25
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma, NOS, invasive																										1
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										4
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*50
Osteosarcoma																										1
BODY CAVITIES																										
Peritoneum	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
Sarcoma, 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
Malig. lymphoma, lymphocytic type				X	X																					4
Malig. lymphoma, histiocytic type																										3
Malignant lymphoma, mixed type																						X				4

* Animals Necropsied

TABLE B4. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE: HIGH DOSE

ANIMAL NUMBER	0030	0009	0255	0004	0114	0224	0226	0237	0248	0006	0008	0550	0522	0629	0449	0528	0003	0527	0001	0112	0332	0441	0466	0055	0111
WEEKS ON STUDY	0000	0003	0179	0229	0229	0229	0229	0229	0232	0355	0355	0560	0676	0782	0885	0889	0899	0890	0900	0900	0900	0900	0900	0901	0991
INTEGUMENTARY SYSTEM																									
Skin	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fibrosarcoma																X									
RESPIRATORY SYSTEM																									
Lungs and bronchi	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																				X					
Alveolar/bronchiolar carcinoma																									
Granulosa cell carcinoma, metas																									
Trachea	+	B	M	–	–	–	+	+	+	+	+	+	–	+	+	–	–	+	+	+	+	+	+	+	+
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Spleen	+	B	M	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph nodes	+	B	M	+	–	+	–	+	–	+	–	–	+	+	+	+	+	–	+	–	–	–	+	+	
Thymus	+	B	M	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	–	+	–	+	+	
CIRCULATORY SYSTEM																									
Heart	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DIGESTIVE SYSTEM																									
Salivary gland	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular adenoma																									
Hepatocellular carcinoma																									
Bile duct	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder & common bile duct	N	B	M	+	+	N	N	+	+	+	N	+	N	+	N	N	N	+	N	N	+	+	+	N	N
Pancreas	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Esophagus	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+
Stomach	–	B	M	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	–	B	M	+	+	+	–	–	–	–	–	+	+	+	+	–	–	+	+	+	+	+	+	+	+
Large intestine	+	B	M	+	+	+	–	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
URINARY SYSTEM																									
Kidney	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Urinary bladder	+	B	M	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Pituitary	+	B	M	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																									
Adrenal	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma, NOS																X									
Pheochromocytoma																									
Thyroid	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+
Parathyroid	–	B	M	–	–	+	–	–	–	+	–	–	–	–	–	–	–	+	+	–	–	+	–	+	–
REPRODUCTIVE SYSTEM																									
Mammary gland	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, NOS															X										
Adenosquamous carcinoma																									
Vagina	N	B	M	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																									
Uterus	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Ovary	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papillary cystadenoma, NOS																				X					
Granulosa cell tumor															X							X	X		
Granulosa cell carcinoma																									
Tubular adenoma																									
Mixed tumor, benign															X			X			X			X	
NERVOUS SYSTEM																									
Brain	+	B	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ALL OTHER SYSTEMS																									
Multiple organs NOS	N	B	M	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					X
Malig. lymphoma, histiocytic type																									
Malignant lymphoma, mixed type																									

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

ANIMAL NUMBER	01 15	01 17	03 11	01 16	02 23	01 10	03 36	04 44	00 02	00 07	01 13	01 18	01 19	02 00	02 01	03 33	03 34	03 35	03 38	03 39	04 00	04 02	04 03	04 05	04 07	TOTAL
WEEKS ON STUDY	09 91	09 91	09 91	09 92	09 92	09 94	09 94	09 99	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	10 04	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Fibrosarcoma																										1
RESPIRATORY SYSTEM																										
Lungs and bronchi	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Alveolar/bronchiolar adenoma											X			X												3
Alveolar/bronchiolar carcinoma								X																		1
Granulosa cell carcinoma, metas							X														X					2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Lymph nodes	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	38
Thymus	–	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	41
CIRCULATORY SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
DIGESTIVE SYSTEM																										
Salivary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	47
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hepatocellular adenoma																	X				X					2
Hepatocellular carcinoma					X												X									2
Bile duct	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Gallbladder & common bile duct	+	+	+	+	+	+	+	+	+	+	N	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*48
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Stomach	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Small intestine	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	39
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	46
ENDOCRINE SYSTEM																										
Pituitary	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	+	+	+	–	+	+	+	44
Adenoma, NOS													X						X					X		3
Adrenal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma, NOS				X						X	X															4
Pheochromocytoma																							X			1
Thyroid	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Parathyroid	–	–	–	–	+	+	–	–	+	+	–	–	+	+	+	–	–	–	+	+	+	–	+	+	+	19
REPRODUCTIVE SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	N	+	N	+	+	+	+	+	+	+	+	+	+	+	*48
Adenocarcinoma, NOS																										1
Adenosquamous carcinoma																								X		1
Vagina	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	*48
Squamous cell papilloma									X																	1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Hemangioma																			X							1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	47
Papillary cystadenoma, NOS																										1
Granulosa cell tumor	X	X											X	X	X					X			X	X		11
Granulosa cell carcinoma							X														X					2
Tubular adenoma														X												1
Mixed tumor, benign				X	X			X			X						X	X	X							11
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
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	*48
Malig. lymphoma, lymphocytic type				X													X			X						5
Malig. lymphoma, histiocytic type								X																		1
Malignant lymphoma, mixed type							X							X				X					X	X		5

* Animals Necropsied

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN RATS IN THE TWO-YEAR GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE

	CONTROL (VEH)	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)
Abscess, NOS	4 (8%)	2 (4%)	1 (2%)
Inflammation, chronic focal	3 (6%)	4 (8%)	1 (2%)
Inflammation, chronic suppurative			1 (2%)
*Subcutaneous tissue	(50)	(50)	(50)
Edema, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, chronic		1 (2%)	
Granuloma, NOS	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, suppurative	4 (8%)	5 (10%)	4 (8%)
*Maxillary sinus	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	1 (2%)	
#Lung	(50)	(50)	(50)
Congestion, NOS	1 (2%)		
Edema, NOS		1 (2%)	
Bronchopneumonia, NOS			1 (2%)
Inflammation, acute focal		1 (2%)	
Abscess, NOS			1 (2%)
Pneumonia, interstitial chronic	1 (2%)	1 (2%)	
Inflammation, granulomatous focal	7 (14%)	2 (4%)	
Hyperplasia, alveolar epithelium	2 (4%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM			
#Bone marrow	(49)	(49)	(49)
Histiocytosis	1 (2%)		
Myelofibrosis			1 (2%)
Myelosclerosis	1 (2%)		
#Spleen	(50)	(49)	(46)
Congestion, NOS		1 (2%)	
Fibrosis, focal	2 (4%)		
Fibrosis, diffuse			1 (2%)
Hemosiderosis	2 (4%)	4 (8%)	1 (2%)
Atrophy, focal		1 (2%)	1 (2%)
Hematopoiesis	2 (4%)	2 (4%)	1 (2%)
#Mandibular lymph node	(50)	(48)	(50)
Edema, NOS		1 (2%)	
#Mediastinal lymph node	(50)	(48)	(50)
Hemorrhage	1 (2%)		
Plasmacytosis			1 (2%)
#Renal lymph node	(50)	(48)	(50)
Hemorrhage		1 (2%)	
#Inguinal lymph node	(50)	(48)	(50)
Plasmacytosis			1 (2%)
#Liver	(50)	(50)	(50)
Hematopoiesis	1 (2%)		
#Thymus	(46)	(43)	(36)
Cyst, NOS	1 (2%)		1 (3%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
*Multiple organs	(50)	(50)	(50)
Periarteritis	1 (2%)	1 (2%)	
*Mediastinum	(50)	(50)	(50)
Periarteritis	1 (2%)	1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Lymphangiectasis		1 (2%)	
#Spleen	(50)	(49)	(46)
Arteriosclerosis, NOS			1 (2%)
#Heart	(50)	(49)	(50)
Inflammation, chronic focal			2 (4%)
Periarteritis	1 (2%)		1 (2%)
#Heart/atrium	(50)	(49)	(50)
Thrombosis, NOS	3 (6%)	1 (2%)	
#Myocardium	(50)	(49)	(50)
Degeneration, NOS	38 (76%)	32 (65%)	26 (52%)
#Cardiac valve	(50)	(49)	(50)
Thrombosis, NOS	1 (2%)	1 (2%)	
*Pulmonary artery	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
#Pancreas	(50)	(50)	(46)
Periarteritis	2 (4%)		
Arteriosclerosis, NOS			1 (2%)
*Mesentery	(50)	(50)	(50)
Periarteritis	1 (2%)		
#Urinary bladder	(49)	(49)	(47)
Periarteritis	1 (2%)		
#Testis	(50)	(50)	(50)
Periarteritis	1 (2%)		
#Thymus	(46)	(43)	(36)
Periarteritis			1 (3%)
DIGESTIVE SYSTEM			
*Hard palate	(50)	(50)	(50)
Abscess, NOS	1 (2%)		
#Salivary gland	(50)	(49)	(50)
Edema, NOS		1 (2%)	
Inflammation, acute			1 (2%)
#Liver	(50)	(50)	(50)
Mineralization		1 (2%)	1 (2%)
Hernia, NOS	2 (4%)	1 (2%)	1 (2%)
Congestion, NOS		1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, chronic focal			1 (2%)
Inflammation, granulomatous focal		1 (2%)	
Inflammation, pyogranulomatous		1 (2%)	
Adhesion, NOS		1 (2%)	
Degeneration, mucoid	1 (2%)		
Cytoplasmic vacuolization	10 (20%)	4 (8%)	3 (6%)
Basophilic cyto change	4 (8%)	2 (4%)	1 (2%)
Eosinophilic cyto change	7 (14%)	1 (2%)	8 (16%)
Angiectasis	1 (2%)	1 (2%)	1 (2%)
#Hepatic capsule	(50)	(50)	(50)
Mineralization			1 (2%)
Fibrosis, focal			1 (2%)
#Liver/centrilobular	(50)	(50)	(50)
Congestion, NOS		1 (2%)	
Degeneration, NOS	1 (2%)	1 (2%)	
Necrosis, NOS		3 (6%)	1 (2%)
Necrosis, coagulative	1 (2%)		
Cytoplasmic vacuolization		1 (2%)	1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Liver/periportal	(50)	(50)	(50)
Cytoplasmic vacuolization		1 (2%)	
#Liver/hepatocytes	(50)	(50)	(50)
Atrophy, diffuse		1 (2%)	
#Bile duct	(50)	(50)	(50)
Hyperplasia, NOS	42 (84%)	31 (62%)	17 (34%)
#Pancreas	(50)	(50)	(46)
Inflammation, chronic		1 (2%)	
Atrophy, NOS	8 (16%)	10 (20%)	3 (7%)
Hyperplasia, focal	11 (22%)	4 (8%)	1 (2%)
#Esophageal adventiti	(47)	(49)	(49)
Vegetable foreign body			1 (2%)
Inflammation, suppurative			2 (4%)
Inflammation, fibrinous	1 (2%)		
#Glandular stomach	(50)	(50)	(47)
Lymphocytic inflammatory infiltrate			1 (2%)
#Forestomach	(50)	(50)	(47)
Edema, NOS		1 (2%)	
Ulcer, NOS	1 (2%)	2 (4%)	4 (9%)
Inflammation, chronic			1 (2%)
Perforation, inflammatory		1 (2%)	
Adhesion, NOS		1 (2%)	
Hyperplasia, epithelial	1 (2%)	3 (6%)	5 (11%)
#Duodenum	(47)	(48)	(40)
Inflammation, suppurative			1 (3%)
#Colon	(48)	(49)	(44)
Parasitism	3 (6%)	2 (4%)	
#Colonic mucosa	(48)	(49)	(44)
Mineralization	1 (2%)		
*Rectal mucosa	(50)	(50)	(50)
Mineralization	11 (22%)	4 (8%)	3 (6%)
*Rectal muscularis propria	(50)	(50)	(50)
Mineralization			1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(50)
Mineralization		1 (2%)	1 (2%)
Cyst, NOS	1 (2%)		
Lymphocytic inflammatory infiltrate	1 (2%)		
Fibrosis, focal			1 (2%)
Nephropathy	40 (80%)	40 (80%)	34 (68%)
Necrosis, coagulative		1 (2%)	
Hemosiderosis	1 (2%)		1 (2%)
Hyperplasia, tubular cell			1 (2%)
#Kidney/tubule	(50)	(50)	(50)
Pigmentation, NOS	3 (6%)	1 (2%)	
Inclusion, cytoplasmic	1 (2%)		
#Kidney/pelvis	(50)	(50)	(50)
Inflammation chronic suppurative	1 (2%)		
Hyperplasia, epithelial	1 (2%)	2 (4%)	1 (2%)
#Urinary bladder	(49)	(49)	(47)
Calculus, gross observation only	2 (4%)		
Mineralization		1 (2%)	
Lymphocytic inflammatory infiltrate	1 (2%)		
Inflammation, acute focal		1 (2%)	
Hyperplasia, epithelial	1 (2%)		1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(49)	(45)
Cyst, NOS	1 (2%)	3 (6%)	3 (7%)
Cytoplasmic vacuolization	1 (2%)		
Focal cellular change			2 (4%)
Hypertrophy, focal		1 (2%)	
Hyperplasia, focal	7 (14%)	7 (14%)	5 (11%)
Angiectasis	1 (2%)	1 (2%)	2 (4%)
#Adrenal	(50)	(50)	(50)
Angiectasis	1 (2%)		
#Adrenal cortex	(50)	(50)	(50)
Cyst, NOS		1 (2%)	
Lipoidosis	1 (2%)	4 (8%)	1 (2%)
#Adrenal medulla	(50)	(50)	(50)
Hyperplasia, focal	9 (18%)	9 (18%)	4 (8%)
#Thyroid	(48)	(50)	(46)
Inflammation, suppurative	1 (2%)		
Hyperplasia, C-cell	31 (65%)	16 (32%)	17 (37%)
Hyperplasia, follicular cell			1 (2%)
#Thyroid follicle	(48)	(50)	(46)
Hypertrophy, focal			1 (2%)
#Parathyroid	(41)	(40)	(34)
Atrophy, NOS			1 (3%)
Hyperplasia, NOS	1 (2%)	2 (5%)	2 (6%)
#Pancreatic islets	(50)	(50)	(46)
Hyperplasia, focal		2 (4%)	1 (2%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(50)
Dilatation/ducts	2 (4%)	1 (2%)	
Inflammation, granulomatous	1 (2%)	2 (4%)	
Hyperplasia, focal	1 (2%)		1 (2%)
*Preputial gland	(50)	(50)	(50)
Dilatation/ducts	1 (2%)	1 (2%)	
Inflammation, suppurative	2 (4%)		
Inflammation, chronic	8 (16%)	4 (8%)	3 (6%)
Inflammation chronic suppurative	2 (4%)		
Inflammation, granulomatous	3 (6%)	2 (4%)	1 (2%)
#Prostate	(49)	(50)	(49)
Inflammation, chronic	3 (6%)	4 (8%)	3 (6%)
Inflammation chronic suppurative			4 (8%)
Inflammation, granulomatous	1 (2%)		
Fibrosis, focal			1 (2%)
Atrophy, NOS	1 (2%)		
Hypertrophy, focal	15 (31%)	12 (24%)	8 (16%)
Hyperplasia, focal	4 (8%)	4 (8%)	1 (2%)
#Testis	(50)	(50)	(50)
Spermatocele	1 (2%)		
Atrophy, NOS		2 (4%)	3 (6%)
Hyperplasia, interstitial cell	10 (20%)	11 (22%)	4 (8%)
*Epididymis	(50)	(50)	(50)
Inflammation, chronic	1 (2%)		
Inflammation, granulomatous		1 (2%)	
*Scrotum	(50)	(50)	(50)
Necrosis, fat	1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
NERVOUS SYSTEM			
#Brain	(50)	(49)	(50)
Mineralization			1 (2%)
Hemorrhage		1 (2%)	
Inflammation, suppurative		1 (2%)	
#Cerebellum	(50)	(49)	(50)
Mineralization			2 (4%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(50)
Cataract	11 (22%)	4 (8%)	2 (4%)
*Eye/cornea	(50)	(50)	(50)
Vascularization			1 (2%)
*Eye/retina	(50)	(50)	(50)
Atrophy, NOS	9 (18%)	5 (10%)	2 (4%)
*External ear	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
MUSCULOSKELETAL SYSTEM			
*Skull	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)		1 (2%)
*Sternum	(50)	(50)	(50)
Fibrous osteodystrophy	1 (2%)		2 (4%)
Osteosclerosis			1 (2%)
*Skeletal muscle	(50)	(50)	(50)
Inflammation, acute			1 (2%)
BODY CAVITIES			
*Thoracic cavity	(50)	(50)	(50)
Ectopia		1 (2%)	
*Mediastinum	(50)	(50)	(50)
Hemorrhage	1 (2%)		
Inflammation, suppurative	1 (2%)	1 (2%)	
Inflammation, chronic			1 (2%)
Granuloma, NOS			1 (2%)
*Abdominal cavity	(50)	(50)	(50)
Necrosis, fat	1 (2%)		
*Pleura	(50)	(50)	(50)
Inflammation, fibrinous	1 (2%)		
Fibrosis		1 (2%)	
*Pericardium	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)	1 (2%)	
Inflammation chronic suppurative			1 (2%)
*Mesentery	(50)	(50)	(50)
Inflammation, chronic		1 (2%)	
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(50)
Calcification, metastatic	1 (2%)	1 (2%)	1 (2%)
Adipose tissue			
Necrosis, fat	1		
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported	1	4	7

* 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 4-VINYLCYCLOHEXENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	50	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	49
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(49)
Epidermal inclusion cyst		1 (2%)	
Abscess, NOS	4 (8%)	3 (6%)	
Inflammation, chronic focal	2 (4%)	3 (6%)	1 (2%)
Inflammation, pyogranulomatous		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(49)
Granuloma, foreign body	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(49)
Inflammation, suppurative	3 (6%)	3 (6%)	
Inflammation, chronic suppurative		1 (2%)	
*Maxillary sinus	(50)	(50)	(49)
Inflammation, suppurative		1 (2%)	
#Lung	(50)	(50)	(48)
Bronchopneumonia, NOS	1 (2%)		
Inflammation, granulomatous focal	18 (36%)	8 (16%)	4 (8%)
Hyperplasia, alveolar epithelium	1 (2%)		
HEMATOPOIETIC SYSTEM			
#Bone marrow	(48)	(47)	(48)
Hypoplasia, NOS		1 (2%)	1 (2%)
Histiocytosis	2 (4%)	1 (2%)	1 (2%)
Myelofibrosis		1 (2%)	1 (2%)
Myelosclerosis	5 (10%)		
Myelopoiesis	1 (2%)		
#Spleen	(49)	(49)	(47)
Necrosis, focal			1 (2%)
Hemosiderosis	1 (2%)	3 (6%)	3 (6%)
Depletion, lymphoid			1 (2%)
Erythrophagocytosis			1 (2%)
Hyperplasia, lymphoid	1 (2%)		
Hematopoiesis	1 (2%)	2 (4%)	
#Mandibular lymph node	(49)	(48)	(46)
Abscess, NOS			1 (2%)
#Mediastinal lymph node	(49)	(48)	(46)
Hemorrhage			1 (2%)
Hemosiderosis		1 (2%)	
Plasmacytosis	1 (2%)		
#Mesenteric lymph node	(49)	(48)	(46)
Hemorrhage			1 (2%)
Depletion, lymphoid			1 (2%)
#Renal lymph node	(49)	(48)	(46)
Histiocytosis			1 (2%)
#Thymus	(47)	(46)	(40)
Fibrosis, focal		1 (2%)	
Necrosis, focal		1 (2%)	
Myelopoiesis	1 (2%)		

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#Heart	(50)	(50)	(47)
Lymphocytic inflammatory infiltrate		1 (2%)	
Inflammation, chronic focal			3 (6%)
#Myocardium	(50)	(50)	(47)
Inflammation, suppurative			1 (2%)
Degeneration, NOS	9 (18%)	9 (18%)	6 (13%)
#Pancreas	(49)	(49)	(49)
Periarteritis		1 (2%)	
#Uterus	(49)	(49)	(47)
Periarteritis		1 (2%)	
DIGESTIVE SYSTEM			
#Salivary gland	(50)	(49)	(48)
Atrophy, focal		1 (2%)	
#Liver	(49)	(50)	(48)
Hernia, NOS	6 (12%)	6 (12%)	6 (13%)
Congestion, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate	4 (8%)	5 (10%)	
Inflammation, suppurative	2 (4%)		1 (2%)
Inflammation, chronic focal		2 (4%)	
Inflammation, granulomatous focal	22 (45%)	15 (30%)	12 (25%)
Degeneration, NOS			1 (2%)
Necrosis, focal	2 (4%)	1 (2%)	3 (6%)
Cytoplasmic vacuolization	13 (27%)	4 (8%)	2 (4%)
Basophilic cyto change	30 (61%)	18 (36%)	10 (21%)
Eosinophilic cyto change	2 (4%)	1 (2%)	4 (8%)
Hepatocytomegaly		1 (2%)	
Angiectasis	1 (2%)		1 (2%)
#Liver/centrilobular	(49)	(50)	(48)
Degeneration, NOS	1 (2%)	1 (2%)	
Necrosis, NOS	1 (2%)		
Cytoplasmic vacuolization			1 (2%)
#Liver/periportal	(49)	(50)	(48)
Cytoplasmic vacuolization			1 (2%)
#Liver/kupffer cell	(49)	(50)	(48)
Hyperplasia, NOS			1 (2%)
#Liver/hepatocytes	(49)	(50)	(48)
Hypertrophy, NOS		1 (2%)	
Hypertrophy, diffuse		1 (2%)	1 (2%)
#Bile duct	(49)	(50)	(48)
Hyperplasia, NOS	28 (57%)	25 (50%)	10 (21%)
#Pancreas	(49)	(49)	(49)
Ectopia	1 (2%)		
Lymphocytic inflammatory infiltrate	2 (4%)	1 (2%)	1 (2%)
Atrophy, NOS	8 (16%)	4 (8%)	6 (12%)
Hyperplasia, focal	1 (2%)		1 (2%)
#Esophagus	(50)	(50)	(47)
Hemorrhage		1 (2%)	
#Esophageal adventiti	(50)	(50)	(47)
Granuloma, foreign body	1 (2%)		
#Stomach	(49)	(50)	(48)
Edema, NOS	1 (2%)		
#Glandular stomach	(49)	(50)	(48)
Mineralization		1 (2%)	
#Forestomach	(49)	(50)	(48)
Ulcer, NOS		1 (2%)	
Inflammation, acute	1 (2%)		
Hyperplasia, epithelial		2 (4%)	2 (4%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Small intestine	(49)	(49)	(42)
Parasitism		1 (2%)	
#Colon	(49)	(49)	(46)
Parasitism	4 (8%)	4 (8%)	1 (2%)
#Colonic mucosa	(49)	(49)	(46)
Mineralization		1 (2%)	
*Rectum	(50)	(50)	(49)
Parasitism		1 (2%)	
*Rectal mucosa	(50)	(50)	(49)
Mineralization	16 (32%)	7 (14%)	1 (2%)
URINARY SYSTEM			
#Kidney	(50)	(50)	(49)
Mineralization	6 (12%)	6 (12%)	2 (4%)
Hydronephrosis	2 (4%)		
Cyst, NOS	1 (2%)	1 (2%)	
Lymphocytic inflammatory infiltrate	5 (10%)	2 (4%)	
Nephropathy	11 (22%)	16 (32%)	12 (24%)
Nephrosis, NOS		1 (2%)	
Infarct, focal			1 (2%)
Atrophy, focal			1 (2%)
#Kidney/tubule	(50)	(50)	(49)
Pigmentation, NOS	43 (86%)	33 (66%)	15 (31%)
#Kidney/pelvis	(50)	(50)	(49)
Hyperplasia, epithelial		1 (2%)	
#Urinary bladder	(50)	(49)	(47)
Hemorrhage		2 (4%)	
Lymphocytic inflammatory infiltrate	1 (2%)		
Hyperplasia, epithelial		1 (2%)	
ENDOCRINE SYSTEM			
#Anterior pituitary	(50)	(48)	(44)
Cyst, NOS	21 (42%)	15 (31%)	12 (27%)
Hemorrhage			1 (2%)
Necrosis, focal		1 (2%)	
Hyperplasia, focal	11 (22%)	3 (6%)	7 (16%)
Angiectasis	10 (20%)	2 (4%)	5 (11%)
#Adrenal cortex	(50)	(49)	(49)
Congestion, NOS		1 (2%)	
Lipoidosis	7 (14%)	5 (10%)	1 (2%)
Cytoplasmic vacuolization		1 (2%)	
Focal cellular change	1 (2%)	1 (2%)	1 (2%)
Hypertrophy, focal	1 (2%)		
Hyperplasia, focal	4 (8%)	1 (2%)	2 (4%)
Angiectasis	1 (2%)		
#Adrenal medulla	(50)	(49)	(49)
Hyperplasia, focal	3 (6%)	3 (6%)	1 (2%)
#Thyroid	(49)	(50)	(47)
Thyroglossal duct cyst		1 (2%)	
Hyperplasia, C-cell	28 (57%)	30 (60%)	17 (36%)
Hyperplasia, follicular cell		1 (2%)	
#Pancreatic islets	(49)	(49)	(49)
Hyperplasia, focal		1 (2%)	
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(49)
Dilatation/ducts		2 (4%)	
Galactocele			1 (2%)

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*Mammary gland (Continued)	(50)	(50)	(49)
Inflammation, granulomatous	6 (12%)	3 (6%)	
Hyperplasia, NOS	1 (2%)		
*Clitoral gland	(50)	(50)	(49)
Dilatation/ducts	2 (4%)		
Cystic ducts	1 (2%)		
Inflammation, suppurative	1 (2%)		
Inflammation, acute/chronic	1 (2%)		
Inflammation, chronic			2 (4%)
*Vagina	(50)	(50)	(49)
Prolapse		1 (2%)	
Inflammation, suppurative		1 (2%)	
#Uterus	(49)	(49)	(47)
Hydrometra			1 (2%)
Cyst, NOS			1 (2%)
Inflammation, suppurative		2 (4%)	
Hemosiderosis	1 (2%)		
#Cervix uteri	(49)	(49)	(47)
Epidermal inclusion cyst	1 (2%)	2 (4%)	1 (2%)
#Uterus/endometrium	(49)	(49)	(47)
Cyst, NOS	2 (4%)		2 (4%)
Hyperplasia, cystic	3 (6%)	2 (4%)	
#Ovary	(49)	(49)	(47)
Cyst, NOS	3 (6%)	2 (4%)	3 (6%)
NERVOUS SYSTEM			
#Cerebellum	(50)	(50)	(49)
Mineralization			3 (6%)
SPECIAL SENSE ORGANS			
*Eye	(50)	(50)	(49)
Cataract		5 (10%)	4 (8%)
Phthisis bulbi		1 (2%)	
*Eye/retina	(50)	(50)	(49)
Atrophy, NOS		5 (10%)	5 (10%)
MUSCULOSKELETAL SYSTEM			
None			
BODY CAVITIES			
*Mediastinum	(50)	(50)	(49)
Vegetable foreign body			1 (2%)
Hemorrhage		1 (2%)	
Inflammation, suppurative			1 (2%)
Abscess, NOS	1 (2%)		
Inflammation, chronic	1 (2%)		
Inflammation, granulomatous		1 (2%)	2 (4%)
Foreign material, NOS		1 (2%)	
*Abdominal cavity	(50)	(50)	(49)
Necrosis, fat	1 (2%)	2 (4%)	1 (2%)
*Pleura	(50)	(50)	(49)
Inflammation, chronic	1 (2%)		
Granuloma, foreign body		1 (2%)	
Inflammation, pyogranulomatous			1 (2%)
Hemosiderosis		1 (2%)	

TABLE C2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
BODY CAVITIES (Continued)			
*Pericardium	(50)	(50)	(49)
Vegetable foreign body	1 (2%)	1 (2%)	
Inflammation, suppurative			1 (2%)
Inflammation, granulomatous	1 (2%)		1 (2%)
Granuloma, foreign body		2 (4%)	
Inflammation, pyogranulomatous		1 (2%)	1 (2%)
Fibrosis		2 (4%)	
ALL OTHER SYSTEMS			
Adipose tissue			
Necrosis, fat	1		
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported		3	14
Animal missing/no necropsy			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 4-VINYLCYCLOHEXENE

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE

	CONTROL (VEH)	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)
Inflammation, acute focal		1 (2%)	
Abscess, NOS			1 (2%)
Inflammation, active chronic		1 (2%)	
Inflammation, pyogranulomatous			1 (2%)
Hyperplasia, NOS		1 (2%)	1 (2%)
Hyperplasia, focal			1 (2%)
Metaplasia, osseous		1 (2%)	
*Subcutaneous tissue	(50)	(50)	(50)
Inflammation, acute	1 (2%)		
Inflammation, granulomatous	1 (2%)		
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
#Bronchial mucous gland	(49)	(50)	(50)
Dilatation, NOS	1 (2%)		
Inflammation, acute	1 (2%)		
#Lung	(49)	(50)	(50)
Congestion, NOS	2 (4%)	2 (4%)	36 (72%)
Hemorrhage	1 (2%)	3 (6%)	3 (6%)
Lymphocytic inflammatory infiltrate	3 (6%)	1 (2%)	
Inflammation, chronic focal	2 (4%)	1 (2%)	
Calcification, focal			1 (2%)
Hyperplasia, adenomatous		2 (4%)	
Histiocytosis		1 (2%)	
HEMATOPOIETIC SYSTEM			
#Bone marrow	(48)	(50)	(48)
Lymphocytosis	1 (2%)		
Hyperplasia, granulocytic	2 (4%)	1 (2%)	
#Spleen	(49)	(49)	(46)
Hyperplasia, lymphoid	5 (10%)	4 (8%)	
Hematopoiesis	6 (12%)	5 (10%)	1 (2%)
#Splenic red pulp	(49)	(49)	(46)
Atrophy, NOS			9 (20%)
Atrophy, focal			1 (2%)
#Mandibular lymph node	(31)	(44)	(38)
Granuloma, NOS			1 (3%)
Multinucleate giant cell			1 (3%)
#Thoracic lymph node	(31)	(44)	(38)
Hyperplasia, lymphoid		1 (2%)	
#Mediastinal lymph node	(31)	(44)	(38)
Hyperplasia, lymphoid	1 (3%)		
#Mesenteric lymph node	(31)	(44)	(38)
Congestion, NOS		1 (2%)	
Hemorrhage	1 (3%)	4 (9%)	2 (5%)
Necrosis, NOS		1 (2%)	
Angiectasis		3 (7%)	
Hyperplasia, lymphoid	1 (3%)		
Hematopoiesis		1 (2%)	
#Inguinal lymph node	(31)	(44)	(38)
Plasmacytosis		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
HEMATOPOIETIC SYSTEM (Continued)			
#Thymus	(42)	(41)	(43)
Cyst, NOS	1 (2%)		1 (2%)
Inflammation, acute/chronic			1 (2%)
#Thymic lymphocytes	(42)	(41)	(43)
Necrosis, NOS			1 (2%)
CIRCULATORY SYSTEM			
*Skin	(50)	(50)	(50)
Lymphangiectasis	1 (2%)		
#Mesenteric lymph node	(31)	(44)	(38)
Thrombosis, NOS		1 (2%)	
#Lung	(49)	(50)	(50)
Perivasculitis	1 (2%)		
#Heart	(50)	(50)	(50)
Periarteritis	1 (2%)		
Calcification, NOS	1 (2%)		
Hyperplasia, NOS			1 (2%)
#Heart/atrium	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
Inflammation, acute	1 (2%)		
#Myocardium	(50)	(50)	(50)
Inflammation, chronic	1 (2%)	1 (2%)	
Calcification, focal		1 (2%)	
*Pulmonary artery	(50)	(50)	(50)
Thrombosis, NOS	1 (2%)		
*Testicular artery	(50)	(50)	(50)
Necrosis, fibrinoid	1 (2%)		
*Superior mesentric vein	(50)	(50)	(50)
Thrombosis, NOS		1 (2%)	
#Kidney	(49)	(50)	(50)
Periarteritis	1 (2%)		
#Kidney/glomerulus	(49)	(50)	(50)
Embolus, septic	1 (2%)		
DIGESTIVE SYSTEM			
*Oral cavity	(50)	(50)	(50)
Inflammation, pyogranulomatous		1 (2%)	
*Periodontal tissues	(50)	(50)	(50)
Inflammation, active chronic		1 (2%)	
#Salivary gland	(47)	(50)	(49)
Inflammation, chronic focal	1 (2%)		
Calcification, focal	1 (2%)		1 (2%)
Atrophy, NOS	1 (2%)		
Atrophy, focal	1 (2%)		
#Liver	(49)	(50)	(50)
Cyst, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate	3 (6%)	2 (4%)	
Inflammation, acute/chronic	2 (4%)		
Inflammation, chronic focal		1 (2%)	
Inflammation, pyogranulomatous		1 (2%)	
Necrosis, NOS	2 (4%)	1 (2%)	
Necrosis, focal	1 (2%)		
Infarct, NOS	1 (2%)	2 (4%)	1 (2%)
Metamorphosis, fatty	7 (14%)	2 (4%)	3 (6%)
Calcification, focal			1 (2%)
Basophilic cyto change	1 (2%)		
Cytologic alteration, NOS		1 (2%)	
Multinucleate giant cell		1 (2%)	

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Hepatic capsule	(49)	(50)	(50)
Inflammation, acute/chronic			1 (2%)
#Liver/centrilobular	(49)	(50)	(50)
Congestion, NOS			7 (14%)
Metamorphosis, fatty		2 (4%)	
#Liver/periportal	(49)	(50)	(50)
Metamorphosis, fatty			1 (2%)
Cytoplasmic vacuolization			1 (2%)
#Liver/kupffer cell	(49)	(50)	(50)
Hyperplasia, NOS		3 (6%)	1 (2%)
Hyperplasia, focal		1 (2%)	
#Liver/hepatocytes	(49)	(50)	(50)
Multinucleate giant cell			2 (4%)
*Gallbladder	(50)	(50)	(50)
Hyperplasia, epithelial	1 (2%)		
#Bile duct	(49)	(50)	(50)
Hyperplasia, NOS	1 (2%)		
Hyperplasia, focal		1 (2%)	
#Peripancreatic tissue	(48)	(49)	(50)
Necrosis, fat	1 (2%)		
#Esophagus	(49)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Inflammation, acute	1 (2%)		
Inflammation, active chronic	1 (2%)		
Inflammation, acute/chronic			1 (2%)
#Periesophageal tissue	(49)	(50)	(50)
Hemorrhage	1 (2%)		
#Stomach	(47)	(50)	(46)
Edema, NOS		1 (2%)	
Calcification, NOS			1 (2%)
#Gastric serosa	(47)	(50)	(46)
Inflammation, acute/chronic	1 (2%)		
#Forestomach	(47)	(50)	(46)
Ulcer, NOS		3 (6%)	7 (15%)
Inflammation, acute		1 (2%)	5 (11%)
Inflammation, acute focal		2 (4%)	6 (13%)
Inflammation, acute/chronic		4 (8%)	5 (11%)
Hyperplasia, epithelial		7 (14%)	7 (15%)
Hyperkeratosis			1 (2%)
#Peyers patch	(43)	(49)	(35)
Hyperplasia, NOS		7 (14%)	2 (6%)
URINARY SYSTEM			
#Kidney	(49)	(50)	(50)
Hydronephrosis	1 (2%)	1 (2%)	
Polycystic kidney		1 (2%)	
Lymphocytic inflammatory infiltrate	17 (35%)	13 (26%)	2 (4%)
Glomerulonephritis, chronic		2 (4%)	
Hyperplasia, tubular cell		1 (2%)	1 (2%)
#Kidney/interstitium	(49)	(50)	(50)
Inflammation, chronic	1 (2%)	1 (2%)	
Inflammation, chronic focal	1 (2%)		
#Kidney/cortex	(49)	(50)	(50)
Cyst, NOS	1 (2%)		
#Kidney/glomerulus	(49)	(50)	(50)
Amyloidosis	1 (2%)		
#Kidney/tubule	(49)	(50)	(50)
Atrophy, focal	1 (2%)		

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
URINARY SYSTEM (Continued)			
#Urinary bladder	(45)	(49)	(47)
Calculus, gross observation only		1 (2%)	
Cast, NOS	1 (2%)	1 (2%)	1 (2%)
Lymphocytic inflammatory infiltrate	4 (9%)	2 (4%)	
ENDOCRINE SYSTEM			
#Adrenal	(48)	(50)	(50)
Congestion, NOS			3 (6%)
#Adrenal/capsule	(48)	(50)	(50)
Hyperplasia, NOS		1 (2%)	
#Adrenal cortex	(48)	(50)	(50)
Cyst, NOS		1 (2%)	
Cytologic alteration, NOS		2 (4%)	
Hyperplasia, focal		2 (4%)	1 (2%)
#Adrenal medulla	(48)	(50)	(50)
Hyperplasia, focal	1 (2%)		
#Thyroid	(45)	(47)	(45)
Follicular cyst, NOS	1 (2%)	3 (6%)	
Cholesterol deposit	1 (2%)		
#Thyroid follicle	(45)	(47)	(45)
Atrophy, focal	1 (2%)	1 (2%)	
#Parathyroid	(24)	(29)	(15)
Ectopia			1 (7%)
REPRODUCTIVE SYSTEM			
*Preputial gland	(50)	(50)	(50)
Dilatation/ducts	1 (2%)		
Cyst, NOS		1 (2%)	
Abscess, NOS	6 (12%)	9 (18%)	1 (2%)
Inflammation chronic suppurative	1 (2%)		
#Testis	(50)	(50)	(50)
Lymphocytic inflammatory infiltrate			1 (2%)
Calcification, NOS			1 (2%)
Calcification, focal	9 (18%)	11 (22%)	5 (10%)
Atrophy, NOS		2 (4%)	
Metaplasia, squamous	1 (2%)		
#Testis/tubule	(50)	(50)	(50)
Calcification, focal		1 (2%)	1 (2%)
Atrophy, focal			1 (2%)
*Epididymis	(50)	(50)	(50)
Granuloma, spermatic	1 (2%)		
Calcification, focal	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(50)	(50)
Hydrocephalus, NOS	1 (2%)		
Calcification, focal	25 (50%)	23 (46%)	15 (30%)
SPECIAL SENSE ORGANS			
None			

TABLE D1. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
*Maxilla	(50)	(50)	(50)
Inflammation, active chronic		1 (2%)	
*Tarsal joint	(50)	(50)	(50)
Dysplasia, NOS			1 (2%)
BODY CAVITIES			
*Thoracic cavity	(50)	(50)	(50)
Hemothorax	2 (4%)		
*Mediastinum	(50)	(50)	(50)
Vegetable foreign body			2 (4%)
Hemorrhage	1 (2%)		
Inflammation, suppurative	1 (2%)		2 (4%)
Inflammation, fibrinous	1 (2%)		
*Inguinal region	(50)	(50)	(50)
Necrosis, fat			1 (2%)
*Pleura	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		1 (2%)
Inflammation, acute/chronic	1 (2%)		
*Pericardium	(50)	(50)	(50)
Inflammation, suppurative			1 (2%)
ALL OTHER SYSTEMS			
Adipose tissue			
Inflammation, granulomatous	1		
Infarct, NOS		1	
Perihepatic region			
Necrosis, fat	1		
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported			2
Auto/necropsy/histo perf	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 4-VINYLCYCLOHEXENE

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING			1
ANIMALS NECROPSIED	50	50	48
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	50	48
INTEGUMENTARY SYSTEM			
*Skin	(50)	(50)	(48)
Epidermal inclusion cyst	1 (2%)		
Edema, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate	1 (2%)		
*Subcutaneous tissue	(50)	(50)	(48)
Inflammation, calc granulomatous		1 (2%)	
RESPIRATORY SYSTEM			
*Nasal cavity	(50)	(50)	(48)
Cyst, NOS		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, acute suppurative		1 (2%)	
#Lung/bronchiole	(50)	(49)	(48)
Hyperplasia, epithelial			1 (2%)
#Lung	(50)	(49)	(48)
Atelectasis		1 (2%)	1 (2%)
Congestion, NOS		1 (2%)	19 (40%)
Hemorrhage	1 (2%)	2 (4%)	1 (2%)
Lymphocytic inflammatory infiltrate	3 (6%)	1 (2%)	2 (4%)
Inflammation, acute/chronic	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic focal	2 (4%)		
Hyperplasia, adenomatous	1 (2%)		1 (2%)
Histiocytosis	1 (2%)		
HEMATOPOIETIC SYSTEM			
*Multiple organs	(50)	(50)	(48)
Myeloproliferative disorder			1 (2%)
Leukemoid reaction	1 (2%)		
#Bone marrow	(50)	(48)	(48)
Myelosclerosis			1 (2%)
Hyperplasia, granulocytic		1 (2%)	
#Spleen	(50)	(48)	(47)
Infarct, NOS	2 (4%)		1 (2%)
Hyperplasia, lymphoid	12 (24%)	5 (10%)	3 (6%)
Hematopoiesis	4 (8%)	6 (13%)	6 (13%)
#Mandibular lymph node	(47)	(47)	(38)
Inflammation, granulomatous		1 (2%)	
Hyperplasia, lymphoid	3 (6%)		1 (3%)
Mastocytosis		1 (2%)	
#Mediastinal lymph node	(47)	(47)	(38)
Amyloidosis		1 (2%)	
Hyperplasia, lymphoid	2 (4%)		
#Mesenteric lymph node	(47)	(47)	(38)
Congestion, NOS	1 (2%)		
Hemorrhage		2 (4%)	
Hyperplasia, lymphoid		1 (2%)	
#Liver	(50)	(49)	(48)
Hematopoiesis			1 (2%)
#Forestomach	(49)	(49)	(45)
Mastocytosis		1 (2%)	
#Thymus	(45)	(45)	(41)
Hemorrhage	2 (4%)		

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#Spleen	(50)	(48)	(47)
Thrombosis, NOS	1 (2%)		
#Mesenteric lymph node	(47)	(47)	(38)
Lymphangiectasis			2 (5%)
#Lung	(50)	(49)	(48)
Perivasculitis	1 (2%)	1 (2%)	
#Heart	(50)	(50)	(48)
Thrombosis, NOS			1 (2%)
Fibrosis, focal	1 (2%)		
Periarteritis	1 (2%)		
Degeneration, NOS	1 (2%)		
Calcification, focal	1 (2%)	1 (2%)	
Hyperplasia, NOS		1 (2%)	
#Myocardium	(50)	(50)	(48)
Calcification, focal		1 (2%)	
#Cardiac valve	(50)	(50)	(48)
Thrombosis, NOS	1 (2%)		
*Ovarian artery	(50)	(50)	(48)
Thrombosis, NOS	1 (2%)		
*Renal vein	(50)	(50)	(48)
Thrombosis, NOS	1 (2%)		
*Ovarian vein	(50)	(50)	(48)
Thrombosis, NOS			2 (4%)
*Splenic vein	(50)	(50)	(48)
Thrombosis, NOS	1 (2%)		
#Liver	(50)	(49)	(48)
Thrombus, organized	1 (2%)		
#Hepatic sinusoid	(50)	(49)	(48)
Dilatation, NOS	1 (2%)		
#Urinary bladder	(46)	(49)	(46)
Perivasculitis		1 (2%)	
#Uterus	(49)	(50)	(48)
Perivasculitis	1 (2%)		
DIGESTIVE SYSTEM			
#Salivary gland	(49)	(48)	(47)
Cystic ducts			1 (2%)
#Liver	(50)	(49)	(48)
Cyst, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate	2 (4%)	4 (8%)	1 (2%)
Inflammation, acute focal			1 (2%)
Inflammation, acute necrotizing	1 (2%)	2 (4%)	
Inflammation, active chronic		1 (2%)	
Inflammation, acute/chronic		2 (4%)	1 (2%)
Inflammation chronic necrotizing			1 (2%)
Necrosis, NOS	2 (4%)	1 (2%)	
Necrosis, focal	2 (4%)	2 (4%)	1 (2%)
Metamorphosis, fatty	1 (2%)	4 (8%)	2 (4%)
Cytoplasmic vacuolization	1 (2%)		
Basophilic cyto change	1 (2%)		
#Hepatic capsule	(50)	(49)	(48)
Lymphocytic inflammatory infiltrate		1 (2%)	
*Gallbladder	(50)	(50)	(48)
Lymphocytic inflammatory infiltrate		1 (2%)	
#Pancreas	(50)	(48)	(48)
Dilatation/ducts		1 (2%)	
Cystic ducts		1 (2%)	
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
Cytoplasmic vacuolization		1 (2%)	

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
DIGESTIVE SYSTEM (Continued)			
#Pancreatic acinus	(50)	(48)	(48)
Atrophy, NOS	1 (2%)	2 (4%)	
#Pancreas/interstitiu	(50)	(48)	(48)
Inflammation, acute		1 (2%)	
Inflammation, acute/chronic		1 (2%)	
#Periesophageal tissue	(50)	(49)	(47)
Inflammation, chronic	1 (2%)		
#Stomach	(49)	(49)	(45)
Ulcer, acute	1 (2%)		
Inflammation, acute/chronic		1 (2%)	
Erosion		1 (2%)	
Calcification, focal	1 (2%)		
#Gastric mucosa	(49)	(49)	(45)
Cyst, NOS	2 (4%)	1 (2%)	
#Forestomach	(49)	(49)	(45)
Cyst, NOS			1 (2%)
Ulcer, NOS			3 (7%)
Inflammation, acute			2 (4%)
Ulcer, acute			1 (2%)
Inflammation, acute focal		1 (2%)	2 (4%)
Inflammation, active chronic			1 (2%)
Inflammation, acute/chronic		1 (2%)	4 (9%)
Inflammation, chronic	1 (2%)		1 (2%)
Hyperplasia, epithelial	1 (2%)	3 (6%)	4 (9%)
#Peyers patch	(47)	(46)	(39)
Hyperplasia, NOS		4 (9%)	2 (5%)
URINARY SYSTEM			
#Kidney	(50)	(49)	(48)
Lymphocytic inflammatory infiltrate	14 (28%)	15 (31%)	6 (13%)
Glomerulonephritis, chronic	1 (2%)		
Infarct, NOS	1 (2%)		
Calcification, NOS	1 (2%)		
Hyperplasia, tubular cell		1 (2%)	
#Kidney/capsule	(50)	(49)	(48)
Lymphocytic inflammatory infiltrate		1 (2%)	
#Kidney/interstitium	(50)	(49)	(48)
Inflammation, chronic		1 (2%)	
#Kidney/cortex	(50)	(49)	(48)
Scar		2 (4%)	
#Kidney/tubule	(50)	(49)	(48)
Pigmentation, NOS		1 (2%)	1 (2%)
Atrophy, focal	1 (2%)		
#Kidney/pelvis	(50)	(49)	(48)
Calcification, focal			1 (2%)
*Ureter	(50)	(50)	(48)
Lymphocytic inflammatory infiltrate	1 (2%)		
#Urinary bladder	(46)	(49)	(46)
Lymphocytic inflammatory infiltrate	6 (13%)	4 (8%)	2 (4%)
Inflammation, acute/chronic			1 (2%)
ENDOCRINE SYSTEM			
#Pituitary	(49)	(49)	(44)
Angiectasis		1 (2%)	
#Anterior pituitary	(49)	(49)	(44)
Dilatation/sinus	2 (4%)		
Cyst, NOS		1 (2%)	1 (2%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#Anterior pituitary (Continued)	(49)	(49)	(44)
Hemorrhage			1 (2%)
Hyperplasia, NOS	1 (2%)	1 (2%)	
Hyperplasia, focal	3 (6%)		
Angiectasis	1 (2%)	3 (6%)	
#Adrenal	(50)	(49)	(48)
Congestion, NOS			8 (17%)
Hemorrhage			1 (2%)
Degeneration, lipoid		1 (2%)	
Cytologic alteration, NOS			1 (2%)
#Adrenal/capsule	(50)	(49)	(48)
Hyperplasia, NOS		4 (8%)	1 (2%)
#Adrenal cortex	(50)	(49)	(48)
Accessory structure			1 (2%)
Cyst, NOS	1 (2%)	1 (2%)	2 (4%)
Degeneration, lipoid	1 (2%)		
Cytoplasmic vacuolization	2 (4%)		
Cytologic alteration, NOS		24 (49%)	14 (29%)
Hypertrophy, focal			1 (2%)
Hyperplasia, NOS			1 (2%)
#Adrenal medulla	(50)	(49)	(48)
Hyperplasia, focal	1 (2%)	2 (4%)	
#Thyroid	(47)	(46)	(45)
Follicular cyst, NOS		3 (7%)	
Inflammation, chronic	1 (2%)	1 (2%)	
Hyperplasia, follicular cell	2 (4%)		
#Thyroid follicle	(47)	(46)	(45)
Hyperplasia, papillary		1 (2%)	
#Parathyroid	(30)	(29)	(19)
Ectopia			1 (5%)
REPRODUCTIVE SYSTEM			
*Mammary gland	(50)	(50)	(48)
Dilatation/ducts	4 (8%)	2 (4%)	5 (10%)
*Mammary lobule	(50)	(50)	(48)
Hyperplasia, NOS	1 (2%)	1 (2%)	
#Uterus	(49)	(50)	(48)
Hydrometra	5 (10%)		
Hematoma, NOS		1 (2%)	
Lymphocytic inflammatory infiltrate	1 (2%)		
Pyometra		1 (2%)	
Calcification, focal			1 (2%)
#Cervix uteri	(49)	(50)	(48)
Cyst, NOS	1 (2%)		
Inflammation, acute			1 (2%)
#Uterus/endometrium	(49)	(50)	(48)
Cyst, NOS	6 (12%)	2 (4%)	2 (4%)
Hematoma, NOS			1 (2%)
Hyperplasia, cystic	35 (71%)	40 (80%)	28 (58%)
#Fallopian tube	(49)	(50)	(48)
Cyst, NOS	1 (2%)		
#Ovary	(49)	(48)	(47)
Cyst, NOS	19 (39%)	16 (33%)	11 (23%)
Hematoma, NOS			1 (2%)
Hemorrhagic cyst			1 (2%)
Abscess, NOS		1 (2%)	
Inflammation, chronic	1 (2%)		
Infarct, NOS			1 (2%)
Hyperplasia, tubular cell	1 (2%)	10 (21%)	13 (28%)

TABLE D2. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	CONTROL (VEH)	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
#Ovary (Continued)			
Hyperplasia, granulosa cell		5 (10%)	1 (2%)
Hyperplasia, papillary			2 (4%)
Hyperplasia, stromal	1 (2%)		
NERVOUS SYSTEM			
#Brain	(50)	(49)	(48)
Hemorrhage	1 (2%)		
Lymphocytic inflammatory infiltrate			1 (2%)
Calcification, focal	27 (54%)	16 (33%)	10 (21%)
SPECIAL SENSE ORGANS			
*Eye/cornea	(50)	(50)	(48)
Inflammation, acute		1 (2%)	
Inflammation, chronic		1 (2%)	
*Nasolacrimal duct	(50)	(50)	(48)
Inflammation, acute		2 (4%)	
MUSCULOSKELETAL SYSTEM			
*Sternum	(50)	(50)	(48)
Fibrous osteodystrophy	40 (80%)	40 (80%)	27 (56%)
Cytologic alteration, NOS			1 (2%)
Osteosclerosis	2 (4%)	1 (2%)	1 (2%)
BODY CAVITIES			
*Mediastinum	(50)	(50)	(48)
Lymphocytic inflammatory infiltrate		1 (2%)	
*Mesentery	(50)	(50)	(48)
Steatitis	1 (2%)		
Inflammation, granulomatous		1 (2%)	
Necrosis, fat	1 (2%)		
Infarct, NOS			1 (2%)
ALL OTHER SYSTEMS			
*Multiple organs	(50)	(50)	(48)
Inflammation, acute/chronic			1 (2%)
SPECIAL MORPHOLOGY SUMMARY			
No lesion reported		1	
Animal missing/no necropsy			1
No necropsy performed			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 4-VINYLCYCLOHEXENE

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE

	Vehicle Control	200 mg/kg	400 mg/kg
Skin: Squamous Cell Papilloma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	3.6%	31.9%
Terminal Rates (c)	0/33 (0%)	0/13 (0%)	1/5 (20%)
Week of First Observation		88	80
Life Table Tests (d)	P=0.004	P=0.450	P=0.006
Incidental Tumor Tests (d)	P=0.052	P=0.718	P=0.102
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.121
Skin: Squamous Cell Papilloma or Carcinoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	4/50 (8%)
Adjusted Rates (b)	0.0%	3.6%	37.5%
Terminal Rates (c)	0/33 (0%)	0/13 (0%)	1/5 (20%)
Week of First Observation		88	80
Life Table Tests (d)	P<0.001	P=0.450	P=0.001
Incidental Tumor Tests (d)	P=0.024	P=0.718	P=0.070
Cochran-Armitage Trend Test (d)	P=0.026		
Fisher Exact Test (d)		P=0.500	P=0.059
Subcutaneous Tissue: Fibroma or Neurofibroma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	3.0%	15.2%	0.0%
Terminal Rates (c)	1/33 (3%)	1/13 (8%)	0/5 (0%)
Week of First Observation	104	82	
Life Table Tests (d)	P=0.435	P=0.116	P=0.862N
Incidental Tumor Tests (d)	P=0.523N	P=0.310	P=0.862N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Subcutaneous Tissue: Fibroma or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	3/50 (6%)	0/50 (0%)
Adjusted Rates (b)	3.0%	12.8%	0.0%
Terminal Rates (c)	1/33 (3%)	1/13 (8%)	0/5 (0%)
Week of First Observation	104	56	
Life Table Tests (d)	P=0.529	P=0.145	P=0.862N
Incidental Tumor Tests (d)	P=0.552N	P=0.254	P=0.862N
Cochran-Armitage Trend Test (d)	P=0.378N		
Fisher Exact Test (d)		P=0.309	P=0.500N
Subcutaneous Tissue: Fibroma, Neurofibroma, or Fibrosarcoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	0/50 (0%)
Adjusted Rates (b)	3.0%	17.4%	0.0%
Terminal Rates (c)	1/33 (3%)	1/13 (8%)	0/5 (0%)
Week of First Observation	104	56	
Life Table Tests (d)	P=0.413	P=0.060	P=0.862N
Incidental Tumor Tests (d)	P=0.493N	P=0.199	P=0.862N
Cochran-Armitage Trend Test (d)	P=0.390N		
Fisher Exact Test (d)		P=0.181	P=0.500N
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	14/50 (28%)	8/50 (16%)	1/50 (2%)
Adjusted Rates (b)	35.0%	40.4%	11.1%
Terminal Rates (c)	8/33 (24%)	3/13 (23%)	0/5 (0%)
Week of First Observation	49	81	98
Life Table Tests (d)	P=0.189N	P=0.522	P=0.109N
Incidental Tumor Tests (d)	P<0.001N	P=0.081N	P<0.001N
Cochran-Armitage Trend Test (d)	P<0.001N		
Fisher Exact Test (d)		P=0.114N	P<0.001N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
Pituitary Gland: Adenoma			
Overall Rates (a)	15/50 (30%)	11/49 (22%)	7/45 (16%)
Adjusted Rates (b)	44.1%	45.1%	43.1%
Terminal Rates (c)	14/33 (42%)	3/13 (23%)	1/5 (20%)
Week of First Observation	100	82	67
Life Table Tests (d)	P=0.071	P=0.164	P=0.071
Incidental Tumor Tests (d)	P=0.369N	P=0.488N	P=0.515
Cochran-Armitage Trend Test (d)	P=0.060N		
Fisher Exact Test (d)		P=0.266N	P=0.077N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	17/50 (34%)	16/50 (32%)	8/50 (16%)
Adjusted Rates (b)	48.6%	83.0%	73.0%
Terminal Rates (c)	15/33 (45%)	10/13 (77%)	3/5 (60%)
Week of First Observation	100	90	84
Life Table Tests (d)	P=0.001	P=0.003	P=0.014
Incidental Tumor Tests (d)	P=0.204	P=0.091	P=0.490
Cochran-Armitage Trend Test (d)	P=0.028N		
Fisher Exact Test (d)		P=0.500N	P=0.032N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	4/48 (8%)	5/50 (10%)	0/46 (0%)
Adjusted Rates (b)	11.5%	24.9%	0.0%
Terminal Rates (c)	3/33 (9%)	1/13 (8%)	0/5 (0%)
Week of First Observation	86	82	
Life Table Tests (d)	P=0.552N	P=0.157	P=0.365N
Incidental Tumor Tests (d)	P=0.097N	P=0.619	P=0.184N
Cochran-Armitage Trend Test (d)	P=0.075N		
Fisher Exact Test (d)		P=0.526	P=0.064N
Testis: Interstitial Cell Tumor			
Overall Rates (a)	35/50 (70%)	30/50 (60%)	29/50 (58%)
Adjusted Rates (b)	89.7%	96.5%	100.0%
Terminal Rates (c)	29/33 (88%)	12/13 (92%)	5/5 (100%)
Week of First Observation	80	68	47
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Incidental Tumor Tests (d)	P=0.010	P=0.398	P=0.027
Cochran-Armitage Trend Test (d)	P=0.128N		
Fisher Exact Test (d)		P=0.201N	P=0.149N
Preputial Gland: Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	2.4%	5.3%	20.9%
Terminal Rates (c)	0/33 (0%)	0/13 (0%)	0/5 (0%)
Week of First Observation	70	100	80
Life Table Tests (d)	P=0.038	P=0.675	P=0.082
Incidental Tumor Tests (d)	P=0.411	P=0.600N	P=0.637
Cochran-Armitage Trend Test (d)	P=0.202		
Fisher Exact Test (d)		P=0.753	P=0.309
All Sites: Mesothelioma			
Overall Rates (a)	3/50 (6%)	0/50 (0%)	0/50 (0%)
Adjusted Rates (b)	7.4%	0.0%	0.0%
Terminal Rates (c)	1/33 (3%)	0/13 (0%)	0/5 (0%)
Week of First Observation	34		
Life Table Tests (d)	P=0.100N	P=0.189N	P=0.297N
Incidental Tumor Tests (d)	P=0.014N	P=0.068N	P=0.042N
Cochran-Armitage Trend Test (d)	P=0.037N		
Fisher Exact Test (d)		P=0.121N	P=0.121N

TABLE E1. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier 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 E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE

	Vehicle Control	200 mg/kg	400 mg/kg
Hematopoietic System: Mononuclear Cell Leukemia			
Overall Rates (a)	9/50 (18%)	13/50 (26%)	5/49 (10%)
Adjusted Rates (b)	20.0%	39.8%	31.2%
Terminal Rates (c)	5/40 (13%)	9/28 (32%)	2/13 (15%)
Week of First Observation	68	81	94
Life Table Tests (d)	P=0.125	P=0.074	P=0.277
Incidental Tumor Tests (d)	P=0.336	P=0.233	P=0.599
Cochran-Armitage Trend Test (d)	P=0.193N		
Fisher Exact Test (d)		P=0.235	P=0.205N
Pituitary Gland: Adenoma			
Overall Rates (a)	19/50 (38%)	23/48 (48%)	7/44 (16%)
Adjusted Rates (b)	44.9%	65.0%	39.9%
Terminal Rates (c)	17/40 (43%)	15/27 (56%)	3/13 (23%)
Week of First Observation	68	85	66
Life Table Tests (d)	P=0.212	P=0.022	P=0.512
Incidental Tumor Tests (d)	P=0.522	P=0.095	P=0.444N
Cochran-Armitage Trend Test (d)	P=0.020N		
Fisher Exact Test (d)		P=0.216	P=0.015N
Pituitary Gland: Adenoma or Carcinoma			
Overall Rates (a)	19/50 (38%)	24/48 (50%)	7/44 (16%)
Adjusted Rates (b)	44.9%	66.0%	39.9%
Terminal Rates (c)	17/40 (43%)	15/27 (56%)	3/13 (23%)
Week of First Observation	68	85	66
Life Table Tests (d)	P=0.195	P=0.014	P=0.512
Incidental Tumor Tests (d)	P=0.516	P=0.073	P=0.444N
Cochran-Armitage Trend Test (d)	P=0.021N		
Fisher Exact Test (d)		P=0.160	P=0.015N
Adrenal Gland: Pheochromocytoma			
Overall Rates (a)	3/50 (6%)	3/49 (6%)	1/49 (2%)
Adjusted Rates (b)	7.5%	10.0%	7.1%
Terminal Rates (c)	3/40 (7%)	2/28 (7%)	0/13 (0%)
Week of First Observation	104	100	95
Life Table Tests (d)	P=0.541	P=0.502	P=0.715
Incidental Tumor Tests (d)	P=0.564N	P=0.577	P=0.648N
Cochran-Armitage Trend Test (d)	P=0.246N		
Fisher Exact Test (d)		P=0.651	P=0.316N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	3/49 (6%)	4/50 (8%)	0/47 (0%)
Adjusted Rates (b)	7.7%	14.3%	0.0%
Terminal Rates (c)	3/39 (8%)	4/28 (14%)	0/13 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.452N	P=0.322	P=0.367N
Incidental Tumor Tests (d)	P=0.452N	P=0.322	P=0.367N
Cochran-Armitage Trend Test (d)	P=0.125N		
Fisher Exact Test (d)		P=0.511	P=0.129N
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	5/49 (10%)	4/50 (8%)	0/47 (0%)
Adjusted Rates (b)	12.4%	14.3%	0.0%
Terminal Rates (c)	4/39 (10%)	4/28 (14%)	0/13 (0%)
Week of First Observation	103	104	
Life Table Tests (d)	P=0.231N	P=0.573	P=0.216N
Incidental Tumor Tests (d)	P=0.192N	P=0.637N	P=0.170N
Cochran-Armitage Trend Test (d)	P=0.032N		
Fisher Exact Test (d)		P=0.487N	P=0.031N

TABLE E2. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
Mammary Gland: Fibroadenoma			
Overall Rates (a)	7/50 (14%)	9/50 (18%)	4/49 (8%)
Adjusted Rates (b)	17.5%	27.2%	24.0%
Terminal Rates (c)	7/40 (18%)	5/28 (18%)	2/13 (15%)
Week of First Observation	104	87	51
Life Table Tests (d)	P=0.177	P=0.163	P=0.301
Incidental Tumor Tests (d)	P=0.432	P=0.310	P=0.553
Cochran-Armitage Trend Test (d)	P=0.243N		
Fisher Exact Test (d)		P=0.393	P=0.274N
Clitoral Gland: Adenoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	0/49 (0%)
Adjusted Rates (b)	2.5%	14.3%	0.0%
Terminal Rates (c)	1/40 (3%)	4/28 (14%)	0/13 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.459	P=0.088	P=0.723N
Incidental Tumor Tests (d)	P=0.459	P=0.088	P=0.723N
Cochran-Armitage Trend Test (d)	P=0.397N		
Fisher Exact Test (d)		P=0.181	P=0.505N
Clitoral Gland: Adenoma or Squamous Cell Carcinoma			
Overall Rates (a)	1/50 (2%)	5/50 (10%)	0/49 (0%)
Adjusted Rates (b)	2.5%	17.9%	0.0%
Terminal Rates (c)	1/40 (3%)	5/28 (18%)	0/13 (0%)
Week of First Observation	104	104	
Life Table Tests (d)	P=0.387	P=0.040	P=0.723N
Incidental Tumor Tests (d)	P=0.387	P=0.040	P=0.723N
Cochran-Armitage Trend Test (d)	P=0.407N		
Fisher Exact Test (d)		P=0.102	P=0.505N
Uterus: Endometrial Stromal Polyp			
Overall Rates (a)	8/49 (16%)	9/49 (18%)	5/47 (11%)
Adjusted Rates (b)	19.8%	30.4%	38.5%
Terminal Rates (c)	7/39 (18%)	7/27 (26%)	5/13 (38%)
Week of First Observation	94	91	105
Life Table Tests (d)	P=0.120	P=0.216	P=0.189
Incidental Tumor Tests (d)	P=0.173	P=0.336	P=0.225
Cochran-Armitage Trend Test (d)	P=0.266N		
Fisher Exact Test (d)		P=0.500	P=0.304N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier 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 E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE

	Vehicle Control	200 mg/kg	400 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	1/49 (2%)	4/50 (8%)	3/50 (6%)
Adjusted Rates (b)	2.7%	9.7%	30.9%
Terminal Rates (c)	1/37 (3%)	3/39 (8%)	2/7 (29%)
Week of First Observation	104	91	76
Life Table Tests (d)	P=0.014	P=0.199	P=0.021
Incidental Tumor Tests (d)	P=0.095	P=0.236	P=0.051
Cochran-Armitage Trend Test (d)	P=0.259		
Fisher Exact Test (d)		P=0.187	P=0.316
Lung: Alveolar/Bronchiolar Carcinoma			
Overall Rates (a)	3/49 (6%)	7/50 (14%)	1/50 (2%)
Adjusted Rates (b)	7.8%	17.3%	14.3%
Terminal Rates (c)	2/37 (5%)	6/39 (15%)	1/7 (14%)
Week of First Observation	99	97	104
Life Table Tests (d)	P=0.234	P=0.185	P=0.579
Incidental Tumor Tests (d)	P=0.229	P=0.177	P=0.579
Cochran-Armitage Trend Test (d)	P=0.273N		
Fisher Exact Test (d)		P=0.167	P=0.301N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	4/49 (8%)	11/50 (22%)	4/50 (8%)
Adjusted Rates (b)	10.4%	26.5%	44.7%
Terminal Rates (c)	3/37 (8%)	9/39 (23%)	3/7 (43%)
Week of First Observation	99	91	76
Life Table Tests (d)	P=0.011	P=0.062	P=0.030
Incidental Tumor Tests (d)	P=0.047	P=0.068	P=0.065
Cochran-Armitage Trend Test (d)	P=0.545N		
Fisher Exact Test (d)		P=0.049	P=0.631N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	3/50 (6%)	3/50 (6%)	3/50 (6%)
Adjusted Rates (b)	8.1%	7.7%	42.9%
Terminal Rates (c)	3/37 (8%)	3/39 (8%)	3/7 (43%)
Week of First Observation	104	104	104
Life Table Tests (d)	P=0.063	P=0.639N	P=0.033
Incidental Tumor Tests (d)	P=0.063	P=0.639N	P=0.033
Cochran-Armitage Trend Test (d)	P=0.583		
Fisher Exact Test (d)		P=0.661N	P=0.661N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	4/50 (8%)	7/50 (14%)	5/50 (10%)
Adjusted Rates (b)	10.5%	16.7%	62.5%
Terminal Rates (c)	3/37 (8%)	5/39 (13%)	4/7 (57%)
Week of First Observation	102	63	101
Life Table Tests (d)	P=0.007	P=0.301	P=0.002
Incidental Tumor Tests (d)	P=0.013	P=0.340	P=0.001
Cochran-Armitage Trend Test (d)	P=0.436		
Fisher Exact Test (d)		P=0.262	P=0.500
Liver: Hepatocellular Adenoma			
Overall Rates (a)	7/49 (14%)	11/50 (22%)	3/50 (6%)
Adjusted Rates (b)	18.9%	27.3%	29.4%
Terminal Rates (c)	7/37 (19%)	10/39 (26%)	1/7 (14%)
Week of First Observation	104	97	90
Life Table Tests (d)	P=0.133	P=0.253	P=0.246
Incidental Tumor Tests (d)	P=0.217	P=0.250	P=0.443
Cochran-Armitage Trend Test (d)	P=0.146N		
Fisher Exact Test (d)		P=0.232	P=0.151N

TABLE E3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
Liver: Hepatocellular Carcinoma			
Overall Rates (a)	11/49 (22%)	10/50 (20%)	3/50 (6%)
Adjusted Rates (b)	26.3%	21.4%	30.9%
Terminal Rates (c)	7/37 (19%)	3/39 (8%)	2/7 (29%)
Week of First Observation	62	62	76
Life Table Tests (d)	P=0.500N	P=0.441N	P=0.607
Incidental Tumor Tests (d)	P=0.023N	P=0.251N	P=0.187N
Cochran-Armitage Trend Test (d)	P=0.018N		
Fisher Exact Test (d)		P=0.479N	P=0.019N
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	18/49 (37%)	20/50 (40%)	6/50 (12%)
Adjusted Rates (b)	43.5%	43.2%	54.5%
Terminal Rates (c)	14/37 (38%)	13/39 (33%)	3/7 (43%)
Week of First Observation	62	62	76
Life Table Tests (d)	P=0.291	P=0.508	P=0.296
Incidental Tumor Tests (d)	P=0.170N	P=0.510N	P=0.388N
Cochran-Armitage Trend Test (d)	P=0.005N		
Fisher Exact Test (d)		P=0.449	P=0.004N

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier 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 4-VINYLCYCLOHEXENE

	Vehicle Control	200 mg/kg	400 mg/kg
Lung: Alveolar/Bronchiolar Adenoma			
Overall Rates (a)	5/50 (10%)	1/49 (2%)	3/48 (6%)
Adjusted Rates (b)	11.7%	2.6%	14.5%
Terminal Rates (c)	3/40 (7%)	1/39 (3%)	2/17 (12%)
Week of First Observation	92	104	90
Life Table Tests (d)	P=0.584N	P=0.109N	P=0.516
Incidental Tumor Tests (d)	P=0.329N	P=0.109N	P=0.495N
Cochran-Armitage Trend Test (d)	P=0.281N		
Fisher Exact Test (d)		P=0.107N	P=0.381N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma			
Overall Rates (a)	6/50 (12%)	1/49 (2%)	4/48 (8%)
Adjusted Rates (b)	14.1%	2.6%	19.3%
Terminal Rates (c)	4/40 (10%)	1/39 (3%)	2/17 (12%)
Week of First Observation	92	104	90
Life Table Tests (d)	P=0.512	P=0.064N	P=0.405
Incidental Tumor Tests (d)	P=0.379N	P=0.063N	P=0.554N
Cochran-Armitage Trend Test (d)	P=0.302N		
Fisher Exact Test (d)		P=0.059N	P=0.397N
Hematopoietic System: Malignant Lymphoma, Lymphocytic Type			
Overall Rates (a)	1/50 (2%)	6/50 (12%)	5/48 (10%)
Adjusted Rates (b)	2.1%	14.2%	21.4%
Terminal Rates (c)	0/40 (0%)	4/39 (10%)	2/17 (12%)
Week of First Observation	88	60	90
Life Table Tests (d)	P=0.012	P=0.061	P=0.020
Incidental Tumor Tests (d)	P=0.146	P=0.066	P=0.199
Cochran-Armitage Trend Test (d)	P=0.088		
Fisher Exact Test (d)		P=0.056	P=0.093
Hematopoietic System: Malignant Lymphoma, Histiocytic Type			
Overall Rates (a)	3/50 (6%)	4/50 (8%)	1/48 (2%)
Adjusted Rates (b)	6.3%	8.9%	5.6%
Terminal Rates (c)	0/40 (0%)	1/39 (3%)	0/17 (0%)
Week of First Observation	55	82	99
Life Table Tests (d)	P=0.488N	P=0.505	P=0.518N
Incidental Tumor Tests (d)	P=0.067N	P=0.525	P=0.064N
Cochran-Armitage Trend Test (d)	P=0.267N		
Fisher Exact Test (d)		P=0.500	P=0.324N
Hematopoietic System: Malignant Lymphoma, Mixed Type			
Overall Rates (a)	11/50 (22%)	5/50 (10%)	5/48 (10%)
Adjusted Rates (b)	26.0%	12.5%	27.4%
Terminal Rates (c)	9/40 (23%)	4/39 (10%)	4/17 (24%)
Week of First Observation	89	101	94
Life Table Tests (d)	P=0.419N	P=0.097N	P=0.598
Incidental Tumor Tests (d)	P=0.273N	P=0.078N	P=0.466N
Cochran-Armitage Trend Test (d)	P=0.065N		
Fisher Exact Test (d)		P=0.086N	P=0.100N
Hematopoietic System: Lymphoma, All Malignant			
Overall Rates (a)	16/50 (32%)	15/50 (30%)	11/48 (23%)
Adjusted Rates (b)	34.3%	33.0%	48.3%
Terminal Rates (c)	10/40 (25%)	9/39 (23%)	6/17 (35%)
Week of First Observation	55	60	90
Life Table Tests (d)	P=0.224	P=0.513N	P=0.222
Incidental Tumor Tests (d)	P=0.225N	P=0.459N	P=0.324N
Cochran-Armitage Trend Test (d)	P=0.189N		
Fisher Exact Test (d)		P=0.500N	P=0.218N

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
Liver: Hepatocellular Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	3/49 (6%)	3/48 (6%)
Adjusted Rates (b)	2.5%	7.7%	15.8%
Terminal Rates (c)	1/40 (3%)	3/39 (8%)	2/17 (12%)
Week of First Observation	104	104	92
Life Table Tests (d)	P=0.049	P=0.296	P=0.081
Incidental Tumor Tests (d)	P=0.099	P=0.296	P=0.171
Cochran-Armitage Trend Test (d)	P=0.225		
Fisher Exact Test (d)		P=0.301	P=0.293
Pituitary Gland: Adenoma			
Overall Rates (a)	9/49 (18%)	7/49 (14%)	3/44 (7%)
Adjusted Rates (b)	21.4%	17.4%	20.0%
Terminal Rates (c)	7/40 (18%)	6/39 (15%)	3/15 (20%)
Week of First Observation	94	99	104
Life Table Tests (d)	P=0.425N	P=0.408N	P=0.545N
Incidental Tumor Tests (d)	P=0.370N	P=0.330N	P=0.492N
Cochran-Armitage Trend Test (d)	P=0.070N		
Fisher Exact Test (d)		P=0.393N	P=0.087N
Pituitary Gland: Adenoma or Adenocarcinoma			
Overall Rates (a)	9/49 (18%)	8/49 (16%)	3/44 (7%)
Adjusted Rates (b)	21.4%	19.4%	20.0%
Terminal Rates (c)	7/40 (18%)	6/39 (15%)	3/15 (20%)
Week of First Observation	94	99	104
Life Table Tests (d)	P=0.459N	P=0.513N	P=0.545N
Incidental Tumor Tests (d)	P=0.384N	P=0.409N	P=0.492N
Cochran-Armitage Trend Test (d)	P=0.076N		
Fisher Exact Test (d)		P=0.500N	P=0.087N
Adrenal Gland Capsule or Cortex: Adenoma			
Overall Rates (a)	0/50 (0%)	3/49 (6%)	4/48 (8%)
Adjusted Rates (b)	0.0%	7.7%	18.3%
Terminal Rates (c)	0/40 (0%)	3/39 (8%)	2/17 (12%)
Week of First Observation		104	89
Life Table Tests (d)	P=0.005	P=0.117	P=0.011
Incidental Tumor Tests (d)	P=0.027	P=0.117	P=0.056
Cochran-Armitage Trend Test (d)	P=0.044		
Fisher Exact Test (d)		P=0.117	P=0.054
Ovary: Mixed Tumor, Benign			
Overall Rates (a)	0/49 (0%)	25/48 (52%)	11/47 (23%)
Adjusted Rates (b)	0.0%	64.1%	43.3%
Terminal Rates (c)	0/39 (0%)	24/38 (63%)	4/16 (25%)
Week of First Observation		100	82
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=0.005		
Fisher Exact Test (d)		P<0.001	P<0.001
Ovary: Granulosa Cell Tumor			
Overall Rates (a)	1/49 (2%)	9/48 (19%)	11/47 (23%)
Adjusted Rates (b)	2.6%	23.7%	47.3%
Terminal Rates (c)	1/39 (3%)	9/38 (24%)	6/16 (38%)
Week of First Observation	104	104	85
Life Table Tests (d)	P<0.001	P=0.008	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.008	P<0.001
Cochran-Armitage Trend Test (d)	P=0.002		
Fisher Exact Test (d)		P=0.007	P=0.001

TABLE E4. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR GAVAGE STUDY OF 4-VINYLCYCLOHEXENE (Continued)

	Vehicle Control	200 mg/kg	400 mg/kg
Ovary: Granulosa Cell Tumor or Carcinoma			
Overall Rates (a)	1/49 (2%)	10/48 (21%)	13/47 (28%)
Adjusted Rates (b)	2.6%	25.5%	54.9%
Terminal Rates (c)	1/39 (3%)	9/38 (24%)	7/16 (44%)
Week of First Observation	104	99	85
Life Table Tests (d)	P<0.001	P=0.005	P<0.001
Incidental Tumor Tests (d)	P<0.001	P=0.006	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P=0.003	P<0.001
Harderian Gland: Papillary Adenoma			
Overall Rates (a)	0/50 (0%)	4/50 (8%)	0/48 (0%)
Adjusted Rates (b)	0.0%	10.3%	0.0%
Terminal Rates (c)	0/40 (0%)	4/39 (10%)	0/17 (0%)
Week of First Observation		104	
Life Table Tests (d)	P=0.375	P=0.060	(e)
Incidental Tumor Tests (d)	P=0.375	P=0.060	(e)
Cochran-Armitage Trend Test (d)	P=0.609		
Fisher Exact Test (d)		P=0.059	(e)

(a) Number of tumor-bearing animals/number of animals examined at the site
(b) Kaplan-Meier 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 400 mg/kg and vehicle control groups.

APPENDIX F

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

TABLE F1. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Diallylphthalate	0/50	0/50	0/50
Tris(2-ethylhexyl)phosphate	1/50	0/50	1/50
2,4-Toluene diisocyanate	1/50	0/50	1/50
TOTAL	2/150 (1.3%)	0/150 (0.0%)	2/150 (1.3%)
SD (b)	1.15%	0.00%	1.15%
Range (c)			
High	1/50	0/50	1/50
Low	0/50	0/50	0/50
Overall Historical Incidence			
TOTAL	12/1,094 (1.1%)	9/1,094 (0.8%)	21/1,094 (1.9%)
SD (b)	1.72%	1.47%	2.65%
Range (c)			
High	3/50	3/50	5/50
Low	0/50	0/50	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

TABLE F2. HISTORICAL INCIDENCE OF MESOTHELIOMAS IN MALE F344/N RATS ADMINISTERED CORN OIL BY GAVAGE (a)

Study	No. of Animals Examined	No. of Tumors in Vehicle Controls	Site	Diagnosis
Historical Incidence at Litton Bionetics, Inc.				
Diallylphthalate	50	1	Multiple organs	NOS
Tris(2-ethylhexyl)phosphate	50	2	Tunica vaginalis	NOS
2,4-Toluene diisocyanate	50	2	Testis	NOS
TOTAL	150	5		
Overall Historical Incidence				
		1	Testis	NOS
		2	Testis	Malignant
		1	Body cavities, NOS	NOS
		1	Peritoneum	NOS
		2	Peritoneum	Malignant
		1	Pleura	Malignant
		1	Mesentery	NOS
		1	Mesentery	Malignant
		15	Tunica vaginalis	NOS
		1	Tunica vaginalis	Malignant
		4	Multiple organs	NOS
		1	Multiple organs	Malignant
TOTAL	1,146	23 NOS 8 Malignant		

(a) Data as of March 16, 1983, for studies of at least 104 weeks

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

	No. of Animals Examined	No. of Tumors in Vehicle Controls	Diagnosis
Historical Incidence at Litton Bionetics, Inc.			
	149	0	
Overall Historical Incidence			
	1,084	1	Papilloma, NOS
		1	Transitional cell papilloma
		1	Transitional cell carcinoma
TOTAL		3 (0.3%)	

(a) Data as of March 16, 1983, for studies of at least 104 weeks

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

Study	No. of Animals Examined	No. of Tumors in Vehicle Controls	Diagnosis
Historical Incidence at Litton Bionetics, Inc.			
MALE			
Diallylphthalate	50	1	Carcinoma, NOS
Tris(2-ethylhexyl)phosphate	50	0	
2,4-Toluene diisocyanate	50	7	Adenoma, NOS
TOTAL	150	8 (5.3%)	
FEMALE			
Diallylphthalate	50	1	Adenoma, NOS
		1	Carcinoma, NOS
Tris(2-ethylhexyl)phosphate	50	1	Adenoma, NOS
2,4-Toluene diisocyanate	50	1	Carcinoma, NOS
TOTAL	150	4 (2.7%)	
Overall Historical Incidence			
MALE (b)			
		19	Adenoma, NOS
		13	Carcinoma, NOS
		2	Squamous cell carcinoma
		7	Adenocarcinoma, NOS
TOTAL	1,146	41 (3.6%)	
FEMALE (c)			
		6	Adenoma, NOS
		14	Carcinoma, NOS
		4	Adenocarcinoma, NOS
TOTAL	1,147	24 (2.1%)	

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Greatest observed incidence of combined tumor types: 7/50
(c) Greatest observed incidence of combined tumor types: 3/48

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

Study	Incidence in Vehicle Controls		
	Adenoma (b)	Carcinoma (c)	Adenoma or Carcinoma
Historical Incidence at Litton Bionetics, Inc.			
Diallylphthalate	23/49	0/49	23/49
Tris(2-ethylhexyl)phosphate	18/50	1/50	19/50
2,4-Toluene diisocyanate	25/50	2/50	27/50
TOTAL	66/149 (44.3%)	3/149 (2.0%)	69/149 (46.3%)
SD (d)	7.36%	2.00%	8.02%
Range (e)			
High	25/50	2/50	27/50
Low	18/50	0/49	19/50
Overall Historical Incidence			
TOTAL	(f) 410/1,092 (37.5%)	(g) 41/1,092 (3.8%)	451/1,092 (41.3%)
SD (d)	10.22%	3.56%	9.28%
Range (e)			
High	28/50	6/46	30/50
Low	8/46	0/49	13/48

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Includes adenomas designated NOS, chromophobe, or acidophil
(c) Includes adenocarcinoma, NOS, and carcinomas designated NOS or chromophobe
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.
(f) Includes 16 adenomas, NOS, of the anterior pituitary in one vehicle control group
(g) Includes two carcinomas, NOS, of the anterior pituitary

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

Study	No. of Animals Examined	No. of Tumors in Vehicle Controls	Diagnosis
Historical Incidence at Litton Bionetics, Inc.			
2,4-Toluene diisocyanate	47	0	
Diallylphthalate	45	1	Papillary adenoma
		1	Teratoma, benign
Tris(2-ethylhexyl)phosphate	49	1	Teratoma, NOS
TOTAL	141	3 (2.1%)	
Overall Historial Incidence (b)			
		1	Adenoma, NOS
		1	Papillary adenoma
		1	Cystadenoma, NOS
		1	Luteoma
		1	Sertoli cell tumor
		1	Teratoma, benign
		2	Granulosa cell tumor
		1	Teratoma, NOS
		1	Adenocarcinoma, NOS
		1	Granulosa cell carcinoma
		1	Teratoma, malignant
TOTAL	1,028	12 (1.2%)	

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) No more than two ovarian tumors were observed in any vehicle control group.

TABLE F7. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN MALE 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.			
2,4-Toluene diisocyanate	1/50	1/50	2/50
Diallylphthalate	3/50	2/50	5/50
Tris(2-ethylhexyl) phosphate	5/50	2/50	7/50
TOTAL	9/150 (6.0%)	5/150 (3.3%)	14/150 (9.3%)
SD (b)	4.00%	1.15%	5.03%
Range (c)			
High	5/50	2/50	7/50
Low	1/50	1/50	2/50
Overall Historical Incidence			
TOTAL	99/1,082 (9.1%)	(d) 58/1,082 (5.4%)	(d) 155/1,082 (14.3%)
SD (b)	4.77%	4.13%	6.31%
Range (c)			
High	10/50	7/50	13/50
Low	0/47	0/50	1/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.
(d) Includes one adenocarcinoma, unclear primary or metastatic

TABLE F8. HISTORICAL INCIDENCE OF HEMATOPOIETIC SYSTEM TUMORS IN MALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Lymphoma	Leukemia	Leukemia or Lymphoma
Historical Incidence at Litton Bionetics, Inc.			
2,4-Toluene diisocyanate	6/50	0/50	6/50
Diallylphthalate	6/50	0/50	6/50
Tris(2-ethylhexyl) phosphate	7/50	0/50	7/50
TOTAL	19/150 (12.7%)	0/150 (0.0%)	19/150 (12.7%)
SD (b)	1.15%	0.00%	1.15%
Range (c)			
High	7/50	0/50	7/50
Low	6/50	0/50	6/50
Overall Historical Incidence			
TOTAL	126/1,090 (11.6%)	6/1,090 (0.6%)	132/1,090 (12.1%)
SD (b)	5.63%	2.24%	6.35%
Range (c)			
High	11/50	5/48	13/48
Low	0/50	0/50	0/50

(a) Data as of March 16, 1983, 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 ADRENAL GLAND TUMORS IN FEMALE B6C3F$_1$ MICE ADMINISTERED CORN OIL BY GAVAGE (a)

Study	Incidence in Vehicle Controls		
	Adenoma	Cortical Adenoma	Adenoma or Cortical Adenoma
Historical Incidence at Litton Bionetics, Inc.			
2,4-Toluene diisocyanate	0/47	0/47	0/47
Diallylphthalate	0/48	0/48	0/48
Tris(2-ethylhexyl) phosphate	0/44	0/44	0/44
TOTAL	0/139 (0.0%)	0/139 (0.0%)	0/139 (0.0%)
SD (b)	0.00%	0.00%	0.00%
Range (c)			
High	0/48	0/48	0/48
Low	0/48	0/48	0/48
Overall Historical Incidence			
TOTAL	2/1,056 (0.2%)	5/1,056 (0.5%)	7/1,056 (0.7%)
SD (b)	0.91%	0.94%	1.23%
Range (c)			
High	2/47	1/36	2/47
Low	0/50	0/50	0/50

(a) Data as of March 16, 1983, for studies of at least 104 weeks
(b) Standard deviation
(c) Range and SD are presented for groups of 35 or more animals.

APPENDIX G

GENETIC TOXICOLOGY OF 4-VINYLCYCLOHEXENE

TABLE G1. MUTAGENICITY OF 4-VINYLCYCLOHEXENE IN *SALMONELLA TYPHIMURIUM*

Strain	Dose (µg/plate)	Revertants/plate (a,b) −S9	+S9 (rat)	+S9 (hamster)
TA100	0	90 ± 6.5	81 ± 3.2	77 ± 4.2
	3.3	71 ± 7.8	---	---
	10	59 ± 0.0	66 ± 5.9	84 ± 2.4
	33	71 ± 1.9	84 ± 5.6	94 ± 12.1
	100	64 ± 2.6	84 ± 6.0	90 ± 5.7
	333	62 ± 4.1	80 ± 2.4	87 ± 8.8
	1,000	--	Toxic	52 ± 14.0
TA1535	0	8 ± 0.3	6 ± 1.3	7 ± 1.5
	3.3	3 ± 0.9	9 ± 1.0	--
	10	3 ± 0.9	9 ± 2.5	5 ± 1.3
	33	3 ± 0.6	8 ± 1.7	7 ± 2.6
	100	4 ± 0.9	5 ± 0.0	7 ± 2.0
	333	2 ± 0.6	10 ± 2.1	7 ± 1.2
	1,000	--	--	4 ± 4.0
TA1537	0	2 ± 0.9	6 ± 1.2	6 ± 0.9
	3.3	2 ± 0.3	--	--
	10	1 ± 0.3	5 ± 0.6	4 ± 0.7
	33	2 ± 0.0	6 ± 1.5	5 ± 0.9
	100	2 ± 0.0	5 ± 0.7	5 ± 0.7
	333	2 ± 0.6	5 ± 0.9	3 ± 0.9
	1,000	--	4 ± 0.9	1 ± 0.3
TA98	0	13 ± 3.8	20 ± 5.8	20 ± 3.2
	3.3	13 ± 2.1	--	--
	10	12 ± 1.2	19 ± 3.5	15 ± 2.6
	33	13 ± 3.0	18 ± 1.0	19 ± 2.9
	100	12 ± 1.0	20 ± 3.0	13 ± 1.2
	333	18 ± 2.3	17 ± 3.2	11 ± 2.4
	1,000	--	13 ± 1.8	15 ± 0.5

(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 (DMSO) 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 was 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) Mean ± standard error

APPENDIX H

CHEMICAL CHARACTERIZATION

OF 4-VINYLCYCLOHEXENE

APPENDIX H. CHEMICAL CHARACTERIZATION

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

A. Lot No. C592777

1. Physical Properties

a. Appearance:	Clear, colorless liquid	
b. Boiling Point:	**Determined**	**Literature Values**
	131° C (visual micro-boiling point),	128.9° C (760 mm Hg) (CRC, 1972)
c. Density:	d_{22}^{20}: 0.82928 ± 0.00017(δ)	d_{4}^{20}: 0.8299 (CRC, 1972)

2. Spectral Data

a. Infrared	**Determined**	**Literature Values**
(1) Instrument:	Beckman IR-12	
(2) Cell:	Thin film between silver chloride plates	
(3) Results:	See Figure 7	Consistent with spectrum obtained from literature (Sadtler Standard Spectra)
b. Ultraviolet/Visible	**Determined**	**Literature Values**
(1) Instrument:	Cary 118	
(2) Solvent:	95% Ethanol	
(3) Results:	No absorbance was seen in the visible region at a concentration of 1%. No absorbance maximum was observed in the ultraviolet region.	No literature reference found. Spectrum consistent with that expected for the structure.

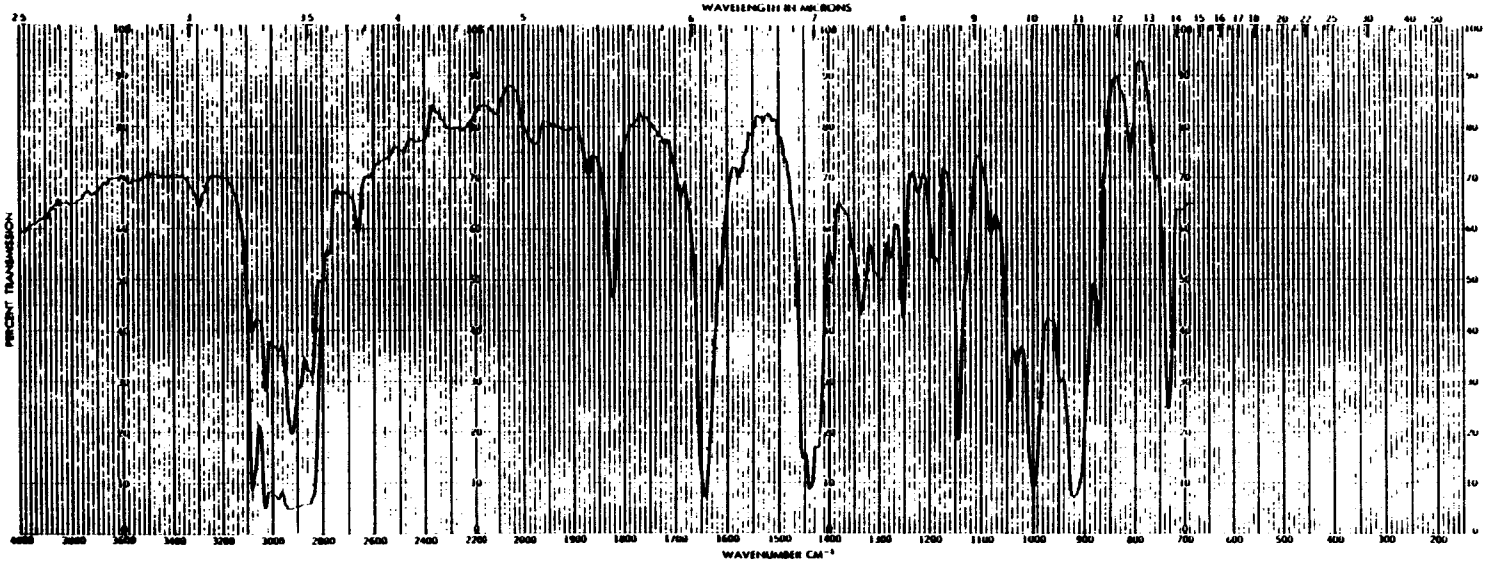

FIGURE 7. INFRARED ABSORPTION SPECTRUM OF 4-VINYLCYCLOHEXENE (LOT NO. C592777)

c. Nuclear Magnetic Resonance

	Determined	Literature Values
(1) Instrument:	Varian EM360A	
(2) Solvent:	Deuterated methanol with internal tetramethylsilane	
(3) Assignments:	See Figure 8	Spectrum is consistent with literature spectrum (Sadtler Standard Spectra)
(4) Chemical Shift (δ):	a 0.87-2.45 ppm b 4.86 ppm c 5.00 ppm d 5.62 ppm e 5.80 ppm	
(5) Integration Ratios:	a 7.05 b, c 1.93 d, e 3.02	

3. Water Analysis (Karl Fischer): 0.012% ± 0.002(δ)%

4. Elemental Analysis

Element	C	H
Theory (T)	88.82	11.18
Determined (D)	88.70 88.80	11.20 11.11
Percent D/T	99.92	99.78

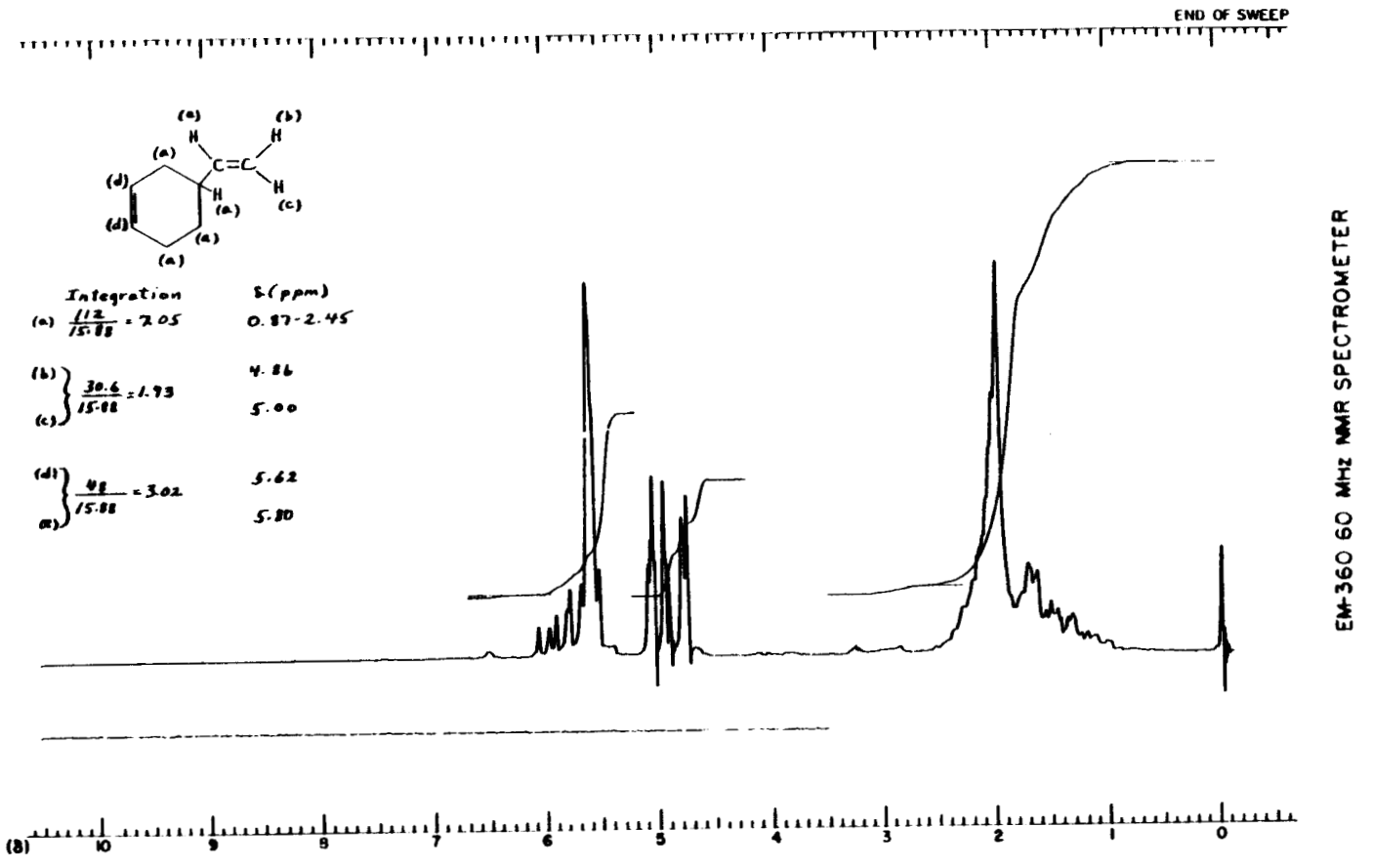

FIGURE 8. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 4-VINYLCYCLOHEXENE (LOT NO. C592777)

5. Chromatographic Analysis

a. Gas Chromatography

(1) Instrument: VA3700
(2) Detector: Flame ionization
(3) Inlet temperature: 200° C
(4) Detector temperature: 250° C
(5) Carrier gas: Nitrogen
(6) Carrier flow rate: 70 ml/min

System 1

(a) Column: GP 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
(b) Oven temperature program: 5 minutes at 50° C, then 50°-170° C at 10° C/minute
(c) Samples injected: 8 µl neat liquid and solutions of 0.5% and 0.25% (v/v) 4-vinylcyclohexene in methylene chloride to quantitate the major peak and check for overloading

(d) Results: Major peak and four impurities. Three impurities had retention times shorter than that of the major peak, and one eluted after the major peak. The combined areas of the impurity peaks totaled 0.22% that of the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	7.4	0.71	0.02
2	8.4	0.81	0.04
3	9.9	0.95	0.07
4	10.4	1.00	100.
5	11.3	1.09	0.09

System 2

(a) Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW)
(b) Carrier flow rate: 70 ml/min
(c) Oven temperature program: 5 minutes at 50° C, then 50°-200° C at 10° C/minute
(d) Samples injected: 5 µl neat liquid and 1.0% and 0.5% 4-vinylcyclohexene in methylene chloride to quantitate the major peak and check for overloading

(e) Results: Major peak and four impurities. The four impurities all eluted before the major peak and had a combined area that totaled 0.15% of the major peak.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	1.14	0.24	0.02
2	2.43	0.51	0.05
3	3.00	0.62 (unresolved)	0.02
4	3.50	0.73	0.06
5	4.81	1.00	100

6. Conclusions: The results of elemental analysis for carbon and hydrogen were in agreement with the theoretical values. Titration with Karl Fischer Reagent indicated 0.012% ± 0.002(δ)% water. Gas chromatography with a 20% SP2100/0.1% Carbowax 1500 column indicated four impurities, three before and one after the major peak with a combined area of 0.22% that of the major peak area. A second gas chromatographic system with a 10% Carbowax 20M-TPA column indicated four impurities, all before the major peak, with a combined area of 0.15% that of the major peak area. The infrared, ultraviolet/visible, and the nuclear magnetic resonance spectra were consistent with the structure of 4-vinylcyclohexene.

The compound was identified as 4-vinylcyclohexene by spectral analysis. Gas chromatography and water analysis indicated less than 0.5% impurities.

B. Lot No. A061181

1. Appearance:	Clear, colorless liquid	
2. Spectral Data		
a. Infrared	**Determined**	**Literature Values**
(1) Instrument:	Perkin-Elmer 283	
(2) Phase:	Thin film between silver chloride plates	
(3) Results:	See Figure 9	Spectrum consistent with literature reference (Sadtler Standard Spectra)
b. Ultraviolet/Visible	**Determined**	**Literature Values**
(1) Instrument:	Cary 219	
(2) Solvent:	95% Ethanol	
(3) Results:	No absorbance from 800 to 350 nm at a concentration of 1% (v/v). No absorbance was seen in the ultraviolet region.	No literature reference found. Spectrum consistent with that expected for structure of 4-vinylcyclohexene.

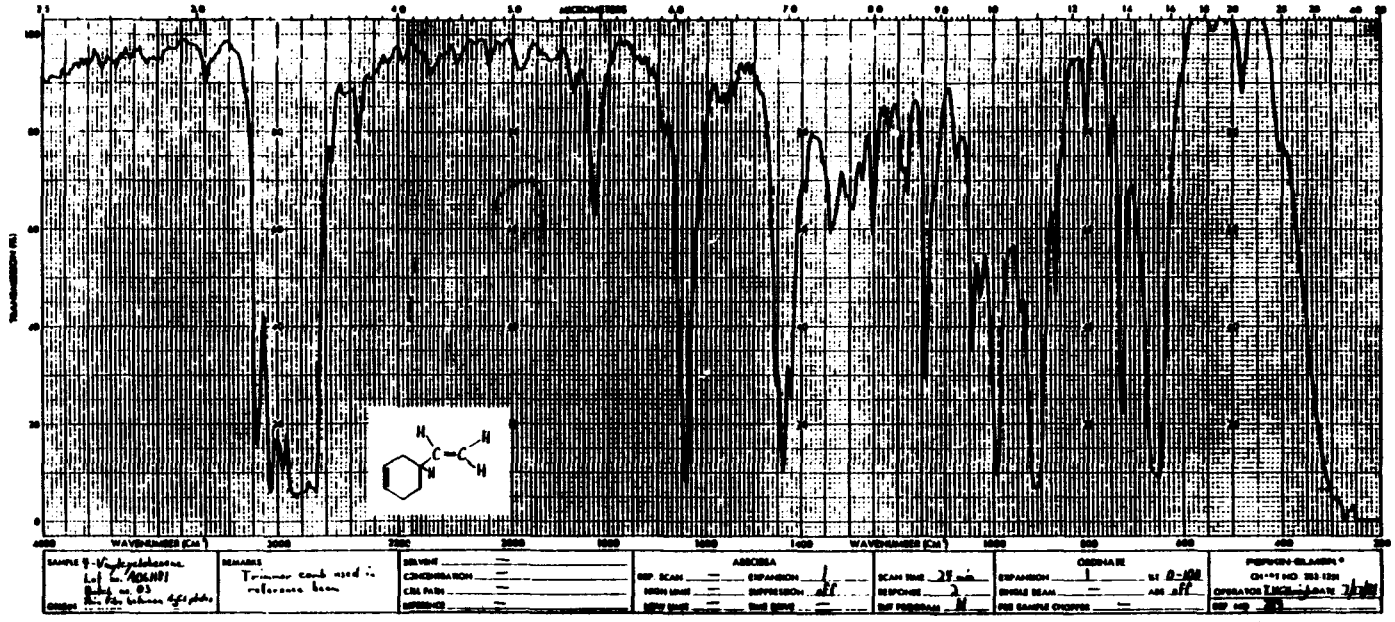

FIGURE 9. INFRARED ABSORPTION SPECTRUM OF 4-VINYLCYCLOHEXENE (LOT NO. A061181)

c. Nuclear Magnetic Resonance	Determined	Literature Values
(1) Instrument:	Varian EM360A	
(2) Solvent:	Deuterated methanol with internal tetramethylsilane	
(3) Assignments:	See Figure 10	Spectrum consistent with literature reference (Sadtler Standard Spectra).
(4) Chemical Shift (δ):	a m of m, 0.92-2.60 ppm b m, 4.88 ppm c m, 4.93 ppm d m, 5.65 ppm e m, 5.83 ppm	
(5) Coupling Constant:	J_{b-e} = 10 Hz J_{b-e} = 18 Hz	
(6) Integration Ratios:	a 7.03 b, c 1.99 d, e 2.99	

3. Water Analysis (Karl Fischer): <0.1%

4. Elemental Analysis

Element	C	H
Theory (T)	88.82	11.18
Determined (D)	89.02 89.19	11.23 11.20
Percent D/T	100.32	100.31

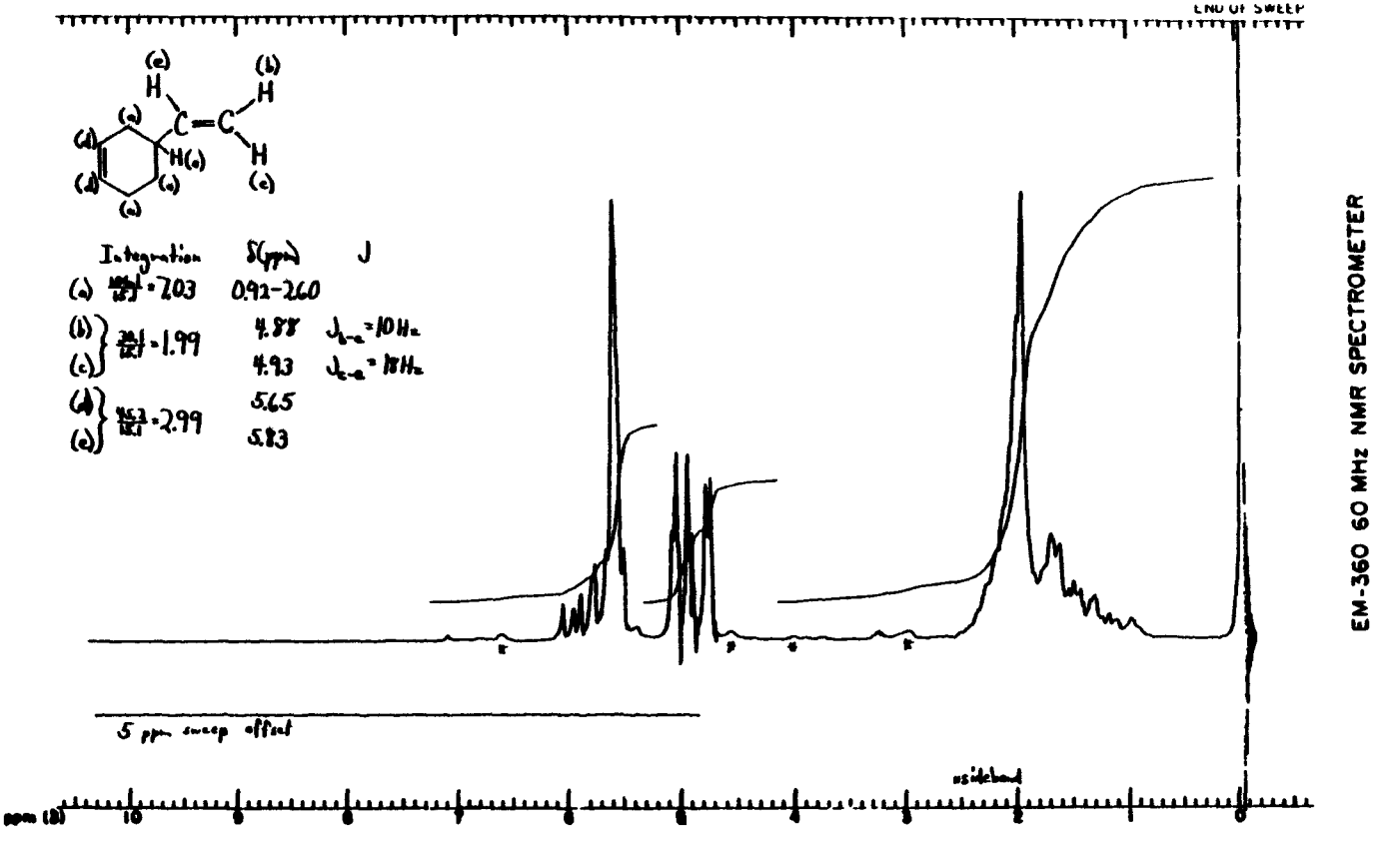

FIGURE 10. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 4-VINYLCYCLOHEXENE (LOT NO. A061181)

5. Gas Chromatographic Analysis

(1) Instrument: VA3700
(2) Detector: Flame ionization
(3) Inlet temperature: 200° C
(4) Detector temperature: 250° C
(5) Carrier gas: Nitrogen
(6) Carrier flow rate: 70 ml/min

System 1

(a) Column: GP 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
(b) Oven temperature program: 5 minutes at 50° C, then 50°-170° C at 10° C/minute
(c) Samples injected: 4 µl neat liquid and solutions of 1% and 0.5% (v/v) 4-vinylcyclohexene in methylene chloride to detect impurities, quantitate the major peak, and check for overloading

(d) Results: Major peak and two impurities before the major peak; one impurity and one group of unresolved impurities after the major peak. The impurities had a combined area of 0.69% relative to the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1	9.2	0.94	0.08
2	9.4	0.96	
3	9.8	1.00	100
4	10.5	1.07	0.30
5 (a)	14.1-15.5	1.58	0.31

(a) Group of unresolved peaks.

System 2

(a) Column: 10% Carbowax 20M-TPA on 80/100 Chromosorb W(AW)
(b) Oven temperature program: 5 minutes at 50° C, then 50°-200° C at 10° C/minute
(c) Samples injected: 4 µl neat liquid and solutions of 1.0% and 0.5% (v/v) 4-vinylcyclohexene in methylene chloride to detect impurities, quantitate the major peak, and check for overloading

(d) Results: Major peak, and one impurity after the major peak, and two groups of unresolved impurities, one before and one after the major peak. The impurity peaks had a combined area of 1.1% relative to the major peak area.

Peak No.	Retention Time (min)	Retention Time Relative to Major Peak	Area (percent of major peak)
1 ┐	2.1	0.46 ┐	
2 |	2.6	0.56 |	
3 ├a	2.8	0.61 ├	0.51
4 |	3.1	0.67 |	
5 ┘	3.7	0.80 ┘	
6	4.6	1.00	100
7	8.4	1.83	0.31
8[a]	16.0-19.1	3.48-4.15	0.32

(a) Group of unresolved peaks

6. Conclusion: The results of elemental analysis for carbon and nitrogen were in agreement with the theoretical values. Karl Fischer analysis indicated 0.07% ± 0.00 (δ)% water. Gas chromatography with a 20% SP2100/0.1% Carbowax 1500 column indicated a major peak, two impurities before the major peak, and one impurity and one group of unresolved impurities after the major peak. The impurities had a combined area of 0.69% relative to the major peak area. A second gas chromatographic system with a 10% Carbowax 20M-TPA column indicated a major peak, one impurity after the peak, and two groups of unresolved impurities (one before and one after the major peak). The impurities had a combined area of 1.1% relative to the major peak area. The infrared and nuclear magnetic resonance spectra were consistent with the structure of 4-vinylcyclohexene. The ultraviolet/visible spectrum varied slightly from that obtained from lot no. C592777, but the only absorbances observed in both are probably due to impurities; therefore, neither spectrum is believed inconsistent with the structure of 4-vinylcyclohexene.

The compound was identified as 4-vinylcyclohexene by spectroscopy. The material contained 0.07% ± 0.00(δ)% water. Gas chromatography by two systems indicated impurities totaling 0.69% and 1.1% relative to the major peak, respectively. The data indicate that this batch of 4-vinylcyclohexene is slightly less pure than lot no. C592777.

II. Chemical Stability Study Performed by the Analytical Chemistry Laboratory

A. Sample Preparation and Storage: Samples were stored in glass vials with Teflon®-lined screw caps for 2 weeks at −20°, 5°, 25°, and 60° C.

B. Analytical Method: Samples from each storage temperature were dissolved in chloroform containing 0.5% octane as an internal standard. The samples, analyzed on the gas chromatographic system described below, were compared with the internal standard peak. The recovery of 4-vinylcyclohexene for each sample was compared with the recovery for the −20° C sample.

(1) Instrument: Varian 3700 with autoinjector
(2) Detector: Flame ionization
(3) Inlet temperature: 200° C
(4) Detector temperature: 250° C
(5) Oven temperature: 100° C (isothermal)
(6) Carrier gas: Nitrogen, 70 ml/min
(7) Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
(8) Sample injected: From each storage temperature solutions (3.5 µl) of 4-vinylcyclohexene (0.5%) in chloroform containing 0.5% octane internal standard
(9) Retention times: 4-Vinylcyclohexene--3.5 min
Octane (Internal standard)--2.8 min

C. Results

Storage Temperature	Percent Purity
-20° C	100.0 ± 0.1 (δ)
5° C	100.0 ± 0.1 (δ)
25° C	99.9 ± 0.1 (δ)
60° C	99.6 ± 0.1 (δ)

D. Conclusion: 4-Vinylcyclohexene is stable as the bulk chemical when stored for 2 weeks at temperatures of up to 25° C. There may have been slight decomposition in the sample stored for 2 weeks at 60° C.

III. Chemical Stability Study at the Study Laboratory

A. Storage Conditions: The reference samples were stored at −20° C and the bulk chemical at 4°-5° C.

B. Analytical Method:

1. Purity Determination: Gas chromatographic analyses were performed by the system described below.

(a) Instrument: Shimadzu GC Mini-2 with C-R1A Chromatopac integrator
(b) Detector: Flame ionization
(c) Inlet temperature: 225° C
(d) Detector temperature: 225° C
(e) Oven temperature program: 50° C for 5 minutes, then 50°-170° C at 10° C/minute
(f) Carrier gas: Nitrogen, 70 ml/min
(g) Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 2.6 mm ID, glass, silanized
(h) Sample injected: Neat liquid and 1% and 0.5% dilution of study material in methylene chloride to quantitate the major peak and check column and detector for overloading

2. Identity Determination: The infrared absorption spectra of the sample was obtained as potassium bromide disks using a Perkin-Elmer 283B.

C. Results

1. Purity

Date of Analysis	Lot No.	Area of the Major Peak (percent total area) Bulk (a)	Reference (a)	Percent Purity (b)
01/07/79	C592777	98.90 (7)	--	--
02/18/80	C592777	99.95 (2)	99.88 (3)	99.92
06/23/80	C592777	99.65 (4)	99.65 (4)	100.00
10/03/80	C592777	99.77 (4)	99.75 (4)	99.98
02/12/81	C592777	99.72 (4)	99.71 (4)	99.99
06/09/81	C592777	99.74 (4)	99.73 (4)	99.99
09/02/81	A061181	99.67 (6)	--	--
01/12/82	A061181	99.44 (8)	99.43 (8)	99.99
05/13/82	A061181	99.50 (7)	99.50 (8)	100.00
09/24/82	A061181	99.37 (6)	99.39 (6)	100.02

(a) Number of impurities is in parenthesis
(b) Purity of material stored at 5° C relative to reference standard stored at −20° C.

2. Identity: All spectra were consistent with the original spectra supplied by the analytical laboratory.

D. Conclusion: No notable degradation of 4-vinylcyclohexene occurred during the studies.

APPENDIX I

PREPARATION AND CHARACTERIZATION OF DOSE MIXTURES

APPENDIX I. PREPARATION AND CHARACTERIZATION

I. Studies Conducted at the Analytical Chemistry Laboratory

A. Sample Preparation and Storage: 4-Vinylcyclohexene was weighed to the nearest 0.001 g into a 50-ml volumetric flask and diluted to volume with corn oil with frequent mixing. The concentration of 4-vinylcyclohexene was 52.4 mg/ml (5.24% w/v).

The solution described above was sampled on days 0, 1, 4, 5, 6, and 7 in duplicate by weighing approximately 1.51-g aliquots to the nearest 0.1 mg into separate 8.5-ml septum vials. The total weight of the stock mixture described above was 45.74 g; therefore, the concentration of the 4-vinylcyclohexene in the aliquot was 57.3 mg/g or 86.52 mg/corn oil aliquot.

B. Extraction and Analysis: Storage samples were extracted by pipetting 2 ml of a solution of *n*-octane in methanol (40.52 mg/ml) into each septum vial, shaking vigorously in a vortex mixer for 1 minute, and then sonicating in an ultrasonic bath for an additional 30 seconds. The top (methanol) layer was sampled by 10-µl syringe and analyzed by the gas chromatographic system described below.

(a) Instrument: Tracor MT-220
(b) Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass
(c) Detection: Flame ionization
(d) Temperatures: Injector--125° C
Oven--67° C, isothermal
Detector--207° C
(e) Carrier gas: Nitrogen, 25 ml/min
(f) Retention times: 4-Vinylcyclohexene--9.0 minutes
Internal standard--7.5 minutes

C. Quality Control: Analyses were carried out by making duplicate injections of duplicate extractions on all sample and recovery determinations. Results were related to an internal standard incorporated in each extract. Recovery studies were conducted with study material at the same concentrations as samples.

D. Results

Storage Time (days)	Average Percent (w/w) Chemical Found in Chemical/Vehicle Mixtures (a,b)
0	(c) 5.7 ± 0.1
1	5.6 ± 0.1
4	5.7 ± 0.1
5	5.6 ± 0.1
6	5.6 ± 0.1
7	5.6 ± 0.1

(a) Corrected for zero-time recovery yield of 32% ± 1%
(b) Target concentration of chemical in corn oil--5.73% ± 0.01% w/w
(c) Mean ± instrumental error

E. Conclusion

4-Vinylcyclohexene is stable when dissolved in corn oil at a concentration of 5.2% w/v and stored at room temperature for 7 days.

II. Studies Conducted at the Study Laboratory

A 23-day stability study was performed to determine the stability of 4-vinylcyclohexene/corn oil mixtures at room temperature. The amount of 4-vinylcyclohexene in the samples stored for 23 days was 94.6%-94.9% that found in the samples analyzed after 3 days (regularly scheduled analysis).

A. Preparation: 4-Vinylcyclohexene standards were prepared in undosed corn oil to give concentrations of 42-140 mg/ml.

B. Extraction and Analysis: One-milliliter aliquots of the standards and the samples were extracted in duplicate in 2 ml methanol containing *n*-octane (approximately 40 mg/ml) as internal standard. The tubes were vortexed for 1 minute followed by sonication for 30 seconds. The concentration of the chemical in the methanol layer was determined by the gas chromatographic system described below.

(1) Instrument: Shimadzu GC Mini-2 with C-R1A Chromatopac
(2) Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, 1.8 m × 2 mm ID, glass, silanized
(3) Detection: Flame ionization
(4) Temperatures: Injection/Detector: 125° C
Oven: 67° C isothermal
(5) Carrier gas: Nitrogen, 43 ml/minute
(6) Retention times: 4-Vinylcyclohexene--8.5 minutes
Internal standard--6.9 minutes

C. Results

Date Mixed	Date Analyzed	Target Concentration (mg/ml)	Concentration Found (mg/ml)	Concentration Stability Analysis / Concentration Original Analysis × 100 (percent)
5/1/81	5/04/81	60.1	60.7	--
	5/27/81		57.6	94.9
5/1/81	5/04/81	120.1	120.5	--
	5/27/81		114.0	94.6

APPENDIX J

METHODS OF ANALYSIS OF DOSE MIXTURES

APPENDIX J. METHODS OF ANALYSIS

The analytical procedures used by the study and referee laboratories were similar. Both used an octane-in-methanol extraction procedure and a gas chromatographic quantitation step.

I. Study Laboratory

A. Preparation: 4-Vinylcyclohexene standards were prepared in undosed corn oil to give concentrations of 42-140 mg/ml.

B. Extraction and Analysis: One-milliliter aliquots of the standards and the samples were extracted in duplicate in 2 ml methanol containing *n*-octane (approximately 40 mg/ml) as internal standard. The tubes were vortexed for 1 minute followed by sonication for 30 seconds. The concentration of the chemical in the methanol layer was determined by the gas chromatographic system described below.

(1) Instrument: Shimadzu GC Mini-2 with C-R1A Chromatopac
(2) Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 mesh Supelcoport, 1.8 m × 2 mm ID, glass, silanized
(3) Detection: Flame ionization
(4) Temperatures: Injection/Detector: 125° C
Oven: 67° C
(5) Carrier gas: Nitrogen, 43 ml/minute
(6) Retention times: 4-Vinylcyclohexene--8.5 minutes
Internal standard--6.9 minutes

II. Analytical Chemistry Laboratory

A. Procedure

1. Preparation of Spiked Corn Oil Standards: Two standard solutions of 4-vinylcyclohexene were prepared independently in methanol. These solutions were diluted with methanol to make a total of six standards. Twenty-milliliter aliquots 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 samples bracketing the specified dose range. One 35-ml centrifuge bottle containing 2 g of undosed corn oil was treated with 20 ml of methanol for use as a blank. The spiked corn oil mixtures and the corn oil blank were sealed and analyzed by the following analytical procedure.

2. Preparation of Dosed (Referee) Corn Oil Sample: Triplicate weights of the dosed corn oil sample (approximately 2 g weighed to the nearest 0.001 g) were transferred to individual 35-ml septum vials. Twenty milliliters of methanol was pipetted into each sample; then the vials were sealed and analyzed by the following procedure.

3. Analysis: 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 wrist-action shaker. After the extraction mixtures were centrifuged for 3 minutes, a 5-ml aliquot of the methanol layer from each vial was mixed with 5 ml of internal standard solution (isooctane in methanol, 4.5 mg/ml) and diluted to 25 ml with methanol. The solutions were mixed and analyzed by the gas chromatographic system described below.

(a) Instrument: Varian 3700 Gas Chromatograph with Autosampler and Varian CDS 111-C integrator
(b) Column: 20% SP2100/0.1% Carbowax 1500 on 100/120 Supelcoport, 1.8 m × 4 mm ID, glass, silanized
(c) Detection: Flame ionization
(d) Temperatures: Inlet--200° C
Oven--80° C, isothermal
Detector--250° C
(e) Carrier gas: Nitrogen, 30 ml/min
(f) Volume of solution injected: 3 µl

The amount of 4-vinylcyclohexene in the referee corn oil samples was determined from the linear regression equation computed from the standard data. The regression equation was obtained by dividing the peak area of each spiked corn oil standard by the peak area of the corresponding internal standard and relating the quotient to the amount of chemical in that standard.

B. Quality Assurance Measures

The referee corn oil sample was analyzed in triplicate, and the undosed corn oil sample was analyzed once. For calibration, six spiked corn oil standards bracketing the specified dose range of the referee sample were made with two independently prepared standard solutions. 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

APPENDIX K. RESULTS OF ANALYSIS

I. Thirteen-Week Studies: Dose mixtures were analyzed once during the 13-week studies. The high concentration dose mixtures were diluted with corn oil to a range of 15-20 mg/ml before analysis. All samples were within ± 10% of the target concentrations.

Target Concentration (mg/ml)	Nominal Concentration of the Diluted Mixture (mg/ml)	Determined Concentration (mg/ml)
22.5	22.5	23.75
45	22.5	23.7
90	22.5	22.8
180	18	18.0
360	18	18.4
15	15	16.2
30	15	16.1
60	15	16.0
120	15	16.5
240	15	16.0

II. Two-Year Studies: Samples of dose mixtures were analyzed weekly initially and then every eight mixes. Only two of the analyzed mixtures were out of tolerance during the 2-year studies, one of which was remixed (Table K1). It is assumed that the number of remixes required reflects the number of mixes out of specification (± 10%) of the target concentrations. The mixes were out of specification 6% of the time. The mixes ranged from 82.7% to 110.1% of the 60.1 mg/ml target concentration. The high dose mixes ranged from 91.6% to 105.7% of the target concentration.

Split sample analyses were performed by the study and analytical (referee) laboratories to verify analytical procedures. The analyses by both laboratories were within 10% of the target concentrations. The interlaboratory values were within 10% of each other (98.7%-108.5% agreement) (Table K2).

Animal room samples taken after dosing showed good agreement with the corresponding preparation room samples--98.7-104.0% (Table K3).

TABLE K1. CONCENTRATIONS OF 4-VINYLCYCLOHEXENE IN CORN OIL IN THE TWO-YEAR GAVAGE STUDIES (a)

Date Mixed	Determined Concentration for Target Concentration of 60.1 mg/ml	120.1 mg/ml
11/07/80	60.0	111.0
11/14/80	58.8	114.5
11/21/80	60.0	117.4
11/30/80	61.6	118.0
12/05/80	60.6	117.1
12/12/80	60.6	117.8
01/09/81	57.4	110.0
03/06/81	(b) 66.2	124.5
05/01/81	60.7	120.5
06/26/81	57.4	113.5
08/20/81	61.4	111.5
10/16/81	(c) 49.7	117.5
10/20/81	(d) 58.2	
12/11/81	63.6	126.9
02/05/82	55.9	122.5
04/02/82	57.1	119.5
05/28/82	58.2	117.5
07/23/82	58.4	118.0
Mean (mg/ml)	59.3	117.5
Standard deviation	3.54	4.58
Coefficient of variation (percent)	6.0	3.9
Range (mg/ml)	49.7-66.2	110.0-126.9
Number of samples	17	17

(a) Results of duplicate analysis
(b) Out of tolerance; not remixed.
(c) Out of tolerance; not used in study.
(d) Remix. Not included in total.

TABLE K2. RESULTS OF REFEREE ANALYSIS IN THE TWO-YEAR GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration	
		Study Laboratory	Analytical Laboratory
11/07/80	60.1	60.0	57.2
05/01/81	120.1	120.5	117.2
12/11/81	60.1	63.6	58.6
05/28/82	120.1	117.5	119.0
07/23/82	60.1	58.4	56.5

TABLE K3. ANIMAL ROOM SAMPLE DATA IN THE TWO-YEAR GAVAGE STUDIES OF 4-VINYLCYCLOHEXENE

Date Mixed	Date Analyzed (a)	Target Concentration (mg/ml)	Determined Concentration	
			Preparation Room	Animal Room
06/12/81	06/29/81	120.1	115.5	114
04/09/82	04/28/82	120.1	123.5	128.5

(a) Date of analysis of animal room sample

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) MHV (6 mo) Sendai (6, 12, 18 mo)	M.Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus) Sendai (24 mo)	MHV (mouse hepatitis virus) (12,18, 24 mo)
Rats	PVM Sendai (6, 12, 18, 24 mo) KRV (Kilham rat virus) H-1 (Toolan's H-1 virus)	RCV (rat coronavirus)	

II. Results

Results are presented in Table L1.

TABLE L1. MURINE VIRUS ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR GAVAGE STUDIES (a) OF 4-VINLYCYCLOHEXENE

	Interval (months)	No. of Animals	Positive Serologic Reaction for
RATS			
	6	--	None positive
	12	--	None positive
	18	1/9	RCV
	24	--	None positive
MICE			
	6	--	None positive
	12	5/10	MHV
	18	4/10	MHV
	24	3/8 4/10	Sendai MHV

(a) Blood samples were taken from sentinel animals at 6, 12, and 18 months after the start of dosing and from the vehicle control animals just before they were killed; samples were sent to Microbiological Associates, Inc. (Bethesda, MD) for the Animal Disease Screening Program.

APPENDIX M

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

Pelleted Diet: September 1980 to October 1982

(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 ± Standard Deviation	Range	Number of Samples
Crude protein (percent by weight)	23.91 ± 0.79	22.7-25.3	24
Crude fat (percent by weight)	4.99 ± 0.43	4.2-5.7	24
Crude fiber (percent by weight)	3.32 ± 0.23	2.9-3.8	24
Ash (percent by weight)	6.49 ± 0.47	5.7-7.43	24
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)	10,920 ± 1,824	8,300-15,000	24
Vitamin D (IU/kg)	6,300		1
α-Tocopherol (ppm)	37.6	31.1-44.0	2
Thiamine (ppm)	17.2 ± 1.8	14.0-21.0	(b) 23
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)	1.28 ± 0.18	1.08-1.69	24
Phosphorus (percent)	0.99 ± 0.06	0.88-1.10	24
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) was not analyzed for thiamine.

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

Contaminant	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.44 ± 0.19	<0.05-1.06	24
Cadmium (ppm) (a)	< 0.10		24
Lead (ppm)	1.00 ± 0.73	0.42-3.37	24
Mercury (ppm) (a)	< 0.05		
Selenium (ppm)	0.31 ± 0.07	0.14-0.52	24
Aflatoxins (ppb) (a,b)	< 10	< 5.0-< 10.0	24
Nitrate nitrogen (ppm) (c)	8.70 ± 3.67	2.1-17.0	24
Nitrite nitrogen (ppm) (d)	2.20 ± 1.59	0.4-6.9	24
BHA (ppm) (d,e)	6.02 ± 4.57	<0.5-16.0	24
BHT (ppm) (d)	3.03 ± 1.82	0.8-7.0	24
Aerobic plate count (CFU/g)	35,950 ± 27,857	4,900-88,000	24
Coliform (MPN/g) (f)	27.4 ± 52.6	<3-240	22
Coliform (MPN/g) (g)	90.0 ± 237.9	<3-1,100	24
E. Coli (MPN/g) (h)	< 3		24
Total nitrosamines (ppb) (i,j)	6.48 ± 5.82	<0.8-18.5	21
Total nitrosamines (ppb) (i,k)	28.76 ± 64.88	<0.8-273.2	24
N-Nitrosodimethylamine (ppb) (i,j)	5.24 ± 5.66	<0.8-16.5	21
N-Nitrosodimethylamine (ppb) (i,k)	27.29 ± 64.45	<0.8-272	24
N-Nitrosopyrrolidine (ppb)	1.23 ± 0.79	<0.3-3.5	24
Pesticides (ppm)			
α-BHC (a,l)	<0.01		24
β-BHC (a)	<0.02		24
γ-BHC-Lindane (a)	<0.01		24
δ-BHC (a)	<0.01		24
Heptachlor (a)	<0.01		24
Aldrin (a)	<0.01		24
Heptachlor epoxide (a)	<0.01		24
DDE (a)	<0.01		24
DDD (a)	<0.01		24
DDT (a)	<0.01		24
HCB (a)	<0.01		24
Mirex (a)	<0.01		24
Methoxychlor (a, m)	<0.05	0.09 (8/26/81)	24
Dieldrin (a)	<0.01		24
Endrin (a)	<0.01		24
Telodrin (a)	<0.01		24
Chlordane (a)	<0.05		24
Toxaphene (a)	<0.1		24
Estimated PCB's (a)	<0.2		24
Ronnel (a)	<0.01		24
Ethion (a)	<0.02		24
Trithion (a)	<0.05		24
Diazinon (a,m)	<0.1	0.2 (4/27/81)	24
Methyl parathion (a)	<0.02		24
Ethyl parathion (a)	<0.02		24
Malathion (n)	0.09 ± 0.06	<0.05-0.27	24
Endosulfan I (a)	<0.01		24
Endosulfan II (a)	<0.01		24
Endosulfan sulfate (a)	<0.03		24

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) Detection limit 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) Two batches contained less than 0.5 ppm.
(f) Excludes one very high value of 1,100 obtained in the batch produced on 12/16/80, and one high value of 460 obtained in the batch produced on 9/23/82.
(g) Includes the high values listed in footnote (f)
(h) All values were less than 3 MPN/g (MPN = most probable number).
(i) All values were corrected for percent recovery.
(j) Mean, standard deviation, and range exclude three very high values in the range of 115-273.2 ppb in batches produced on 1/26/81, 2/23/81, and 4/27/81.
(k) Mean, standard deviation, and range include the very high values given in footnote (j).
(l) BHC = hexachlorocyclohexane or benzene hexachloride
(m) There was one observation above the detection limit; the value and the date it was obtained are given under the range.
(n) Ten batches contained more than 0.05 ppm.

APPENDIX N

DATA AUDIT SUMMARY

APPENDIX N. DATA AUDIT SUMMARY

An audit was conducted on the archival data and pathology materials for the 2-year toxicology and carcinogenesis studies of 4-vinylcyclohexene in rats and mice. These studies were performed at Litton Bionetics, Inc., Kensington, Maryland, under a subcontract with Tracor Jitco, Inc., from the National Cancer Institute. The studies were conducted from November 1980 to November 1982 and were begun before the requirement of compliance to Good Laboratory Practice standards was initiated by the NTP in October 1981. The audit was conducted at the NTP Archives, Rockville, Maryland, by the following personnel from Dynamac Corporation: Chris Dippel, M.Phil.; Floris Garner, D.V.M.; James Konz, M.S.; James Plautz, M.S.; Ronald Ramsey, B.S.; Ronald Schueler, D.V.M.; Christine Sexsmith, B.S.; and Paul Wennerberg, D.V.M. The full audit report is on file at the National Toxicology Program, Research Triangle Park, North Carolina.

The audit consisted of an indepth review of the data and pathology materials collected during the conduct of the studies as well as a review of the correspondence (e.g., protocol and amendments) and short-term studies. For the inlife toxicology data, all records on animal receipt and husbandry, mortality, environmental conditions, sentinel animals, and dosing were examined. Body weight and clinical observation data for 10% of the animals were examined. Review of the inlife toxicology data identified no outstanding problems that would adversely affect the interpretation of the results of the studies. High mortality was noted and reported for the high dose male animals of both species and for the high dose female rats. No explanation or contributing factor for this mortality was found in the inlife data. Several minor discrepancies were noted in the records of clinical observations and mortality. In the clinical observation data, eight rats and six mice had inguinal or abdominal masses less than 1 cm in size which were recorded in the inlife data but not found at necropsy. It is possible these masses were structures, such as swollen lymph nodes or preputial glands, which would not be expected to be seen at necropsy; review of the wet tissues for these animals found no corresponding tissue masses. In the mortality records, several animals were lacking disposition coding (i.e., whether found dead or killed in a moribund condition) and two instances of misidentification were found.

In the review of the chemistry portion of the studies, all of the records were examined pertaining to receipt and use of the study chemical, analysis of the bulk chemical and dose solutions by the contract laboratory, and characterization of the bulk chemical and analysis of the dose solutions by the reference laboratory. A complete review of the available analytical chemistry raw data showed no problems that would compromise the conclusions of the studies. The only deficiency in the data was the lack of a chemical-use log, but the dose formulation and chemical/vehicle analysis records substantiated that sufficient bulk chemical was available for use during the studies.

The audit of the pathology materials included review of all Individual Animal Data Records (IADR's) for correlation between gross and microscopic diagnoses and clerical errors, examination of the wet tissues of 10% of the animals for unidentified lesions and correct identification, correlation of slides and tissue blocks for six of eight sex groups, and verification of the reported pathology on a 10% sample of the animals. No significant problems or discrepancies were found in the review of the pathology records and materials. Minor discrepancies were found but were determined not to affect the interpretation of the results of the studies. A number of gross observations did not have corresponding microscopic diagnoses, and liver nodules or masses were found in a vehicle control male and low dose female mouse (one in each). Although high mortality occurred in both species, no consistent pathologic changes were found in these animals which identified a cause of death. The incidence of suspected or probable gavage death was greatest in the high dose male rats (8/50). Several errors were found in the designation of tissues examined in the final pathology tables.

Overall, the audit identified no substantive problems that would have an adverse effect on the studies. Although some problems and discrepancies were identified as discussed in the audit report, these were adequately resolved or were determined not to have affected the outcome of the studies. In conclusion, the data examined in this audit are considered adequate to meet the objectives of the studies.

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