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TOXICOLOGY AND CARCINOGENESIS STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

(CAS NO. 106-87-6)

IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

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

NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

(CAS NO. 106-87-6)

IN F344/N RATS AND B6C3F$_1$ MICE

(DERMAL STUDIES)

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Public Health Service
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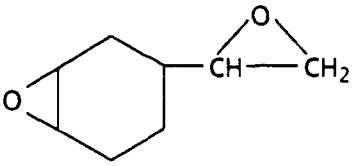

4-VINYL-1-CYCLOHEXENE DIEPOXIDE

CAS No. 106-87-6

$C_8H_{12}O_2$ Molecular weight 140.2

Synonyms: 4-vinylcyclohexene diepoxide; 4-vinyl-1,2-cyclohexene diepoxide; 1-vinyl-3-cyclohexene dioxide; 4-vinylcyclohexene dioxide; 1,2-epoxy-4-(epoxyethyl)cyclohexane; 1-epoxyethyl-3,4-epoxycyclohexane

ABSTRACT

4-Vinyl-1-cyclohexene diepoxide is used as a chemical intermediate and as a reactive diluent for diepoxides and epoxy resins. Toxicology and carcinogenesis studies were conducted by administering 4-vinyl-1-cyclohexene diepoxide (97% pure) in acetone by dermal application to individually housed F344/N rats and B6C3F$_1$ mice for 14 days, 13 weeks, 15 months, and 2 years. Additional studies included evaluation of immune function after a 5-day dermal exposure and evaluation of the oral toxicity of 4-vinyl-1-cyclohexene diepoxide in 16-day and 13-week corn oil gavage studies. Genetic toxicology studies were conducted in *Salmonella typhimurium*, mouse L5178Y lymphoma cells, and Chinese hamster ovary (CHO) cells.

Fourteen-Day Dermal Studies: In the 14-day studies, all rats that received 924 mg/kg or higher (equivalent to 139 mg/rat or higher for males and 112 mg/rat or higher for females) died before the end of the studies. Final mean body weights were lower than those of vehicle controls in males receiving 68 mg/rat and in females receiving 57 mg/rat. Excoriations on the skin at the application site were observed in the groups receiving 57 mg/rat or more. Males receiving 139 mg/rat and females receiving 112 mg/rat had congestion and/or hypoplasia of the bone marrow; most had acute nephrosis. Skin lesions, including epidermal necrosis and ulceration, epidermal hyperplasia, and hyperkeratosis, were found in the 139 and 112 mg/rat groups; similar lesions of lesser severity were seen in the two lowest dose groups of each sex.

All mice that received 1,787 mg/kg (equivalent to 43 mg/mouse for males and 37 mg/mouse for females) and 3/5 male mice and 5/5 female mice that received 889 mg/kg (equivalent to 19-21 mg/mouse) died before the end of the 14-day dermal studies. Final mean body weights of exposed and vehicle control mice were generally similar. Lesions of the skin at the site of application were seen in 4/5 males and 4/5 females receiving 5 mg/mouse and all mice receiving 10 and 21 (males) or 19 (females) mg/mouse and included epidermal and sebaceous gland hyperplasia, hyperkeratosis, and ulceration.

Thirteen-Week Studies: In the 13-week dermal studies, all rats survived to the end of the studies (doses up to 60 mg/rat). The final mean body weights of the 60 mg/rat groups were 9%-14% lower than those of the vehicle controls. Compound-related clinical signs in the 60 mg/rat groups observed during the second half of the studies included redness, scabs, and ulceration at the application site and burrowing behavior after dermal application. Hyperplasia of the sebaceous glands and acanthosis (hyperplasia) and hyperkeratosis of the squamous epithelium were seen at the site of application.

In mice, no compound-related deaths occurred after applications of up to 10 mg/mouse in 13-week dermal studies, and final mean body weights of exposed and vehicle control mice were similar. Relative liver and kidney weights increased with dose. Compound-related lesions of the skin included sebaceous gland hyperplasia and acanthosis (hyperplasia) and hyperkeratosis of the stratified squamous epithelium at the site of application; ovarian atrophy was also considered to be compound related.

In the 13-week oral studies, the major target organ of toxicity in rats and mice was the forestomach, as indicated by hyperkeratosis and hyperplasia of the stratified squamous epithelium. In female mice, ovarian atrophy was seen in 4-vinyl-1-cyclohexene diepoxide-dosed groups.

Two-year studies were conducted by administering 4-vinyl-1-cyclohexene diepoxide in acetone by dermal application, 5 days per week for 105 weeks to groups of 60 rats of each sex at 0, 15, or 30 mg/animal. Groups of 60 mice of each sex were administered 0, 2.5, 5, or 10 mg/animal on the same schedule for 103 weeks. None of the doses selected had produced ulceration of skin in 13-week studies. Ten animals from each group were killed and examined during month 15 for toxicologic evaluation.

Immune Function Studies: The immunotoxic effects of 4-vinyl-1-cyclohexene diepoxide were studied in male $B6C3F_1$ mice after a 5-day dermal exposure at doses ranging from 2.5 to 10 mg/mouse per day. 4-Vinyl-1-cyclohexene diepoxide was immunosuppressive at 10 mg/mouse and, to a lesser extent, at 5 mg/mouse, as indicated by a decrease in peripheral lymphocytes and the in vitro lymphoproliferative response to phytohemagglutinin and concanavalin A in the high dose group and suppression of the antibody plaque-forming-cell response in the 5 and 10 mg/mouse groups.

Fifteen-Month Evaluation: Two of 10 male rats that received 30 mg had a squamous cell carcinoma of the skin at or adjacent to the site of application. Acanthosis was seen in exposed rats (mild severity at 30 mg/rat and minimal severity at 15 mg/rat); hyperkeratosis was observed for rats in the 30 mg/rat groups.

Compound-related nonneoplastic skin lesions in mice included acanthosis, hyperkeratosis, and sebaceous gland hyperplasia/hypertrophy. Squamous cell papillomas and carcinomas were seen in mice that received 5 or 10 mg/mouse; none was seen in vehicle control or low dose groups (papillomas--male: mid dose, 1/10; high dose, 2/10; female: 1/10; 1/10; carcinomas--male: 2/10; 8/10; female: 2/10; 5/10). One vehicle control and all exposed female mice had atrophy of the ovary. Hyperplasia of the ovarian surface epithelium was seen in 8/10 females receiving 5 mg/mouse and 9/9 females receiving 10 mg/mouse. Two of nine females receiving 10 mg/mouse had granulosa cell tumors of the ovary, and 1/9 females receiving 10 mg/mouse had an ovarian papillary cystadenoma.

Body Weights and Survival in the Two-Year Studies: In general, the body weights and survival were lower in mid and high dose groups than in vehicle controls. The survival was lower in exposed groups, primarily because of neoplasms (survival at week 105--male rats: vehicle control, 7/50; low dose, 8/50; high dose, 4/50; female rats: 27/50; 23/50; 15/50; male mice: vehicle control, 38/50; low dose, 35/50; mid dose, 4/50; high dose, 0/50; female mice: 30/50; 31/50; 15/50; 0/50). All high dose male mice died by week 83; the 10 surviving high dose female mice were killed during week 85.

Nonneoplastic and Neoplastic Effects in the Two-Year Studies: Acanthosis and sebaceous gland hypertrophy of skin from the scapula or back were observed at substantially increased incidences in exposed male and female rats. Squamous cell papillomas in male rats and squamous cell carcinomas in male and female rats were observed only in exposed rats (squamous cell carcinomas--male: vehicle control, 0/50; low dose, 33/50; high dose, 36/50; female: 0/50; 16/50; 34/50). The incidences of basal cell adenomas or carcinomas (combined) were increased (male: 0/50; 1/50; 6/50; female: 0/50; 3/50; 4/50).

For exposed mice, acanthosis, hyperkeratosis, and necrotizing inflammation of the skin were observed over the scapula or back. Squamous cell carcinomas were found only in exposed mice (male: vehicle control, 0/50; low dose, 14/50; mid dose, 39/50; high dose, 42/50; female: 0/50; 6/50; 37/50; 41/50).

Follicular atrophy and tubular hyperplasia of the ovary in female mice were increased (atrophy: 12/50; 43/49; 42/49; 47/50; tubular hyperplasia: 5/50; 35/49; 38/49; 34/50). Mid and high dose females had benign or malignant granulosa cell tumors (0/50; 0/49; 7/49; 12/50) and benign mixed tumors (0/50; 0/49; 11/49; 6/50). The combined incidences of luteomas, granulosa cell tumors, benign mixed tumors, or malignant granulosa cell tumors in mid and high dose female mice were increased (1/50; 0/49; 17/49; 18/50).

The incidences of alveolar/bronchiolar adenomas or carcinomas (combined) in exposed female mice were marginally increased (4/50; 9/50; 11/50; 7/50).

Genetic Toxicology: 4-Vinyl-1-cyclohexene diepoxide was mutagenic in *S. typhimurium* strains TA98, TA100, and TA1535 with and without exogenous metabolic activation; the compound was equivocally mutagenic in strain TA1537 without S9 but gave a positive response in the presence of activation. 4-Vinyl-1-cyclohexene diepoxide induced resistance to trifluorothymidine in mouse L5178Y/TK cells without exogenous metabolic activation; it was not tested with activation. 4-Vinyl-1-cyclohexene diepoxide induced sister chromatid exchanges and chromosomal aberrations in CHO cells in the presence and absence of exogenous metabolic activation.

Conclusions: Under the conditions of these 2-year dermal studies, there was *clear evidence of carcinogenic activity** of 4-vinyl-1-cyclohexene diepoxide for male and female F344/N rats, as shown by squamous cell and basal cell neoplasms of the skin. There was *clear evidence of carcinogenic activity* of 4-vinyl-1-cyclohexene diepoxide for male and female $B6C3F_1$ mice, as shown by squamous cell carcinomas of the skin in males and squamous cell carcinomas of the skin and ovarian neoplasms in females; increased incidences of lung neoplasms in females may also have been related to chemical application.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

SUMMARY OF THE LONG-TERM DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Male F344/N Rats	Female F344/N Rats	Male B6C3F$_1$ Mice	Female B6C3F$_1$ Mice
Dose			
0, 15, or 30 mg/animal 4-vinyl-1-cyclohexene diepoxide in acetone, 5 d/wk	0, 15, or 30 mg/animal 4-vinyl-1-cyclohexene diepoxide in acetone, 5 d/wk	0, 2.5, 5, or 10 mg/animal 4-vinyl-1-cyclohexene diepoxide in acetone, 5 d/wk	0, 2.5, 5, or 10 mg/animal 4-vinyl-1-cyclohexene diepoxide in acetone, 5 d/wk
Body weights in the 2-year study			
High dose lower than vehicle controls	High dose lower than vehicle controls	Mid and high dose lower than vehicle controls	High dose lower than vehicle controls
Survival rates in the 2-year study			
7/50; 8/50; 4/50	27/50; 23/50; 15/50	38/50; 35/50; 4/50; 0/50	30/50; 31/50; 15/50; 10/50 (wk 85)
Nonneoplastic effects			
Acanthosis and sebaceous gland hypertrophy of the skin	Acanthosis and sebaceous gland hypertrophy of the skin	Acanthosis, hyperkeratosis, and necrotizing inflammation of the skin	Acanthosis, hyperkeratosis, and necrotizing inflammation of the skin; follicular atrophy and tubular hyperplasia of the ovary
Neoplastic effects			
Skin neoplasms: basal cell (2/50; 4/50; 8/50); squamous cell (0/50; 33/50; 36/50)	Skin neoplasms: basal cell (2/50; 5/50; 5/50); squamous cell (0/50; 16/50; 34/50)	Skin neoplasms: squamous cell carcinomas (0/50; 14/50; 40/50; 43/50)	Skin neoplasms: squamous cell carcinomas (0/50; 6/50; 37/50; 43/50); ovary: granulosa cell neoplasms, benign mixed tumors, or luteomas (combined) (1/50; 0/49; 17/49; 18/50) Other possible effect--lung: alveolar/bronchiolar adenomas or carcinomas (combined) (4/50; 9/50; 11/50; 7/50)
Level of evidence of carcinogenic activity			
Clear	Clear	Clear	Clear

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence including: animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results ("Clear Evidence" and "Some Evidence"); one category for uncertain findings ("Equivocal Evidence"); one category for no observable effects ("No Evidence"); and one category for experiments that because of major flaws cannot be evaluated ("Inadequate Study"). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is 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 Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

- **Some Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

- **Equivocal Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.

- **No Evidence of Carcinogenic Activity** is demonstrated by studies that are interpreted as showing no chemically related increases in malignant or benign neoplasms.

- **Inadequate Study of Carcinogenic Activity** is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct;
- Occurrence of common versus uncommon neoplasia;
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue;
- Latency in tumor induction;
- Multiplicity in site-specific neoplasia;
- Metastases;
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- The presence or absence of dose relationships;
- The statistical significance of the observed tumor increase;
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- Survival-adjusted analyses and false positive or false negative concerns;
- Structure-activity correlations; and
- In some cases, genetic toxicology.

CONTRIBUTORS

The NTP Technical Report on the Toxicology and Carcinogenesis Studies of 4-Vinyl-1-cyclohexene Diepoxide is based on 13-week studies that began in September 1981 and ended in December 1981 and on 2-year studies that began in September 1982 and ended in October 1984 at Battelle Columbus Laboratories (Columbus, OH).

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PEER REVIEW PANEL

The members of the Peer Review Panel who evaluated the draft Technical Report on 4-vinyl-1-cyclohexene diepoxide on March 13, 1989, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, Panel members have 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-VINYL-1-CYCLOHEXENE DIEPOXIDE

On March 13, 1989, the draft Technical Report on the toxicology and carcinogenesis studies of 4-vinyl-1-cyclohexene diepoxide received public review by the National Toxicology Program Board of Scientific Counselors' Technical Reports Review Subcommittee and associated Panel of Experts. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. R.S. Chhabra, NIEHS, began the discussion by reviewing the experimental design, results, and proposed conclusions (clear evidence of carcinogenic activity for male and female rats; clear evidence of carcinogenic activity for male and female mice).

Dr. Gold, a principal reviewer, agreed with the conclusions. She suggested that if the few skin tumors that were reported as not being found directly at the site of application were near the site and were believed to be related to chemical administration, then they should be included with those at the site for purposes of evaluation. Dr. Chhabra said that the tumors away from, but adjacent to, the site of application were attributed to inadvertent spread of the chemical from the site and that the tumors would be combined for analysis. Dr. Gold said that, for clarity, findings of lung neoplasms in female mice should be stated as equivocal evidence of carcinogenic activity. Dr. Chhabra commented that only the highest level of evidence per study is stated. Dr. J. Huff, NIEHS, added that the lung tumors in female mice were duly labeled as "may have been related" and thus were not an integral part of the selected level of clear evidence.

Dr. Ashby, the second principal reviewer, agreed with the conclusions. He thought that the discussion of the ovarian tumors was unnecessarily complicated. Dr. Chhabra responded that there did seem to be a differential retention of the chemical in the ovaries and a relationship between chemical metabolism and activity in the tissue. Dr. R. Griesemer, NIEHS, observed that the finding of ovarian atrophy and neoplasia was an important toxic event and deserved appropriate discussion.

In response to a request by Dr. Perera, Dr. Chhabra said that he would try to obtain more recent information from the producer on potential human exposure to the chemical (page 12). There was some discussion as to whether the irritant properties of the chemical, in contrast to the alkylating activity, may have played a role in skin tumor initiation.

Dr. Gold moved that the Technical Report on 4-vinyl-1-cyclohexene diepoxide be accepted with the conclusions as written for male and female rats and mice, clear evidence of carcinogenic activity. Dr. Gallo seconded the motion, which was accepted by nine panelists, with one abstention (Dr. Garman).

I. INTRODUCTION

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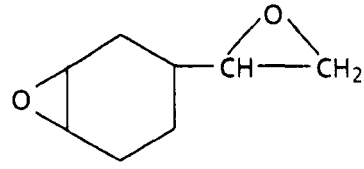

4-VINYL-1-CYCLOHEXENE DIEPOXIDE

CAS No. 106-87-6

$C_8H_{12}O_2$ Molecular weight 140.2

Synonyms: 4-vinylcyclohexene diepoxide; 4-vinyl-1,2-cyclohexene diepoxide; 1-vinyl-3-cyclohexene dioxide; 4-vinylcyclohexene dioxide; 1,2-epoxy-4-(epoxyethyl)cyclohexane; 1-epoxyethyl-3,4-epoxycyclohexane

Physical and Chemical Properties

4-Vinyl-1-cyclohexene diepoxide is a colorless, water-soluble liquid. It has a specific gravity of 1.0986 at 20° C, a freezing point of −108.9° C, a boiling point of 228° F, a vapor pressure of 0.1 torr at 20° C, an open-cup flash point of 230° F (110° C), and a viscosity of 7.77 centipoise at 20° C (ACGIH, 1986).

Use, Production, and Exposure

4-Vinyl-1-cyclohexene diepoxide is used as a reactive diluent for other diepoxides and for epoxy resins derived from bisphenol A and epichlorohydrin. It has been proposed for use as a chemical intermediate, e.g., in condensation reactions with dicarboxylic acids, and as a monomer for preparation of polyglycols containing epoxy groups and for homopolymerization to a three-dimensional resin (IARC, 1976).

4-Vinyl-1-cyclohexene diepoxide is manufactured by epoxidation of 4-vinylcyclohexene with peroxyacetic acid in an inert solvent (Wallace, 1964). The public portion of the Toxic Substances Control Act Chemical Substances Inventory (1977 TSCA Inventory) reported one manufacturer and one importer of 4-vinyl-1-cyclohexene diepoxide in 1977 (USEPA, 1988). The major manufacturer of 4-vinyl-1-cyclohexene diepoxide in the United States is Union Carbide Corporation. Production volumes for both the producer and the importer are confidential.

The National Occupational Exposure Survey (NOES), conducted by the National Institute for Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 1,997 workers in the United States were potentially exposed to 4-vinyl-1-cyclohexene diepoxide (NIOSH, 1988). A threshold limit value/time-weighted average of 10 ppm (60 mg/m^3) for skin has been recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 1986).

Absorption, Distribution, Metabolism, and Disposition

4-Vinyl-1-cyclohexene diepoxide is absorbed by rodents exposed dermally, orally, or by inhalation (Weil et al., 1963). The National Toxicology Program (NTP) has studied the fate of a single dermal application of [^{14}C]4-vinyl-1-cyclohexene diepoxide in female F344/N rats and B6C3F$_1$ mice (Sipes et al., 1988). These studies were conducted to determine if there were differences in disposition which could explain the differences in toxicity observed in rats and mice (Chhabra et al., 1985). Rats and mice received 0.1 ml and 0.01 ml, respectively, of dose mixtures containing 500 mg/ml (200 µC/ml) [ethylene-^{14}C]4-vinyl-1-cyclohexene diepoxide in acetone. The preliminary results indicate that 30% of the dose applied to the skin is absorbed over a 24-hour period for both rats and mice; only 1%-3% of the dose remained on the skin at the site of application. By 24 hours, 70%-80% of the absorbed dose had been eliminated from the body, virtually all in the urine. The radioactivity remaining in the body was distributed over a number of tissues, with no tissue containing more than 1% of the

applied dose. The liver, muscle, and adipose tissue, however, contained 0.5%-1.6% and 1.2%-2.9% of the absorbed dose in rat and mouse tissue, respectively. Tissue to blood ratios ranged from 0.3 to 1.5 in rats and from 0.8 to 2.8 in mice (NTP unpublished data).

In vitro studies with rabbit liver microsomal preparations showed that 4-vinyl-1-cyclohexene diepoxide can be metabolized to monoepoxy-monoglycols, 1,2-hydroxy-4-vinylcyclohexane oxide, and 4-(1',2'-dihydroxyethyl)-1-cyclohexane oxide (Watabe and Sawahata, 1976). Formation of these products is catalyzed by epoxide hydrolase. Conjugation with glutathione is another pathway for metabolism of 4-vinyl-1-cyclohexene diepoxide, proposed by Giannarini et al. (1981), who reported depletion of reduced glutathione in the liver of mice given intraperitoneal injections of 500 mg/kg 4-vinyl-1-cyclohexene diepoxide.

Toxicity

4-Vinyl-1-cyclohexene diepoxide is an irritant to the skin, eyes, and respiratory system. It can penetrate rabbit skin and is more toxic when applied dermally than by other routes. The dermal LD_{50} in rabbits is reported to be 0.62 ml/kg body weight. In rabbits, dermal application of the undiluted material caused edema and redness comparable to a mild-to-moderate first-degree burn. The oral LD_{50} for rats is 2,130 mg/kg, and the inhalation LC_{50} is 800 ppm for 4 hours (NIOSH, 1981-1982; Holmberg, 1984). 4-Vinyl-1-cyclohexene diepoxide is a mild-to-moderate skin irritant in humans; when tested in guinea pigs, skin sensitization occurred infrequently (ACGIH, 1986).

Epoxy compounds are alkylating agents. The effects of cytotoxic alkylating agents are similar to those of ionizing radiation in that they are both selectively active against rapidly dividing cells, such as the blood-forming elements in the bone marrow, lymphoid tissues, and reproductive organs (Kodama et al., 1961). Repeated intramuscular injections of 400 mg/kg 4-vinyl-1-cyclohexene diepoxide to male Long-Evans rats for 7 days decreased the size of the spleen, thymus, and testis and resulted in enlarged adrenal glands. The leukocyte count fell more than 60%, and the myeloid to erythroid ratio was increased.

Immunotoxicity

The NTP has carried out immunotoxicity studies on 4-vinyl-1-cyclohexene diepoxide, the details of which are described in Appendix G of this Report. The immunotoxic effects of 4-vinyl-1-cyclohexene diepoxide were studied in $B6C3F_1$ mice after a 5-day dermal exposure at doses ranging from 2.5 to 10.0 mg/mouse per day. In addition to evaluation of selected organ weights and hematologic values, the primary antibody responses to sheep erythrocytes (SRBCs), as measured by a plaque-forming-cell assay, and the lymphoproliferative response to the T-cell mitogens, phytohemagglutinin (PHA) and concanavalin A (ConA), were determined. There were no consistent chemical-related effects on body or lymphoid organ weights (i.e., spleen, thymus, or mesenteric lymph nodes). Hematologic studies indicated a significant decrease in the leukocyte count at a 4-vinyl-1-cyclohexene diepoxide dose of 10 mg/mouse, which was related to the decreased numbers of circulating lymphocytes. Immune function tests indicated that 4-vinyl-1-cyclohexene diepoxide was immunosuppressive at 10 mg/mouse and, to a lesser extent, at 5 mg/mouse. This was indicated by a decrease in the lymphoproliferative response to PHA and ConA in the high dose group and suppression of the antibody plaque-forming-cell responses in the 5 and 10 mg/mouse groups. PHA and ConA are plant lectins that produce a nonspecific activation of T cells, stimulating the proliferation of T cells in response to antigens. The antibody response to SRBCs is more complex and involves maturation of B cells into plasma cells and accessory support by T cells and macrophages. Thus, the current results indicate that 4-vinyl-1-cyclohexene diepoxide can alter T-cell proliferation and may have effects on other cell types as well. Additional studies will be required to determine the exact cell population affected and the extent of immunosuppression (e.g., whether it is severe enough to alter host resistance to infectious agents). The mechanisms for the immunologic effects of 4-vinyl-1-cyclohexene diepoxide are unknown.

In another immunotoxicity study conducted by the NTP, effects of dermal application of 4-vinyl-1-cyclohexene diepoxide for 14 consecutive days were examined in $B6C3F_1$ mice. The doses applied were 1.25, 2.5, or 5 mg in 0.1 ml of vehicle.

As in the current 5-day study, the most significant inhibition occurred in the antibody plaque-forming-cell response to SRBCs, which was suppressed at the 2.5 and 5 mg doses. In addition, there was a decrease in the peripheral lymphocyte count, as well as in vitro inhibition of the lymphoproliferative response to lipopolysaccharide-induced lymphocyte proliferation in the high dose group. No changes were observed in T-cell responsiveness at these doses.

Genetic Toxicology

There are numerous reports of the mutagenic activity of 4-vinyl-1-cyclohexene diepoxide in *Salmonella typhimurium*, particularly in the base-substitution strains TA100 and TA1535 in the presence or absence of S9 metabolic activation (Wade et al., 1979; Murray and Cummins, 1979; Simmon and Baden, 1980; Frantz and Sinsheimer, 1981; Turchi et al., 1981). The NTP found that treatment with 100-10,000 µg/plate 4-vinyl-1-cyclohexene diepoxide produced a significant, dose-related increase in revertant colonies in *S. typhimurium* strains TA98, TA100, and TA1535 with and without S9 activation (Mortelmans et al., 1986; Table L1). In *S. typhimurium* strain TA1537, the response in the absence of S9 was equivocal, but with S9, a significant increase in mutant colonies was observed. There are only two genetic toxicology studies with 4-vinyl-1-cyclohexene diepoxide in eukaryotic cells. Bronzetti et al. (1980) reported positive results in tests for gene reversion and conversion and mitotic crossing-over in *Saccharomyces cerevisiae* exposed to 4-vinyl-1-cyclohexene diepoxide; Turchi et al. (1981) reported gene mutation induction and anaphase bridge formation in Chinese hamster V79 cells exposed to 4-vinyl-1-cyclohexene diepoxide. In both of these studies, the exposures were carried out in the absence of S9.

A metabolite of 4-vinyl-1-cyclohexene diepoxide, 4-ethylenoxycyclohexan-1,2-diol (Gervasi et al., 1981), did not induce gene mutations in *S. typhimurium* strain TA100 or in Chinese hamster V79 cells, but at a concentration of 2.0 mM this metabolite was reported to have induced anaphase bridge formation and micronuclei in V79 cells (Turchi et al., 1981).

The structural analogs of 4-vinyl-1-cyclohexene diepoxide, 3-ethenyl,7-oxabicyclo[4.1.0]heptane and 1,2-epoxycyclohexane, demonstrate similar mutagenic profiles to 4-vinyl-1-cyclohexene diepoxide. Mutagenic activity, independent of S9, was reported for both analogs in *S. typhimurium* strains TA100 and TA1535 (Wade et al., 1978; Simmon and Baden, 1980; Frantz and Sinsheimer, 1981; Jung et al., 1981) and in Chinese hamster V79 cells (Turchi et al., 1981). Also, anaphase bridge formation and induction of micronuclei were observed in V79 cells (Turchi et al., 1981). De Raat (1978) reported the induction of sister chromatid exchanges in Chinese hamster ovary cells by 0.5 µl/ml 1,2-epoxycyclohexane in the absence of S9.

Carcinogenicity

A number of studies have demonstrated the carcinogenicity of 4-vinyl-1-cyclohexene diepoxide in rodents. Hendry et al. (1951) reported that dermal application of 16 mg 4-vinyl-1-cyclohexene diepoxide, 5 days per week for 12 months, resulted in skin neoplasms in 11/20 exposed male mice. Nine of these animals had squamous cell carcinomas or sarcomas. Ten male and 4 female albino rats were given intraperitoneal injections of 250 mg/kg 4-vinyl-1-cyclohexene diepoxide (5% in arachis oil), 2 days per week for 10 weeks. Seven months after the start of the study, one rat had a mixed cell sarcoma that widely disseminated to the peritoneal cavity; no data were reported for the arachis oil vehicle controls. Kotin and Falk (1963) noted one skin neoplasm and four malignant lymphomas in 16/20 mice surviving a total dermal dose of about 70 mg over a 14-month period. In another study, 4/18 C3H mice developed skin neoplasms when 4-vinyl-1-cyclohexene diepoxide was applied as a 10% solution in acetone for 21 months; the total dose was 78 mg; no data were reported for controls (Weil et al., 1963). Van Duuren et al. (1963) evaluated the carcinogenicity of a number of epoxides, lactones, and peroxy compounds by dermal application to male Swiss ICR/Ha mice. 4-Vinyl-1-cyclohexene diepoxide was applied as 0.1 ml of a 10% solution in benzene, 3 days per week. Fourteen of 30 mice developed neoplasms; 9 of these had squamous cell carcinomas of the skin. The mean survival time was 326 days. In controls, 11/150 benzene vehicle control mice and 13/207 untreated control mice had skin neoplasms; one squamous cell carcinoma was seen

in the benzene vehicle controls, and one was seen in the untreated controls.

Based on these studies, the International Agency for Research on Cancer (IARC) (1976) designated 4-vinyl-1-cyclohexene diepoxide as a carcinogen in mice when applied dermally. NIOSH listed 4-vinyl-1-cyclohexene diepoxide as a suspect occupational carcinogen (Stokinger, 1981). Union Carbide Corporation, the major manufacturer of this chemical, has also labeled it as carcinogenic in mice when applied to skin (Union Carbide, 1978). Users have been warned to avoid skin contact and exposure to vapors.

No information is available in the literature on the carcinogenicity of 4-vinyl-1-cyclohexene diepoxide in humans.

4-Vinylcyclohexene, which is used primarily as an intermediate in the production of 4-vinyl-1-cyclohexene diepoxide, has been studied by the NTP for its toxicity and carcinogenicity (NTP, 1986a). 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. There was clear evidence of carcinogenicity for female mice, as shown by markedly increased incidences of uncommon ovarian neoplasms at both doses. The studies in male and female rats and male mice were considered inadequate studies of carcinogenicity because of extensive and early deaths at the high dose or at both doses.

Study Rationale

4-Vinyl-1-cyclohexene diepoxide was nominated for study by NIOSH because of the lack of carcinogenicity data in rats. At the time of this nomination, NIOSH estimated that 70,000 workers were exposed to 4-vinyl-1-cyclohexene diepoxide. Another reason for selecting 4-vinyl-1-cyclohexene diepoxide was the structure/activity implications presented by this chemical.

Previous carcinogenicity studies were performed primarily in male mice and focused mainly on skin as a target tissue of 4-vinyl-1-cyclohexene diepoxide toxicity and carcinogenicity. The NTP conducted short-term toxicity studies in rats and mice of either sex by dermal and oral routes of exposure to better characterize the toxicity of 4-vinyl-1-cyclohexene diepoxide. The long-term studies were conducted by the dermal route of exposure because human exposure is mainly dermal. Thus, the dermal studies are the primary focus of this Report. The results of short-term oral toxicity studies are described in Appendix H.

II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

CHARACTERIZATION OF DOSE MIXTURES

SINGLE-ADMINISTRATION DERMAL STUDIES

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Study Design

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II. MATERIALS AND METHODS

PROCUREMENT AND CHARACTERIZATION OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

4-Vinyl-1-cyclohexene diepoxide (labeled Bakelite Epoxy Resin ERL-4206) was obtained in one lot (lot no. TF3-91614) from Union Carbide Corporation (Danbury, CT) as a clear, pale yellow liquid. Purity and identity analyses were conducted at Midwest Research Institute (Kansas City, MO) (Appendix K).

The study chemical was identified as 4-vinyl-1-cyclohexene diepoxide by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy.

Lot no. TF3-91614 was found to be approximately 97% pure, as determined by elemental analysis, Karl Fischer water analysis, potentiometric titration of the epoxide group in chloroform (by in situ generation of hydrogen iodide from excess tetrabutylammonium iodide and 0.1 N perchloric acid), thin-layer chromatography, and gas chromatography.

The stability of the chemical during the toxicology and carcinogenicity studies was monitored by gas chromatography. No deterioration of the study material was seen over the course of the studies.

CHARACTERIZATION OF DOSE MIXTURES

4-Vinyl-1-cyclohexene diepoxide in acetone at a concentration of 500 mg/ml was found by gas chromatography to be stable for at least 2 weeks when stored in the dark at room temperature, at 5° C, or for at least 3 hours when open to light and air at room temperature.

Periodic analysis by gas chromatography of 4-vinyl-1-cyclohexene diepoxide/acetone dose mixtures was conducted at the study laboratory and at the analytical chemistry laboratory. Dose mixtures were analyzed twice during the 13-week studies. All mixtures were within ±10% of the target concentrations.

During the 2-year studies, the dose mixtures were analyzed at approximately 8-week intervals. For the 4-vinyl-1-cyclohexene diepoxide dermal studies, the mixtures were estimated to have been formulated within ±10% of the target concentrations approximately 93% of the time throughout the studies; the other mixtures were within ±13% of the target concentration (Table K3). Results of periodic referee analysis performed by the analytical chemistry laboratory indicated generally good agreement with the results from the study laboratory (Table K4).

SINGLE-ADMINISTRATION DERMAL STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Harlan Industries and observed for 14 days before the studies began. Groups of five rats of each sex were administered a single dermal application of 198, 388, 773, or 1,568 mg/kg 4-vinyl-1-cyclohexene diepoxide in acetone to the clipped dorsal interscapular region. Groups of five mice of each sex were administered 338.3, 671.6, 1,378, or 2,741 mg/kg 4-vinyl-1-cyclohexene diepoxide in acetone on the same schedule. A 3,074 mg/kg dose for rats and a 5,487 mg/kg dose for mice were administered neat. Animals were observed twice per day for 14 days. A necropsy was performed on all animals. Details of animal maintenance are presented in Table 1.

FOURTEEN-DAY DERMAL STUDIES

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and were held for 19 days (rats) or 21 days (mice) before the studies began. The rats were 7 weeks old when placed on study, and the mice were 9 weeks old.

Groups of five male rats were administered 0, 35, 68, 139, or 289 mg/rat 4-vinyl-1-cyclohexene diepoxide in acetone or 358 mg/rat neat by dermal application to the clipped dorsal interscapular region for 14 consecutive days. Groups of five female rats were administered 0, 27, 57, 112, 211, or 290 mg/rat. Groups of five male mice

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Fifteen-Month and Two-Year Studies
EXPERIMENTAL DESIGN			
Size of Study Groups			
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species	15 mo--10 males and 10 females of each species; 2 y--50 males and 50 females of each species
Doses			
Rats--198, 388, 773, or 1,568 mg/kg 4-vinyl-1-cyclohexene diepoxide in acetone or 3,074 mg/kg neat by dermal application to the dorsal interscapular region; mice--338.3, 671.6, 1,378, or 2,741 mg/kg in acetone or 5,487 mg/kg neat; dose vol--3 × 0.1 ml (rats) or 0.1 ml (mice)	Rats--0, 35, 68, 139, 289, or 358 mg/rat for males and 0, 27, 57, 112, 211, or 290 mg/rat for females by dermal application to the dorsal interscapular region, equivalent to 0, 227, 468, 924, or 1,867 mg/kg 4-vinyl-1-cyclohexene diepoxide in acetone or 2,338 mg/kg neat; mice--0, 3, 5, 10, 21, or 43 mg/mouse for males and 0, 2, 5, 10, 19, or 37 mg/mouse for females, equivalent to 0, 108, 224, 488, 889, or 1,787 mg/kg; dose vol--3 × 0.1 ml (rats) or 0.1 ml (mice)	Rats--0, 3.75, 7.5, 15, 30, or 60 mg/rat 4-vinyl-1-cyclohexene diepoxide in acetone by dermal application to the dorsal interscapular region; mice--0, 0.625, 1.25, 2.5, 5, or 10 mg/mouse; dose vol--3 × 0.1 ml (rats) or 0.1 ml (mice)	Rats--0, 15, or 30 mg/rat 4-vinyl-1-cyclohexene diepoxide in acetone by dermal application to the dorsal interscapular region; mice--0, 2.5, 5, or 10 mg/mouse; dose vol--3 × 0.1 ml (rats) or 0.1 ml (mice)
Date of First Dose			
3/18/81	Rats--6/3/81; mice-- 6/5/81	Rats--9/15/81-9/16/81; mice--9/17/81-9/18/81	Rats--10/4/82; mice--9/27/82
Date of Last Dose			
N/A	Rats--6/16/81; mice--6/18/81	Rats--12/14/81-12/15/81; mice--12/16/81-12/17/81	15 mo--1/3/84-1/4/84 (rats) or 12/27/83-12/28/83 (mice); 2 y--10/5/84 (rats) or 9/14/84 (mice)
Duration of Dosing			
Single dose	14 consecutive d	5 d/wk for 13 wk	2 y--105 wk (rats) or 103 wk (mice); high dose female mice: 85 wk
Type and Frequency of Observation			
Observed 2 × d	Observed 2 × d	Observed 2 × d; weighed initially and 1 × wk thereafter	Observed 2 × d; weighed initially, 1 × wk for 13 wk, and then 1 × mo
Necropsy, Histologic Examinations, and Supplemental Analyses			
Necropsy performed on all animals	Necropsy performed on all animals; histologic examinations performed on all vehicle controls, rats receiving 27, 35, 57, 68, 112, or 139 mg/animal, and mice receiving 5, 10, 19, or 21 mg/animal. Tissues examined from lower dose groups include: bone marrow and skin from the site of application for rats receiving 27 or 35 mg/animal and skin from the site of application for mice	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and highest dose groups and mice dying before the end of the studies: adrenal glands, brain, cecum, colon, duodenum, esophagus, femur (including marrow), gallbladder (mice), gross lesions and tissue masses with regional lymph nodes, heart, ileum, jejunum, kidneys, liver, lungs and	Necropsy performed on all animals; the following tissues examined histologically for vehicle control and high dose groups in the 15-mo studies and all animals in the 2-y studies: adrenal glands, brain, colon, esophagus, eyes (if grossly abnormal), femur or sternebrae or vertebrae including marrow, gallbladder (mice), gross lesions and tissue masses with regional lymph nodes, heart, kidneys, liver, lungs and mainstem

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Fifteen-Month and Two-Year Studies
EXPERIMENTAL DESIGN			
Necropsy, Histologic Examinations, and Supplemental Analyses (Continued)			
	receiving 5 mg/animal; organs weighed at necropsy	mainstem bronchi, mammary gland, mandibular lymph nodes, nasal cavity and turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland (rats), prostate/testes/epididymis or ovaries/uterus, rectum, salivary glands, skin, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder. Skin (both application and nonapplication sites) examined for rats receiving 15 or 30 mg/rat and mice receiving 5 mg/mouse; ovaries/uterus examined for mice in the 2.5 and 5 mg/mouse groups. Blood for hematologic analyses and organ weights obtained at necropsy	bronchi, mammary gland, mandibular or mesenteric lymph nodes, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland, prostate/testes or ovaries/uterus, salivary glands, skin (both application and nonapplication sites), small intestine, spinal cord (if neurologic signs present), thyroid gland, trachea, and urinary bladder. Tissues examined for lower dose groups in the 15-mo studies include skin from application and nonapplication sites for rats and mice and ovaries for mice. Blood for hematologic analyses and organ weights obtained at necropsy
ANIMALS AND ANIMAL MAINTENANCE			
Strain and Species			
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source			
Harlan Industries (Indianapolis, IN)	Charles River Breeding Laboratories (Portage, MI)	Frederick Cancer Research Facility (Frederick, MD)	Charles River Breeding Laboratories (Portage, MI)
Study Laboratory			
Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories
Method of Animal Identification			
Toe clip	Toe clip	Toe clip	Toe clip
Time Held Before Study			
14 d	Rats--19 d; mice--21 d	Rats--21-22 d; mice--22-23 d	18 d
Age When Placed on Study			
Rats--6 wk; mice--8 wk	Rats--7 wk; mice--9 wk	Rats--10 wk; mice--9 wk	Rats--7-8 wk; mice--8-9 wk
Age When Killed			
Rats--8 wk; mice--10 wk	Rats--9 wk; mice--11 wk	Rats--23 wk; mice--22 wk	15 mo--72-73 wk (rats) or 73-74 wk (mice); 2 y--114 wk (rats) or 113 wk (mice); high dose female mice: 93 wk
Necropsy Dates			
4/1/81	Rats--6/17/81; mice--6/19/81	Rats--12/15/81-12/16/81; mice--12/17/81-12/18/81	15 mo--1/4/84-1/5/84 (rats) or 12/28/83-12/29/83 (mice); 2 y--10/15/84-10/16/84 (rats) or 9/24/84-9/27/84 (mice)

TABLE 1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Fifteen-Month and Two-Year Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)			
Method of Animal Distribution			
Animals distributed to weight classes and then assigned to cages by one table of random numbers and to groups by another table of random numbers	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Diet			
NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Bedding			
Absorb-Dri® hardwood chips (Absorb-Dri, Inc., Garfield, NJ)	Same as single-administration studies	Absorb-Dri® hardwood chips (Weisheimer's, Columbus, OH)	Same as single-administration studies
Water			
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cages			
Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Cage Filters			
Spun-bonded polyester, Dupont 2024® (Snow Filtration, Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies	Same as single-administration studies
Animals per Cage			
1	1	1	1
Other Chemicals on Study in the Same Room			
None	None	None	None
Animal Room Environment			
Temp--22°-24° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Temp--22°-24° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Temp--21°-23° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Temp--13°-26° C; hum--23%-81%; fluorescent light 12 h/d; 17-23 room air changes/h

were administered 0, 3, 5, 10, 21, or 43 mg/mouse and groups of five female mice were administered 0, 2, 5, 10, 19, or 37 mg/mouse in acetone by dermal application to the clipped dorsal interscapular region on the same schedule. Animals were observed twice per day for 14 days. A necropsy was performed on all animals. Histologic examinations were performed on all vehicle controls, the three lowest dose groups of rats, and mice that received 5 or more mg/mouse. Skin from the application site was examined for rats that received 27 or 35 mg/rat and for mice that received 5 mg/mouse. Details of animal maintenance and groups and tissues examined are presented in Table 1.

THIRTEEN-WEEK DERMAL STUDIES

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of 4-vinyl-1-cyclohexene diepoxide and to determine the doses to be used in the 2-year studies.

Seven-week-old male and female F344/N rats and 6-week-old male and female B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility. Rats were observed for 21-22 days and mice for 22-23 days. Rats and mice were distributed to weight classes and assigned to dose groups according to tables of random numbers. Rats were 10 weeks old when placed on study, and mice were 9 weeks old.

Ten rats of each sex were administered 0, 3.75, 7.5, 15, 30, or 60 mg 4-vinyl-1-cyclohexene diepoxide in acetone by dermal application to the clipped dorsal interscapular region, 5 days per week for 13 weeks. Ten mice of each sex were administered 0, 0.625, 1.25, 2.5, 5, or 10 mg on the same schedule. The interscapular region was clipped once per week. The volume and concentration of the dose mixtures were not adjusted with changes in body weight. Three 0.1-ml consecutive applications were administered to rats with a 100-µl micropipette. For mice, a single application of 0.1 ml was applied to the interscapular region. The dose mixture was applied uniformly at the site of application.

Animals were observed two times per day; moribund animals were killed. Individual animal weights were recorded once per week. Further details on animal maintenance are described in Table 1.

At the end of the 13-week studies, survivors were killed. Blood was collected from the vena cava of rats only and analyzed for hematocrit values, hemoglobin concentration, and erythrocyte, leukocyte, and reticulocyte counts. A necropsy was performed on all animals except for tissues that were excessively autolyzed or missing. Body weights and liver, thymus, right kidney, heart, brain, right testis, and lung weights were recorded at necropsy. Total cellularity in bone marrow from rat femurs was determined.

Histopathologic examinations were performed on all vehicle controls, animals in the 60 mg/rat and 10 mg/mouse groups, and all mice that died before the end of the studies. The application site and a nonapplication skin site of the 15 and 30 mg/rat and 5 mg/mouse groups and ovaries and uterus of the 2.5 and 5 mg/mouse groups were examined microscopically. Tissues and groups examined are listed in Table 1.

FIFTEEN-MONTH AND TWO-YEAR STUDIES

Study Design

4-Vinyl-1-cyclohexene diepoxide in acetone was administered to groups of 60 rats of each sex at doses of 0, 15, or 30 mg/animal by dermal application to the clipped dorsal interscapular region, 5 days per week for 15 months or 105 weeks. 4-Vinyl-1-cyclohexene diepoxide in acetone was administered to groups of 60 mice of each sex at doses of 0, 2.5, 5, or 10 mg/animal by dermal application to the clipped dorsal interscapular region for 15 months or 103 weeks. The interscapular region was clipped once per week. The volume and concentration of the dose mixtures were not adjusted with changes in body weight. Three 0.1-ml consecutive applications were administered to rats with a 100-µl micropipette. For mice, a single application of 0.1 ml was applied to the interscapular region. The dose mixture was applied uniformly at the site of application. All male mice receiving 10 mg/animal died by week 83; the surviving female mice receiving 10 mg/animal were killed during week 85.

For animals evaluated at 15 months, blood was collected from the orbital sinus of 10 animals of each sex and dose group for hematologic analyses. A necropsy was performed on all animals. Body weights and the weights of the brain, right kidney, liver, right testis, uterus, and ovaries were recorded.

Source and Specifications of Animals

The male and female F344/N rats and B6C3F$_1$ (C57BL/6N, female × C3H/HeN MTV$^-$, male) mice used in these studies were produced under strict barrier conditions at Charles River Breeding Laboratories. 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 and were shipped to the study laboratory at 5-6 weeks of age. The animals were quarantined at the study laboratory for 2-3 weeks. Thereafter, a complete necropsy was performed on five animals of each sex and species to assess their health status. Rats were placed on study at 7-8 weeks of age and mice at 8-9 weeks of age. The health of the animals was monitored during the course of the studies according to the protocols of the National Toxicology Program (NTP) Sentinel Animal Program (Appendix E).

Animal Maintenance

Animals were individually housed. Feed (Appendix F) and water were available ad libitum. Cages were rotated vertically within the rack columns, and racks were rotated in a clockwise direction every 2 weeks.

Clinical Examinations and Pathology

All animals were observed two times per day, and clinical signs were recorded at least once per month. Body weights 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. Animals found moribund and those surviving to the end of the studies were humanely killed. A necropsy was performed on all animals including those found dead except for tissues that were excessively autolyzed or or missing. Thus, the number of animals from which particular organs or tissues were examined microscopically varies and is not necessarily equal to the number of animals that were placed on study.

During necropsy, all organs and tissues were examined for grossly visible lesions. Tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Tissues examined are listed in Table 1. Skin, application site, included sections from the interscapular region where the chemical was applied (skin, scapula) and skin directly adjacent to the site of chemical application (skin, back). Skin, nonapplication site, is skin distant from the application site.

When the pathology evaluation was completed by the laboratory pathologist and the pathology data entered into the Toxicology Data Management System, the slides, paraffin blocks, and residual formalin-fixed tissues were sent to the NTP Archives. The slides, blocks, and residual wet tissues were audited for accuracy of labeling and animal identification and for thoroughness of tissue trimming. The slides, individual animal necropsy records, and pathology tables were sent to an independent pathology quality assessment laboratory. The individual animal records and pathology tables were compared for accuracy, slides and tissue counts were verified, and histotechnique was evaluated. All tissues with a tumor diagnosis, all potential target tissues (male rats: pancreatic islets, skin; female rats: skin, thyroid gland; male mice: adrenal glands, epididymis, harderian gland, prostate, skin; female mice: adrenal glands, harderian gland, lung, ovary, skin), and all tissues from a randomly selected 10% of the animals from each vehicle control and high dose group were re-evaluated microscopically by a quality assessment pathologist. Nonneoplastic lesions were evaluated for accuracy and consistency of diagnosis only in the potential target organs, in the randomly selected 10% of animals, and in tissues with unusual incidence patterns or trends. Tissues are generally not evaluated in a "blinded" fashion (i.e., without knowledge of dose group) unless the lesions in question are subtle.

The quality assessment report and slides were submitted to a Pathology Working Group (PWG) Chairperson, who reviewed microscopically all potential target tissues and any other tissues for which there was a disagreement in diagnosis between the laboratory and quality assessment pathologists. Representative examples of potential chemical-related nonneoplastic lesions and neoplasms and examples of disagreements in diagnosis between the laboratory and quality assessment pathologists were shown to the PWG. The PWG, which included the laboratory pathologist, the quality assessment pathologist, and other pathologists experienced in rodent toxicology, examined the tissues without knowledge of dose group or previously rendered diagnoses. When the consensus diagnosis of the PWG differed from that of the laboratory pathologist, the diagnosis was changed to reflect the opinion of the PWG. This procedure has been described, in part, by Maronpot and Boorman (1982) and Boorman et al. (1985). The final pathology data represent a consensus of contractor pathologists and the NTP Pathology Working Group. For subsequent analysis of pathology data, the diagnosed lesions for each tissue type are combined according to the guidelines of McConnell et al. (1986).

Statistical Methods

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 to be missing or dead from other than natural causes; 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: The majority of tumors in this study were considered to be incidental to the cause of death or not rapidly lethal. Thus, the primary statistical method used was a logistic regression analysis, which assumed that the diagnosed tumors were discovered as the result of death from an unrelated cause and thus did not affect the risk of death. In this approach, tumor prevalence was modeled as a logistic function of chemical exposure and time. Both linear and quadratic terms in time were incorporated initially, and the quadratic term was eliminated if it did not significantly enhance the fit of the model. The dosed and vehicle control groups were compared on the basis of the likelihood score test for the regression coefficient of dose. This method of adjusting for intercurrent mortality is the prevalence analysis of Dinse and Lagakos (1983), further described and illustrated by Dinse and Haseman (1986). When tumors are incidental, this comparison of the time-specific tumor prevalences also provides a comparison of the time-specific tumor incidences (McKnight and Crowley, 1984).

In addition to logistic regression, alternative methods of statistical analysis were used, and the results of these tests are summarized in the appendixes. These include the life table test (Cox, 1972; Tarone, 1975), appropriate for rapidly lethal tumors, and the Fisher exact test and the Cochran-Armitage trend test (Armitage, 1971; Gart et al., 1979), procedures based on the overall proportion of tumor-bearing animals.

Tests of significance include pairwise comparisons of each dosed group with vehicle controls and a test for an overall dose-response trend. Continuity-corrected tests were used in the

analysis of tumor incidence, and reported P values are one-sided. The procedures described above also were used to evaluate selected nonneoplastic lesions. (For further discussion of these statistical methods, see Haseman, 1984.)

Analysis of Continuous Variables: The statistical analysis of organ weight, hematologic, and immunotoxicologic data was carried out by using the multiple comparison procedures of Dunnett (1980) or Williams (1971, 1972) to assess the significance of pairwise comparisons between dosed and vehicle control groups. Jonckheere's test (Jonckheere, 1954) was used to evaluate the significance of dose-response trends and to determine whether Dunnett's or Williams' test should be used for pairwise comparisons.

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, 1985) are included for those tumors appearing to show compound-related effects.

III. RESULTS

RATS

SINGLE-ADMINISTRATION DERMAL STUDIES

FOURTEEN-DAY DERMAL STUDIES

THIRTEEN-WEEK DERMAL STUDIES

FIFTEEN-MONTH STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

MICE

SINGLE-ADMINISTRATION DERMAL STUDIES

FOURTEEN-DAY DERMAL STUDIES

THIRTEEN-WEEK DERMAL STUDIES

FIFTEEN-MONTH STUDIES

TWO-YEAR STUDIES

Body Weights and Clinical Signs
Survival
Pathology and Statistical Analyses of Results

GENETIC TOXICOLOGY

SINGLE-ADMINISTRATION DERMAL STUDIES

All rats lived to the end of the studies (doses up to 3,074 mg/kg). Decreased activity was considered a compound-related clinical sign in the 773, 1,568, and 3,074 mg/kg groups. No lesions were observed at necropsy

FOURTEEN-DAY DERMAL STUDIES

All rats that received the three highest doses died before the end of the studies (Table 2). The final mean body weights of males that received 35 or 68 mg/rat and females that received 27 or 57 mg/rat were 7% or 16% lower than that of the vehicle controls for males and 5% or 12% lower for females. In the 358 mg/rat group, males had scabs at the dermal application site; females receiving 290 mg/rat were hunched and exhibited hyperpnea and ataxia. Burrowing behavior, decreased activity, ataxia, hyperpnea, and half-closed eyelids were observed in the second highest dose groups. The dermal application site was reddened and scaly for males in the 68 and 139 mg/rat groups and for females in the 57 and 112 mg/rat groups. The relative kidney and brain weights for the male 68 mg/rat group were significantly greater than those for the vehicle controls (Table I1). The relative thymus weight was decreased at 68 mg/rat for males and at 57 mg/rat for females. Excoriations on the dorsal skin at the application site were observed in the groups receiving 57 mg/rat or more. Males receiving 139 mg/rat and females receiving 112 mg/rat had congestion and/or hypoplasia of the bone marrow; most had acute nephrosis. Skin lesions including epithelial necrosis and ulceration, epidermal hyperplasia, hyperkeratosis, and sebaceous gland hyperplasia were found in males receiving 139 mg/rat and females receiving 112 mg/rat; skin lesions of lesser severity were seen in the 57 and 68 mg/rat groups (Table 3). Mild hyperkeratosis was seen in skin from the application site in 1/5 male rats that received 35 mg/rat and in 1/5 females that received

TABLE 2. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE FOURTEEN-DAY DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Dose (mg/rat)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	153 ± 4	221 ± 3	+68 ± 3	
35	5/5	156 ± 6	206 ± 10	+50 ± 6	93.2
68	5/5	146 ± 2	186 ± 2	+40 ± 2	84.2
139	(d) 0/5	150 ± 6	(e)	(e)	(e)
289	(f) 0/5	155 ± 6	(e)	(e)	(e)
358	(g) 0/5	153 ± 3	(e)	(e)	(e)
FEMALE					
0	5/5	125 ± 5	152 ± 5	+27 ± 1	
27	5/5	119 ± 2	144 ± 2	+25 ± 1	94.7
57	5/5	121 ± 3	133 ± 3	+12 ± 2	87.5
112	(h) 0/5	121 ± 4	(e)	(e)	(e)
211	(i) 0/5	113 ± 2	(e)	(e)	(e)
290	(j) 0/5	124 ± 3	(e)	(e)	(e)

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean
(d) Day of death: 7,7,8,9,13
(e) No data are reported due to 100% mortality in this group
(f) Day of death: 4,5,5,6,7
(g) Day of death: 5,5,6,6,6
(h) Day of death: 7,7,7,8,13
(i) Day of death: 4,5,6,6,6
(j) Day of death: 4,4,5,5,6

TABLE 3. NUMBERS OF RATS WITH SELECTED SCAPULAR SKIN LESIONS IN THE FOURTEEN-DAY DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Lesion	Male (mg/rat)				Female (mg/rat)			
	0	35	68	139	0	27	57	112
Epidermal hyperplasia	0	0	5	1	0	0	5	0
Hyperkeratosis	0	1	5	2	0	1	3	2
Necrosis	0	0	0	1	0	0	0	2
Ulcers	0	0	1	1	0	0	1	2
Sebaceous gland hyperplasia	0	0	5	0	0	0	5	0

(a) Five animals were examined in each group.

27 mg/rat. Mild bone marrow hypoplasia was seen in 1/5 females receiving 27 mg/rat.

THIRTEEN-WEEK DERMAL STUDIES

All rats survived to the end of the studies (doses up to 60 mg/rat) (Table 4). The final mean body weights receiving 60 mg/rat were 14% lower than that of vehicle controls for males and 9% lower for females. Compound-related clinical signs observed from week 7 or 11 included redness, scabbiness, and ulceration on the back at the application site and burrowing behavior after dermal application in the 60 mg/rat groups. Thymus weight to body weight ratios for males receiving 30 or 60 mg/rat were significantly lower than that for vehicle controls (Table I2). Bone marrow cellularity did not differ significantly between the dosed groups and the vehicle controls (Table I3). The hemoglobin concentration for males receiving 60 mg/rat was marginally increased compared with that for vehicle controls (Table I4). Yellowish scabs were seen at the site of application at the nape of the neck in 5/10 males and 5/10 females, and thickened skin at the nape of the neck was seen in 1/10 males and 5/10 females receiving 60 mg/rat. Diffuse hyperplasia of the sebaceous gland and/or acanthosis (hyperplasia) and hyperkeratosis of the stratified squamous epithelium in skin from the application site was seen in all 15, 30, and 60 mg/rat groups (Table 5). The severity of the lesions was greatest at 60 mg/rat. Ulcers of the skin were seen in 3/10 males that received 60 mg/rat. Acute to chronic inflammation of the epidermis from the application site was observed for rats administered 60 mg/rat.

Dose Selection Rationale: On the basis of the results of the 13-week dermal studies, doses of 15 and 30 mg/rat per day were selected for the 2-year studies. In the 13-week studies, no chemical-related effects on survival or body weights or clinical signs or life-threatening lesions were observed for the 30 mg/rat group of either sex. Depressed body weights and dermal ulceration observed in the 60 mg/rat groups precluded the selection of this dose for the 2-year studies.

FIFTEEN-MONTH STUDIES

Organ weight to body weight ratios were not affected by dermal administration of 4-vinyl-1-cyclohexene diepoxide (Table J1). Results of hematologic analyses indicated no notable differences between dosed groups and vehicle controls (Table J2).

Two of 10 males that received 30 mg had a squamous cell carcinoma of the skin at or adjacent to the site of application (Table 6). Acanthosis of the skin was seen for exposed rats (mild severity at 30 mg/rat and minimal severity at 15 mg/rat); hyperkeratosis was observed at 30 mg/rat. One female receiving 30 mg/rat had a squamous cell carcinoma of the forestomach.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose rats were generally 9%-13% lower than those of vehicle controls after week 49 for males and were 9%-14% lower after week 57 for females (Table 7 and Figure 1). Hair was discolored at the site of application.

TABLE 4. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Dose (mg/rat)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	160 ± 3	337 ± 6	+177 ± 6	
3.75	10/10	159 ± 4	346 ± 7	+187 ± 4	102.7
7.5	10/10	159 ± 4	333 ± 9	+174 ± 7	98.8
15	10/10	155 ± 4	343 ± 2	+188 ± 4	101.8
30	10/10	157 ± 4	338 ± 6	+181 ± 7	100.3
60	10/10	158 ± 5	291 ± 8	+133 ± 5	86.4
FEMALE					
0	10/10	132 ± 2	200 ± 4	+68 ± 3	
3.75	10/10	128 ± 4	205 ± 3	+77 ± 4	102.5
7.5	10/10	128 ± 3	203 ± 2	+75 ± 3	101.5
15	10/10	121 ± 5	194 ± 3	+73 ± 4	97.0
30	10/10	123 ± 4	197 ± 3	+74 ± 4	98.5
60	10/10	129 ± 3	182 ± 2	+53 ± 2	91.0

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean

TABLE 5. NUMBERS OF RATS WITH SELECTED SKIN LESIONS AT THE APPLICATION SITE IN THE THIRTEEN-WEEK DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Lesion	Male (mg/rat) 0	15	30	60	Female (mg/rat) 0	15	30	60
Acute to chronic inflammation	0	0	0	3	0	3	2	2
Hyperkeratosis	0	2	**9	**10	0	**10	**9	**10
Parakeratosis	0	0	2	**10	0	0	0	**8
Acanthosis	0	1	**9	**10	0	**9	*4	**10
Necrotizing inflammation	0	0	0	3	0	0	0	**6
Ulcers 0	0	0	3	0	0	0	0	
Sebaceous gland hyperplasia	0	0	**6	**10	0	0	2	**10

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

TABLE 6. NUMBERS OF RATS WITH SELECTED SKIN LESIONS IN THE FIFTEEN-MONTH DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Lesion	Male (mg/rat) 0	15	30	Female (mg/rat) 0	15	30
Acanthosis	0	**7	**9	0	*5	**10
Hyperkeratosis	0	0	*5	0	0	**10
Sebaceous gland hyperplasia	0	**7	**8	0	0	**10
Squamous cell carcinoma	0	0	2	0	0	0

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

TABLE 7. MEAN BODY WEIGHTS OF RATS IN THE TWO-YEAR DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Week on Study	Vehicle Control		15 mg/Rat			30 mg/Rat		
	Av. Wt. (grams)	Number Weighed	Av. Wt. (grams)	Wt. (percent of vehicle controls)	Number Weighed	Av. Wt. (grams)	Wt. (percent of vehicle controls)	Number Weighed
MALE								
1	165	60	168	102	60	169	102	60
2	217	60	220	101	60	214	99	60
3	237	60	238	100	60	235	99	60
4	254	60	254	100	60	252	99	60
5	263	60	259	98	60	258	98	60
6	278	60	276	99	60	277	100	60
7	297	60	295	99	(a) 59	295	99	(a) 59
8	307	60	305	99	60	303	99	60
9	319	60	318	100	60	316	99	(a) 58
10	329	60	328	100	60	325	99	60
11	338	60	337	100	60	336	99	60
12	349	60	349	100	(a) 58	344	99	(a) 59
13	353	60	352	100	(a) 58	348	99	60
18	381	60	377	99	59	372	98	60
22	403	60	398	99	59	392	97	60
25	412	60	406	99	59	400	97	60
29	427	60	425	100	59	415	97	60
33	437	60	435	100	59	421	96	60
37	439	60	435	99	59	421	96	59
41	455	60	447	98	59	428	94	59
45	450	60	448	100	59	425	94	59
49	461	60	446	97	59	419	91	59
53	473	60	456	96	59	430	91	58
57	476	59	465	98	56	417	88	58
61	482	59	464	96	55	419	87	57
65	478	(a) 58	465	97	54	432	90	56
69	484	(b) 46	473	98	(b) 43	427	88	(b) 45
73	481	45	474	99	42	427	89	44
77	480	42	467	97	42	429	89	44
81	469	37	457	97	39	423	90	39
85	460	33	454	99	36	411	89	36
89	457	26	453	99	32	411	90	25
93	441	23	434	98	28	400	91	19
97	413	19	415	100	25	392	95	13
101	410	11	411	100	15	388	95	7
106	396	7	403	102	8	354	89	5
FEMALE								
1	125	60	123	98	60	122	98	60
2	147	60	147	100	60	145	99	60
3	156	60	156	100	60	154	99	60
4	164	60	164	100	60	163	99	60
5	174	60	172	99	60	171	98	60
6	182	(a) 59	179	98	60	179	98	60
7	189	60	187	99	(a) 59	187	99	60
8	195	60	191	98	60	190	97	60
9	202	60	199	99	60	195	97	60
10	206	60	202	98	60	200	97	60
11	212	60	207	98	60	209	99	60
12	214	60	215	100	60	208	97	(a) 59
13	218	(a) 59	215	99	(a) 54	214	98	60
18	222	60	218	98	60	220	99	60
22	231	60	229	99	60	229	99	60
25	235	60	231	98	59	231	98	60
29	240	60	236	98	59	234	98	60
33	248	60	244	98	59	242	98	60
37	250	59	247	99	59	243	97	60
41	258	59	253	98	59	248	96	60
45	259	59	255	98	59	248	96	60
49	267	59	266	100	59	257	96	60
53	274	59	272	99	59	259	95	60
57	286	58	280	98	59	261	91	60
61	288	58	279	97	58	261	91	56
65	294	57	287	98	(a) 56	274	93	(a) 55
69	305	(b) 47	295	97	(b) 47	269	88	(b) 45
73	312	47	302	97	46	275	88	43
77	315	(a) 46	305	97	46	279	89	41
81	316	47	290	92	(a) 43	277	88	40
85	321	46	302	94	41	278	87	38
89	323	42	307	95	34	280	87	36
93	322	40	316	98	29	277	86	31
97	322	38	328	102	26	277	86	26
101	321	35	326	102	25	276	86	15
106	312	27	321	103	24	268	86	15

(a) The number of animals weighed was lower than the number of animals surviving.
(b) Interim kill occurred.

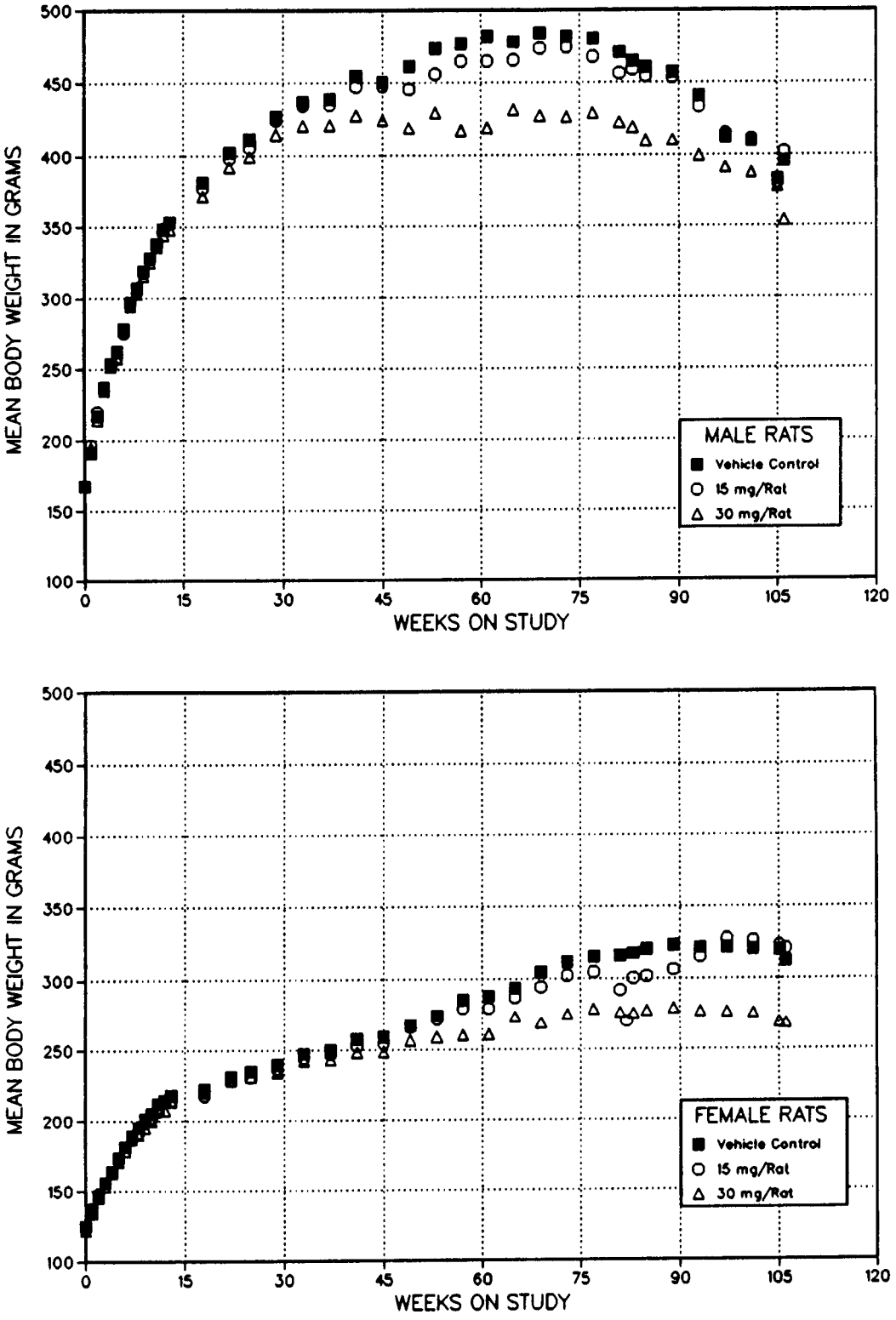


FIGURE 1. GROWTH CURVES FOR RATS ADMINISTERED 4-VINYL-1-CYCLOHEXENE DIEPOXIDE IN ACETONE BY DERMAL APPLICATION FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female rats administered 4-vinyl-1-cyclohexene diepoxide at the doses used in these studies and for vehicle controls are shown in Table 8 and in the Kaplan and Meier curves in Figure 2. The survival of the high dose group of female rats was significantly lower than that of the vehicle controls after day 648. The survival of the low dose group of female rats was significantly lower between days 637 and 715. No significant differences in survival were observed between any groups of male rats; however, survival at the end of the study was very low for all groups, including vehicle controls.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of rats with neoplastic or nonneoplastic lesions of the skin and urinary bladder.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes A and B for male and female rats, respectively.

TABLE 8. SURVIVAL OF RATS IN THE TWO-YEAR DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	15 mg/Rat	30 mg/Rat
MALE (a)			
Animals initially in study	50	50	50
Natural deaths	12	5	16
Moribund kills	31	37	29
Animals surviving until study termination	7	8	4
Killed accidentally	0	0	1
Survival P values (b)	0.524	0.487	0.590
FEMALE (a)			
Animals initially in study	50	50	50
Natural deaths	8	13	21
Moribund kills	15	14	14
Animals surviving until study termination	27	23	15
Survival P values (b)	0.007	0.262	0.005

(a) First day of termination period: 743
(b) 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.

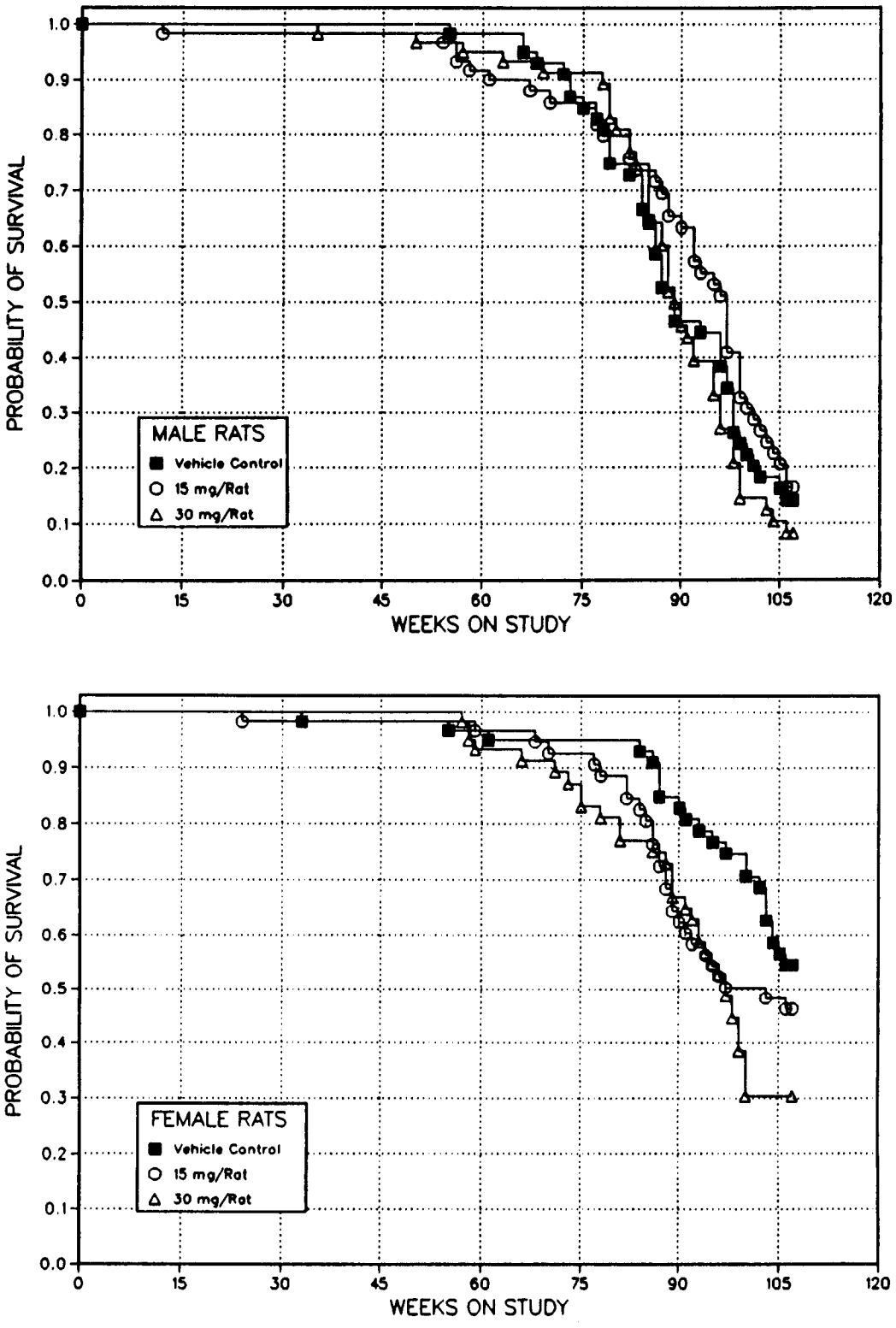


FIGURE 2. KAPLAN-MEIER SURVIVAL CURVES FOR RATS ADMINISTERED 4-VINYL-1-CYCLOHEXENE DIEPOXIDE IN ACETONE BY DERMAL APPLICATION FOR TWO YEARS

Skin: The incidences of neoplasms of the skin, including basal cell adenomas and carcinomas, squamous cell papillomas and carcinomas, and sebaceous gland adenomas, as well as acanthosis and sebaceous gland hypertrophy were increased in exposed male and female rats (Table 9). The incidences of skin neoplasms were significantly greater in exposed male and female rats than in vehicle controls (Table 10). Although the neoplasms were diagnosed according to the predominant cell type present, all were considered to be neoplasms originating primarily from the basal cells of the skin and adnexal structures, which showed different degrees of differentiation to basal, squamous, or sebaceous cells. Basal cell neoplasms consisted entirely of solid sheets and nodules of deeply basophilic basal cells; adenomas were relatively well differentiated and had well-defined borders without invasion, whereas carcinomas showed greater cellular atypia and invasion of the dermis. Squamous cell papillomas were pedunculated skin masses consisting of multiple fingerlike projections composed of branching fibrous tissue cores covered by hyperplastic epithelium. Squamous cell carcinomas varied in morphology. Many carcinomas had the morphology typical of this neoplasm and consisted primarily of well-differentiated squamous cells, which often formed keratin pearls, with disorganized basal layers that extended narrow invasive cords of spindle-shaped cells into the dermis. At the other end of the morphologic spectrum were carcinomas that consisted mainly of small basophilic basal cells with low numbers of squamous cells and only an occasional keratin pearl. In four low dose and three high dose males and in one high dose female, the carcinomas metastasized to the lung and/or multiple organs. Sebaceous gland adenomas were well-demarcated nodules composed almost entirely of well-differentiated sebaceous cells. Acanthosis in exposed animals consisted of an increased number of cell layers in the epithelium, often accompanied by

TABLE 9. NUMBERS OF RATS WITH SELECTED SKIN LESIONS IN THE TWO-YEAR DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Site/Lesion	Male (mg/rat)			Female (mg/rat)		
	0	15	30	0	15	30
Skin, application site (b)						
Skin, scapula						
Acanthosis	0	**39	**40	4	**33	**42
Sebaceous gland hypertrophy	0	**28	**39	1	**20	**43
Basal cell adenoma	0	0	*4	0	0	0
Basal cell carcinoma	0	1	2	0	3	*4
Basal cell carcinoma (multiple)	0	0	1	0	0	0
Sebaceous gland adenoma	0	1	1	0	1	1
Squamous papilloma	0	3	*6	0	0	1
Squamous cell carcinoma	0	**10	**12	0	**8	**12
Squamous cell carcinoma (multiple)	0	**22	**24	0	**8	**22
Skin, back						
Acanthosis	0	*6	**8	1	4	**11
Sebaceous gland hypertrophy	0	4	**8	0	0	**15
Sebaceous gland adenoma	0	1	0	1	0	0
Squamous cell carcinoma	0	2	1	0	0	1
Skin, nonapplication site (c)						
Acanthosis	0	2	1	0	0	0
Sebaceous gland hypertrophy	0	1	1	0	0	0
Basal cell adenoma	1	0	0	1	1	0
Basal cell carcinoma	1	1	0	0	0	0
Trichoepithelioma	0	0	1	0	0	0

(a) Most dosed animals had more than one lesion; 50 animals were examined in each group.
(b) Skin, application site, includes skin from the interscapular region where chemical was applied (skin, scapula) and skin adjacent to site of application (skin, back).
(c) Skin, nonapplication site, is skin from areas distant from application site.
*$P<0.05$ vs. the vehicle controls
**$P<0.01$ vs. the vehicle controls

TABLE 10. SKIN TUMORS IN RATS IN THE TWO-YEAR DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

	Vehicle Control	15 mg/Rat	30 mg/Rat
MALE			
Application Site (Scapula or Back)			
Sebaceous Gland Adenoma			
Overall Rates	0/50 (0%)	2/50 (4%)	1/50 (2%)
Basal Cell Adenoma			
Overall Rates	0/50 (0%)	0/50 (0%)	4/50 (8%)
Terminal Rates	0/7 (0%)	0/8 (0%)	1/4 (25%)
Day of First Observation			668
Logistic Regression Tests	P=0.008	(b)	P=0.040
Basal Cell Carcinoma			
Overall Rates	0/50 (0%)	1/50 (2%)	3/50 (6%)
Terminal Rates	0/7 (0%)	0/8 (0%)	0/4 (0%)
Day of First Observation		642	595
Logistic Regression Tests	P=0.055	P=0.502	P=0.110
Basal Cell Adenoma or Basal Cell Carcinoma			
Overall Rates	0/50 (0%)	1/50 (2%)	6/50 (12%)
Terminal Rates	0/7 (0%)	0/8 (0%)	1/4 (25%)
Day of First Observation		642	595
Logistic Regression Tests	P=0.003	P=0.502	P=0.011
Squamous Cell Papilloma (c)			
Overall Rates	0/50 (0%)	3/50 (6%)	6/50 (12%)
Terminal Rates	0/7 (0%)	1/8 (13%)	0/4 (0%)
Day of First Observation		688	595
Logistic Regression Tests	P=0.006	P=0.159	P=0.015
Squamous Cell Carcinoma (d)			
Overall Rates	0/50 (0%)	33/50 (66%)	36/50 (72%)
Terminal Rates	0/7 (0%)	8/8 (100%)	4/4 (100%)
Day of First Observation		596	543
Logistic Regression Tests	P<0.001	P<0.001	P<0.001
Nonapplication Site			
Basal Cell Adenoma			
Overall Rates	1/50 (2%)	0/50 (0%)	0/50 (0%)
Basal Cell Carcinoma			
Overall Rates	1/50 (2%)	1/50 (2%)	0/50 (0%)
Trichoepithelioma			
Overall Rates	0/50 (0%)	0/50 (0%)	1/50 (2%)
Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma (e)			
Overall Rates	2/50 (4%)	1/50 (2%)	1/50 (2%)

TABLE 10. SKIN TUMORS IN RATS IN THE TWO-YEAR DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
FEMALE			
Application Site			
Basal Cell Carcinoma			
Overall Rates	0/50 (0%)	3/50 (6%)	4/50 (8%)
Terminal Rates	0/27 (0%)	2/23 (9%)	2/15 (13%)
Day of First Observation		739	654
Logistic Regression Tests	P=0.015	P=0.081	P=0.032
Sebaceous Gland Adenoma			
Overall Rates	1/50 (2%)	1/50 (2%)	1/50 (2%)
Squamous Cell Carcinoma (f)			
Overall Rates	0/50 (0%)	16/50 (32%)	(g) 34/50 (68%)
Terminal Rates	0/27 (0%)	14/23 (61%)	15/15 (100%)
Day of First Observation		625	601
Logistic Regression Tests	P<0.001	P<0.001	P<0.001
Nonapplication Site			
Basal Cell Adenoma			
Overall Rates	1/50 (2%)	1/50 (2%)	0/50 (0%)
Sebaceous Gland Adenoma, Basal Cell Adenoma, or Basal Cell Carcinoma (h)			
Overall Rates	1/50 (2%)	1/50 (2%)	0/50 (0%)

(a) For a complete explanation of the entries in this table, see Table A3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) No P value is reported because no tumors were observed in the 15 mg/rat and vehicle control groups.
(c) All squamous cell papillomas were observed in animals also bearing a squamous cell carcinoma.
(d) Historical incidence of squamous cell papillomas or carcinomas (combined) in untreated controls (mean ± SD): 31/1,596 (2% ± 2%)
(e) Historical incidence in untreated controls (mean ± SD): 30/1,596 (2% ± 2%)
(f) Historical incidence of squamous cell papillomas or carcinomas (combined) in untreated controls (mean ± SD): 7/1,643 (0.4% ± 0.8%)
(g) A squamous cell papilloma was observed in an animal also bearing a squamous cell carcinoma.
(h) Historical incidence in untreated controls (mean ± SD): 7/1,643 (0.4% ± 0.8%)

cellular atypia. Sebaceous gland hypertrophy was characterized by increased size of sebaceous glands, due primarily to the increased size of cells.

Neoplastic and nonneoplastic skin lesions occurred in some exposed animals at locations other than the site of application. This was attributed to the inadvertant spread of the study material from the application site.

Urinary Bladder: A single small papilloma of the transitional cell epithelium was present in each of 2/50 low dose female rats; the papillomas were not accompanied by hyperplasia of the urinary bladder transitional epithelium. The historical incidence of urinary bladder transitional cell neoplasms in untreated control female F344/N rats is 3/1,602 (0.2%). No more than one neoplasm has been observed in any control group. Hyperplasia of the transitional epithelium was seen in 1/50 low dose and 1/48 high dose female rats; no proliferative lesions were seen in the urinary bladder of vehicle control or exposed male rats.

SINGLE-ADMINISTRATION DERMAL STUDIES

All mice that received 5,487 mg/kg 4-vinyl-1-cyclohexene diepoxide by dermal application, 1/5 female mice that received 2,741 mg/kg, and 1/5 female mice that received 671.6 mg/kg died before the end of the studies (Table 11). Clinical signs included decreased activity, rapid respiration, and irritation of the skin at the dermal application site. No lesions were observed at necropsy.

FOURTEEN-DAY DERMAL STUDIES

All mice that received 37 or 43 mg/mouse died on the third day. Also, 3/5 male mice and 5/5 female mice that received 21 or 19 mg/mouse, respectively, died before the end of the studies (Table 12). Final mean body weights of exposed and vehicle control mice were generally similar. Compound-related clinical signs included weakness and decreased activity in the 43 and 37 mg/mouse groups and burrowing activity after dermal application in the 5 mg/mouse group of males. The relative liver weight for females that received 10 mg/mouse was significantly greater than that for vehicle controls (Table I5). Also, thymus weights were reduced at 5 and 10 mg/animal in females. Rough, thickened, scaly skin was observed at the site of application. Lesions in skin from the site of application were seen in 4/5 males and 4/5 females receiving 5 mg/mouse and in all mice receiving higher doses (except for the top dose groups, which died on day 3). These lesions included sebaceous gland hyperplasia and acanthosis, hyperkeratosis, and ulceration of the squamous epithelium (Table 13). One male receiving 21 mg/mouse had severe testicular degeneration.

TABLE 11. SURVIVAL OF MICE IN THE SINGLE-ADMINISTRATION DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Dose (mg/kg)	Survival	
	Male	Female (a)
338.3	5/5	5/5
671.6	5/5	(b) 4/5
1,378	5/5	5/5
2,741	5/5	(c) 4/5
5,487	(d) 0/5	(d) 0/5

(a) LD_{50} by probit analysis: 3,216 mg/kg (95% confidence interval 1,766-10,501 mg/kg)
(b) Day of death: 8
(c) Day of death: 2
(d) All deaths occurred within 8 hours of dosing.

TABLE 12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE FOURTEEN-DAY DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Dose (mg/mouse)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	5/5	23.4 ± 0.60	25.0 ± 0.55	+1.6 ± 0.24	
3	5/5	25.0 ± 0.55	26.4 ± 0.68	+1.4 ± 0.40	105.6
5	5/5	23.8 ± 0.49	24.8 ± 0.37	+1.0 ± 0.45	99.2
10	5/5	19.8 ± 0.49	25.2 ± 0.66	+5.4 ± 0.40	100.8
21	(d) 2/5	24.0 ± 0.32	24.5 ± 0.50	+0.0 ± 1.00	98.0
43	(e) 0/5	24.2 ± 0.49	(f)	(f)	(f)
FEMALE					
0	5/5	21.8 ± 0.50	23.2 ± 0.37	+1.4 ± 0.25	
2	5/5	21.2 ± 0.37	22.4 ± 0.68	+1.2 ± 0.37	96.6
5	5/5	20.8 ± 0.37	22.0 ± 0.63	+1.2 ± 0.37	94.8
10	5/5	21.2 ± 0.37	22.4 ± 0.24	+1.2 ± 0.37	96.6
19	(g) 0/5	21.0 ± 0.32	(f)	(f)	(f)
37	(e) 0/5	20.6 ± 0.40	(f)	(f)	(f)

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

TABLE 13. NUMBERS OF MICE WITH SELECTED SCAPULAR SKIN LESIONS IN THE FOURTEEN-DAY DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Lesion	Male (mg/mouse) 0	5	10	21	Female (mg/mouse) 0	5	10	19
Epidermal hyperplasia	0	*4	**5	3	0	*4	**5	*4
Acanthosis	0	0	0	1	0	0	0	1
Hyperkeratosis	0	*4	**5	3	0	3	**5	*4
Ulceration	0	1	0	2	0	0	0	0
Sebaceous gland hyperplasia	0	*4	2	2	0	2	3	2

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

THIRTEEN-WEEK DERMAL STUDIES

No compound-related deaths occurred (doses up to 10 mg/mouse) (Table 14). During weeks 3 and 4, one female in the 1.25 mg/mouse group had scabs and other dermal lesions that were related to a clipping injury. The final mean body weights of exposed and vehicle control mice were comparable. Increased relative liver and kidney weights were compound related (Table I6). Acanthosis of skin from the application site was seen in 8/10 males and 2/10 females that received 10 mg/mouse and 1/10 males that received 5 mg/mouse (Table 15). Hyperkeratosis of the stratified squamous epithelium was seen in skin from the application site of 8/10 males and 8/10 females that received 10 mg/mouse and 5/10 males and 6/10 females that received 5 mg/mouse.

TABLE 14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Dose (mg/mouse)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	10/10	21.8 ± 0.9	28.3 ± 0.5	+6.5 ± 1.0	
0.625	9/10	21.0 ± 0.8	28.0 ± 0.6	+6.9 ± 0.7	98.9
1.25	10/10	23.9 ± 0.6	29.2 ± 0.4	+5.3 ± 0.7	103.2
2.5	10/10	23.3 ± 0.7	27.6 ± 0.5	+4.3 ± 0.4	97.5
5	9/10	21.9 ± 0.8	27.8 ± 0.6	+5.4 ± 0.8	98.2
10	10/10	20.8 ± 0.6	27.4 ± 0.4	+6.6 ± 0.5	96.8
FEMALE					
0	10/10	17.6 ± 0.5	24.2 ± 0.5	+6.6 ± 0.4	
0.625	10/10	17.9 ± 0.4	23.6 ± 0.5	+5.7 ± 0.5	97.5
1.25	10/10	16.5 ± 0.3	24.5 ± 0.5	+8.0 ± 0.5	101.2
2.5	10/10	18.0 ± 0.4	23.4 ± 0.6	+5.4 ± 0.5	96.7
5	10/10	17.7 ± 0.6	24.2 ± 0.6	+6.5 ± 0.5	100.0
10	10/10	17.6 ± 0.4	23.3 ± 0.2	+5.7 ± 0.4	96.3

(a) Number surviving/number initially in the group; all deaths were judged to be accidental.
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean

TABLE 15. NUMBERS OF MICE WITH SELECTED SKIN LESIONS AT THE APPLICATION SITE IN THE THIRTEEN-WEEK DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Lesion	Male (mg/rat) 0	2.5	5	10	Female (mg/rat) 0	2.5	5	10
Acute to chronic inflammation	0	0	1	1	0	0	0	0
Hyperkeratosis	0	0	*5	**8	0	0	**6	**8
Parakeratosis	0	0	0	3	0	0	0	1
Acanthosis	0	0	1	**8	0	0	0	2
Necrotizing inflammation	0	0	0	1	0	0	0	0

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

Diffuse ovarian atrophy was observed in all females that received 10 mg/mouse and in 4/10 females that received 5 mg/mouse. Uterine atrophy was seen in 2/10 females that received 10 mg/mouse.

Dose Selection Rationale: Doses of 2.5 and 5 mg/mouse per day were initially selected for the 2-year studies, based on the results of the 13-week studies. Minimal skin lesions were observed in the 5 mg/mouse groups, whereas the 10 mg/mouse groups had similar skin lesions of greater severity and atrophy of the ovary in all females in the 10 mg/mouse group. A review of the literature on positive studies of 4-vinyl-1-cyclohexene diepoxide with other strains of mice indicated that doses used in those studies were higher than 5 mg/mouse; therefore, an additional group at 10 mg/mouse per day was added to replicate previous studies.

FIFTEEN-MONTH STUDIES

Uterine weight to body weight ratios for females that received 5 and 10 mg/mouse were significantly lower than that for vehicle controls (Table J3). Compound-related nonneoplastic skin lesions included sebaceous gland hyperplasia/hypertrophy, acanthosis, and hyperkeratosis (Table 16). Squamous cell papillomas and carcinomas were seen in mice that received 5 or 10 mg/mouse. One vehicle control and all exposed female mice had atrophy of the ovarian tissue. Tubular hyperplasia of the ovarian surface epithelium was seen in 8/10 females that received 5 mg/mouse and 9/9 females that received 10 mg/mouse. Two of nine females that received 10 mg/mouse had ovarian granulosa cell tumors, and 1/9 females that received 10 mg/mouse had an ovarian papillary cystadenoma.

TWO-YEAR STUDIES

Body Weights and Clinical Signs

Mean body weights of high dose male mice were 5%-8% lower than those of vehicle controls from week 29 to week 53 and were 10%-18% lower thereafter (Table 17 and Figure 3). Mean body weights of mid dose male mice were 9%-12% lower than those of vehicle controls from week 89 to the end of the study. Mean body weights of high dose female mice were 7%-9% lower than those of vehicle controls from week 77 to week 84 (when survivors were killed). Mean body weights of mid dose female mice were 11%-12% lower than those of vehicle controls from week 101 to week 104. Crusts, scales, and ulcers were seen at the site of application.

TABLE 16. NUMBERS OF MICE WITH SELECTED SKIN LESIONS IN THE FIFTEEN-MONTH DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Lesion	Male (mg/mouse)				Female (mg/mouse)			
	0	2.5	5	10	0	2.5	5	10
Acanthosis	0	2	**10	**8	0	2	**9	**10
Hyperkeratosis	0	0	0	2	0	1	0	4
Sebaceous gland hyperplasia/hypertrophy	0	4	**10	**7	0	*5	**9	**10
Sebaceous gland adenoma	0	0	0	0	0	1	1	1
Keratoacanthoma	0	0	0	1	0	0	0	0
Benign basosquamous tumor	0	0	0	1	0	0	0	0
Squamous papilloma	0	0	1	2	0	0	1	1
Squamous cell carcinoma	0	0	2	**8	0	0	2	*5

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

TABLE 17. MEAN BODY WEIGHTS OF MICE IN THE TWO-YEAR DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Week on Study	Vehicle Control		2.5 mg/Mouse			5 mg/Mouse			10 mg/Mouse		
	Av. Wt. (grams)	Number Weighed	Av. Wt. (grams)	Wt. (percent of veh. controls)	Number Weighed	Av. Wt. (grams)	Wt. (percent of veh. controls)	Number Weighed	Av. Wt. (grams)	Wt. (percent of veh. controls)	Number Weighed
MALE											
1	26.1	60	26.9	103.1	60	25.2	96.6	60	26.0	99.6	60
2	27.2	58	27.8	102.2	59	26.9	98.9	56	27.2	100.0	(a) 59
3	28.0	58	27.8	99.3	59	27.5	98.2	56	27.1	96.8	60
5	27.3	58	28.5	104.4	58	27.7	101.5	55	27.6	101.1	59
6	28.4	58	28.6	100.7	57	27.4	96.5	54	26.9	94.7	59
7	29.4	58	29.1	99.0	57	28.7	97.6	54	27.9	94.9	(a) 58
9	29.4	58	29.5	100.3	57	28.2	95.9	54	28.1	95.6	59
10	29.1	58	29.2	100.3	57	28.9	99.3	54	28.8	99.0	59
11	29.9	58	29.5	98.7	57	28.6	95.7	54	27.8	93.0	59
12	30.3	58	30.3	100.0	57	29.0	95.7	54	28.8	95.0	59
13	30.4	58	29.9	98.4	57	29.3	96.4	54	28.8	94.7	59
14	29.9	58	30.4	101.7	57	29.7	99.3	54	29.2	97.7	59
18	32.2	58	32.3	100.3	57	31.1	96.6	54	30.5	94.7	59
22	34.4	58	33.9	98.5	57	32.7	95.1	54	32.1	93.3	59
25	33.8	58	34.3	101.5	57	33.0	97.6	54	32.7	96.7	59
29	35.1	58	35.5	101.1	57	34.0	96.9	54	33.4	95.2	59
33	36.2	57	36.6	101.1	57	35.3	97.5	53	34.2	94.5	57
37	36.9	57	37.3	101.1	57	35.9	97.3	52	34.8	94.3	57
41	38.6	57	38.8	100.5	57	37.2	96.4	52	35.7	92.5	57
45	38.3	57	38.9	101.6	57	37.1	96.9	52	36.2	94.5	57
49	39.9	57	40.1	100.5	57	38.2	95.7	52	36.7	92.0	56
53	40.6	57	41.0	101.0	57	39.7	97.8	52	37.4	92.1	56
57	41.5	57	41.1	99.0	56	40.0	96.4	52	37.3	89.9	54
61	40.6	57	40.9	100.7	56	41.0	101.0	51	36.5	89.9	52
65	41.5	56	40.2	96.9	56	40.9	98.6	49	36.0	86.7	50
69	41.2	(b) 45	40.2	97.6	(b) 45	40.1	97.3	(b) 39	34.9	84.7	(b) 33
73	41.6	45	41.3	99.3	(a) 43	40.0	96.2	(a) 38	35.3	84.9	(a) 22
77	41.5	45	40.7	98.1	43	39.6	95.4	36	34.0	81.9	15
81	41.5	45	40.9	98.6	43	39.0	94.0	35	34.2	82.4	10
84	41.4	44	41.0	99.0	43	38.0	91.8	33			
89	42.1	41	42.5	101.0	41	38.1	90.5	29			
93	40.9	38	41.0	100.2	41	37.2	91.0	22			
97	40.0	38	40.5	101.3	38	36.1	90.3	20			
101	41.3	38	41.9	101.5	36	37.0	89.6	10			
104	39.8	38	41.4	104.0	35	35.0	87.9	5			
FEMALE											
1	18.8	60	19.3	102.7	60	18.3	97.3	60	18.7	99.5	60
2	21.2	60	21.6	101.9	60	21.3	100.5	58	21.5	101.4	59
3	21.9	60	22.1	100.9	60	21.6	98.6	58	21.8	99.5	59
5	23.8	60	23.6	99.2	59	23.1	97.1	58	23.3	97.9	59
6	23.1	60	23.1	100.0	59	23.2	100.4	58	22.9	99.1	59
7	24.3	60	24.2	99.6	59	23.8	97.9	57	23.5	96.7	(a) 58
9	24.6	60	24.4	99.2	59	24.3	98.8	57	24.6	100.0	59
10	25.6	59	25.4	99.2	59	25.2	98.4	57	24.8	96.9	59
11	25.4	59	25.0	98.4	59	24.7	97.2	57	24.7	97.2	59
12	26.6	59	26.4	99.2	59	25.7	96.6	57	25.8	97.0	59
13	26.3	59	26.4	100.4	59	25.7	97.7	57	26.0	98.9	59
14	26.8	59	26.4	98.5	59	26.2	97.8	57	26.7	99.6	59
18	27.8	59	27.7	99.6	59	26.7	96.0	57	26.7	96.0	59
22	28.3	59	28.3	100.0	59	27.9	98.6	57	28.5	100.7	59
25	29.3	59	28.8	98.3	59	28.8	98.3	57	29.0	99.0	58
29	29.7	59	29.8	100.3	58	29.1	98.0	57	29.2	98.3	57
33	31.3	59	31.5	100.6	57	30.3	96.8	57	30.8	98.4	57
37	32.1	59	32.3	100.6	57	31.1	96.9	57	31.5	98.1	57
41	34.4	59	34.3	99.7	57	32.9	95.6	57	33.5	97.4	57
45	34.8	59	35.1	100.9	57	34.0	97.7	57	33.8	97.1	57
49	35.3	59	36.3	102.8	57	35.5	100.6	57	35.7	101.1	57
53	36.1	59	37.7	104.4	57	36.9	102.2	57	36.9	102.2	57
57	38.5	58	37.6	97.7	57	38.7	100.5	57	38.0	98.7	55
61	36.8	58	37.6	102.2	56	38.9	105.7	56	35.4	96.2	54
65	36.1	57	37.2	103.0	55	38.4	106.4	55	36.5	101.1	51
69	37.0	(b) 45	38.5	104.1	(b) 42	40.0	108.1	(b) 43	36.5	98.6	(b) 38
73	38.2	(a) 42	39.7	103.9	(a) 42	41.0	107.3	41	35.8	93.7	(a) 32
77	37.8	43	40.6	107.4	42	40.1	106.1	41	34.6	91.5	18
81	39.3	43	41.1	104.6	40	38.8	98.7	41	36.4	92.6	18
84	39.4	42	42.5	107.9	39	38.8	98.5	35	35.7	90.6	12
89	40.1	40	42.7	106.5	39	38.7	96.5	32			
93	38.3	40	39.8	103.9	38	36.7	95.8	32			
97	37.1	39	39.0	105.1	38	34.9	94.1	29			
101	39.6	35	41.2	104.0	38	35.0	88.4	23			
104	40.3	30	41.2	102.2	31	35.3	87.6	19			

(a) The number of animals weighed was lower than the number of animals surviving.
(b) Interim kill occurred.

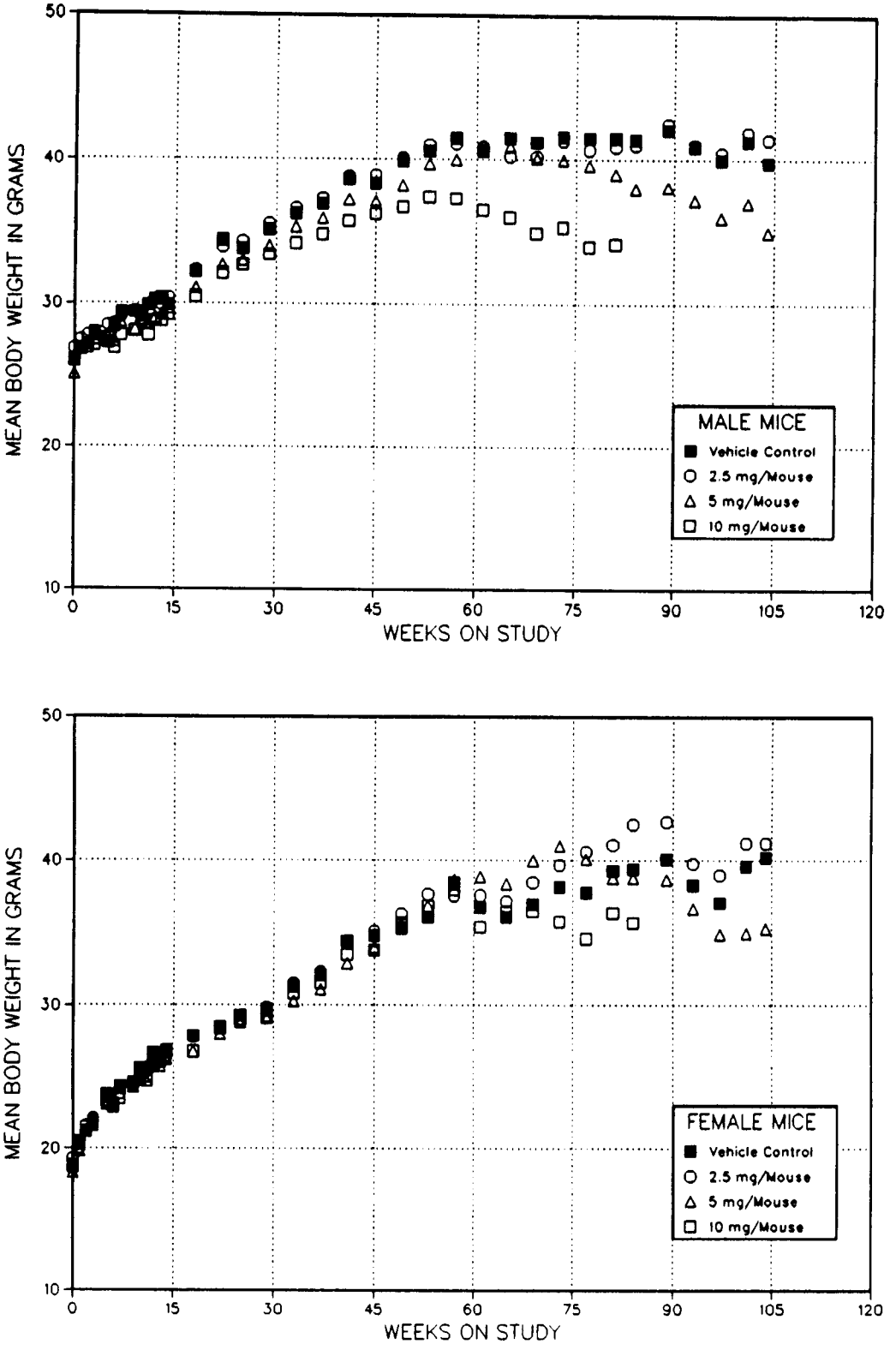


FIGURE 3. GROWTH CURVES FOR MICE ADMINISTERED 4-VINYL-1-CYCLOHEXENE DIEPOXIDE IN ACETONE BY DERMAL APPLICATION FOR TWO YEARS

Survival

Estimates of the probabilities of survival for male and female mice administered 4-vinyl-1-cyclohexene diepoxide at the doses used in these studies and for vehicle controls are shown in Table 18 and in the Kaplan and Meier curves in Figure 4. Survival of both the mid (after day 543) and the high (after day 451) dose groups of male mice was significantly lower than that of the vehicle controls. All surviving females in the 10 mg/mouse group were killed at week 85. Survival of both the mid (after day 666) and the high (after day 474) dose groups of female mice was significantly lower than that of the vehicle controls.

Pathology and Statistical Analyses of Results

This section describes the statistically significant or biologically noteworthy changes in the incidences of mice with neoplastic or nonneoplastic lesions of the skin, ovary, lung, spleen, and epididymis.

Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are presented in Appendixes C and D for male and female mice, respectively.

TABLE 18. SURVIVAL OF MICE IN THE TWO-YEAR DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
MALE (a)				
Animals initially in study	50	50	50	50
Natural deaths	6	11	17	20
Moribund kills	3	4	27	30
Animals surviving until study termination	38	35	4	0
Killed accidentally	3	0	2	0
Survival P values (b)	<0.001	0.306	<0.001	<0.001
FEMALE (a)				
Animals initially in study	50	50	50	50
Natural deaths	7	8	13	9
Moribund kills	10	10	(c) 23	29
Animals surviving until study termination	30	31	15	(d) 12
Killed accidentally	3	1	0	0
Survival P values (b)	<0.001	0.990	0.001	<0.001

(a) First day of termination period: 729
(b) 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.
(c) One moribund animal was killed during the termination period and was combined, for statistical purposes, with those killed at termination.
(d) The number of mice alive at week 85 when all survivors of this group were killed

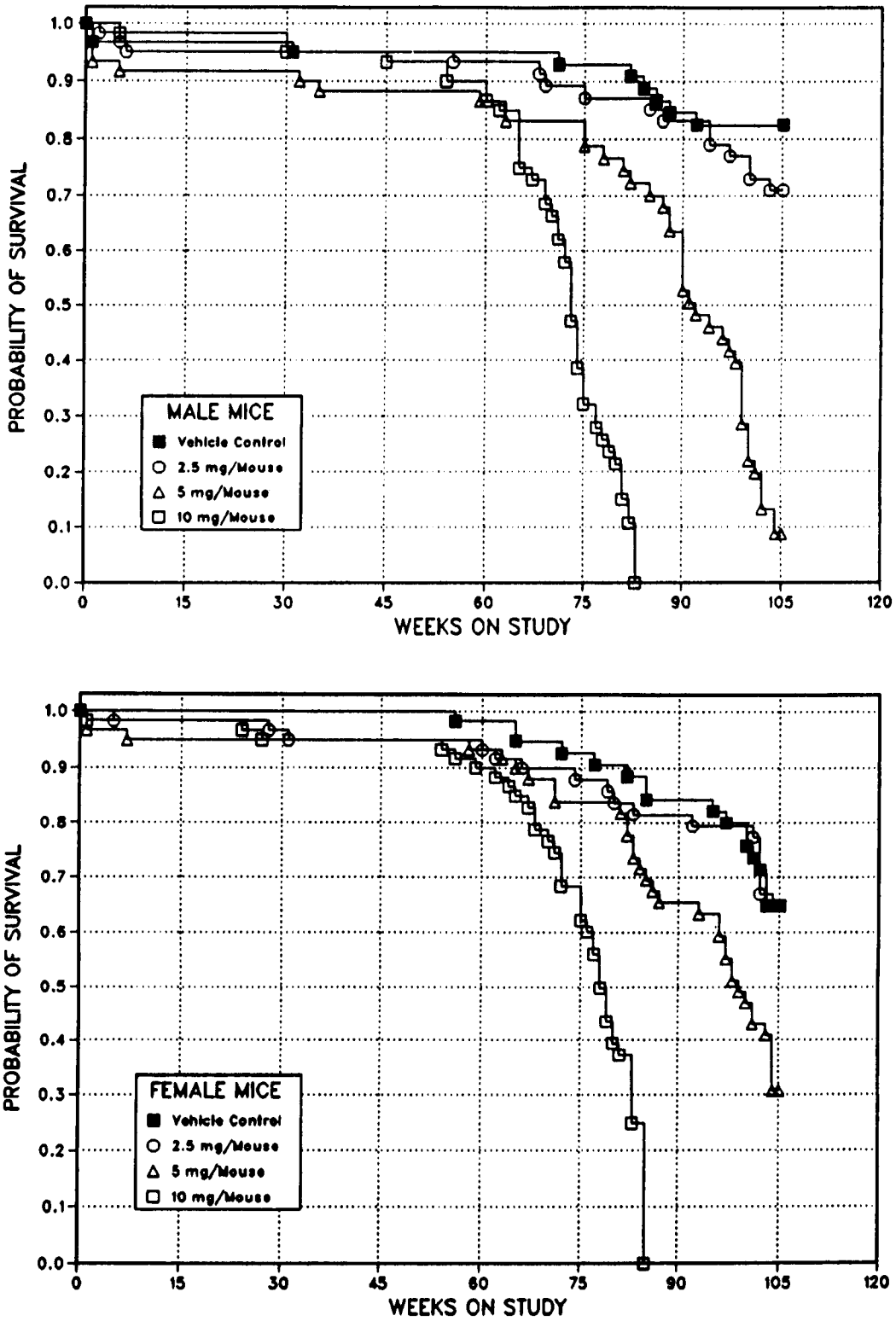


FIGURE 4. KAPLAN-MEIER SURVIVAL CURVES FOR MICE ADMINISTERED 4-VINYL-1-CYCLOHEXENE DIEPOXIDE IN ACETONE BY DERMAL APPLICATION FOR TWO YEARS

Skin: The incidences of squamous cell carcinomas, acanthosis, hyperkeratosis, and necrotizing inflammation of the skin were increased in exposed male and female mice (Table 19). The incidences of squamous cell carcinomas in exposed mice were significantly greater than those in vehicle controls (Table 20). Most of the squamous cell carcinomas had the morphology typical of this neoplasm and consisted of a mixture of basal and squamous cells that formed keratin pearls and invaded the underlying dermis and subcutis. More malignant carcinomas frequently consisted of highly anaplastic cells, some of which assumed a spindle shape resembling sarcoma cells. In many animals, carcinomas metastasized to lymph nodes or visceral organs (male: vehicle control, 0/50; low dose, 2/50; mid dose, 17/50; high dose, 24/50; female: 0/50; 1/50; 13/50; 20/50).

Acanthosis consisted of an increase in the number of epithelial cell layers in the skin, whereas hyperkeratosis was an increase in the thickness of the keratinized layer on the skin surface. Necrotizing inflammation was characterized by ulceration or necrosis of the epithelium or accumulation of inflammatory cells and necrotic epithelial cells in the skin. The high dose group of female mice was killed at week 85 because of ulcerated tumor sites. Squamous cell carcinomas and nonneoplastic changes also occurred in skin away from the site of application of the study material. This was attributed to inadvertent spread of the study material away from the

TABLE 19. NUMBERS OF MICE WITH SELECTED LESIONS OF THE SKIN IN THE TWO-YEAR DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Site/Lesion	Male (mg/mouse)				Female (mg/mouse)			
	0	2.5	5	10	0	2.5	5	10 (b)
Skin, application site (c)								
Skin, scapula								
Acanthosis	1	**35	**38	**35	4	**31	**41	**36
Hyperkeratosis	1	**12	**14	**21	1	**27	**29	**20
Necrotizing inflammation	1	4	**12	**15	2	5	**15	**16
Malignant basosquamous tumor	0	2	0	3	0	0	1	1
Basal cell carcinoma	0	0	1	0	0	0	0	0
Squamous cell carcinoma	0	**10	**27	**37	0	*5	**14	**31
Squamous cell carcinoma (multiple)	0	2	**12	*5	0	1	**23	**10
Skin, back								
Acanthosis	0	*6	*6	2	1	0	5	4
Hyperkeratosis	0	1	4	4	0	1	4	2
Necrotizing inflammation	0	0	0	1	0	0	*5	1
Squamous cell carcinoma	0	4	0	0	0	1	3	0
Squamous cell carcinoma (multiple)	0	0	0	0	0	0	1	0
Skin, nonapplication site (d)								
Acanthosis	0	*5	*6	*5	4	0	5	4
Hyperkeratosis	0	1	2	0	1	0	5	2
Necrotizing inflammation	0	0	*6	1	1	0	6	6
Squamous cell carcinoma	0	1	2	3	0	0	3	2
Squamous cell carcinoma (multiple)	0	0	1	0	0	0	0	1

(a) Fifty animals were examined in each group.
(b) Survivors were killed during week 85.
(c) Skin, application site, includes skin from the interscapular region where chemical was applied (skin, scapula) and skin adjacent to site of application (skin, back).
(d) Skin, nonapplication site, is skin from areas distant from application site.
*P<0.05 vs. vehicle controls
**P<0.01 vs. vehicle controls

TABLE 20. SKIN TUMORS IN MICE IN THE TWO-YEAR DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
MALE				
Application Site (Scapula or Back)				
Squamous Cell Carcinoma (b)				
Overall Rates	0/50 (0%)	14/50 (28%)	39/50 (78%)	42/50 (84%)
Terminal Rates	0/38 (0%)	10/35 (29%)	4/4 (100%)	0/0
Day of First Observation		525	411	376
Logistic Regression Tests	P<0.001	P<0.001	P<0.001	P<0.001
FEMALE				
Application Site (Scapula or Back)				
Squamous Cell Carcinoma (c)				
Overall Rates	0/50 (0%)	6/50 (12%)	37/50 (74%)	41/50 (82%)
Terminal Rates	0/30 (0%)	3/31 (10%)	15/15 (100%)	0/0
Day of First Observation		642	402	376
Logistic Regression Tests	P<0.001	P=0.016	P<0.001	P<0.001

(a) For a complete explanation of the entries in this table, see Table C3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Historical incidence of papillomas or carcinomas (combined) in dermal studies using acetone as a vehicle: 1/100 (1%); historical incidence in untreated controls (mean ± SD): 9/1,692 (0.5% ± 1%)
(c) Historical incidence of papillomas or carcinomas (combined) in dermal studies using acetone as a vehicle: 0/98; historical incidence in untreated controls (mean ± SD): 4/1,689 (0.2% ± 0.8%)

application site. Some carcinomas in the skin distant from the application site, however, appeared to represent metastases to subcutaneous lymph nodes from neoplasms at the application site.

Ovary: Follicular atrophy and tubular hyperplasia were observed at increased (P<0.001) incidences in exposed mice (atrophy: vehicle control, 12/50; low dose, 43/49; mid dose, 42/49; high dose, 47/50; tubular hyperplasia: 5/50; 35/49; 38/49; 34/50).

Benign or malignant granulosa cell tumors (combined) and benign mixed tumors occurred at significantly greater incidences in mid and high dose females than in vehicle controls (Table 21). The historical incidence of granulosa cell tumors in acetone vehicle control $B6C3F_1$ mice in dermal studies is 1%. Granulosa cell tumors consisted of nests of densely packed oval-to-angular cells with oval nuclei and poorly defined cytoplasmic borders mixed with a thin fibrous stroma and occasional fluid-filled spaces. A few of the neoplasms metastasized to the lungs. The benign mixed tumors were discrete masses equal to or greater in size than the ovary and consisted of epithelial-lined tubular structures, some of which were continuous with the surface epithelium, mixed with ovarian stroma and granulosa and luteal cells. In some benign mixed tumors, the tubules extended into the tissue adjacent to the ovary. Ovarian atrophy was characterized by a complete absence of follicles and corpora lutea, whereas tubular hyperplasia consisted of multiple epithelial-lined tubular structures extending from the surface epithelium into the interior of the ovary. There was a morphologic continuum from tubular hyperplasia to benign mixed tumor. A benign mixed tumor was diagnosed when the proliferating tubules had replaced the ovarian tissues and/or had increased the ovarian size; otherwise, the lesion was termed tubular hyperplasia.

TABLE 21. OVARIAN TUMORS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse (b)
Luteoma				
Overall Rates	1/50 (2%)	0/49 (0%)	0/49 (0%)	0/50 (0%)
Benign Mixed Tumor				
Overall Rates	0/50 (0%)	0/49 (0%)	11/49 (22%)	6/50 (12%)
Terminal Rates	0/30 (0%)	0/31 (0%)	5/14 (36%)	0/0
Day of First Observation			497	474
Logistic Regression Tests	P<0.001	(c)	P<0.001	P=0.024
Granulosa Cell Tumor				
Overall Rates	0/50 (0%)	0/49 (0%)	5/49 (10%)	10/50 (20%)
Terminal Rates	0/30 (0%)	0/31 (0%)	2/14 (14%)	0/0
Day of First Observation			679	388
Logistic Regression Tests	P<0.001	(c)	P=0.013	P=0.006
Malignant Granulosa Cell Tumor				
Overall Rates	0/50 (0%)	0/49 (0%)	2/49 (4%)	2/50 (4%)
Granulosa Cell Tumor or Malignant Granulosa Cell Tumor				
Overall Rates	0/50 (0%)	0/49 (0%)	7/49 (14%)	12/50 (24%)
Terminal Rates	0/30 (0%)	0/31 (0%)	2/14 (14%)	0/0
Day of First Observation			579	388
Logistic Regression Tests	P<0.001	(c)	P=0.004	P=0.001
Luteoma, Granulosa Cell Tumor, or Benign Mixed Tumor				
Overall Rates	1/50 (2%)	0/49 (0%)	15/49 (31%)	16/50 (32%)
Terminal Rates	1/30 (3%)	0/31 (0%)	7/14 (50%)	0/0
Day of First Observation	729		497	388
Logistic Regression Tests	P<0.001	P=0.493N	P<0.001	P<0.001
Luteoma, Granulosa Cell Tumor, Benign Mixed Tumor, or Malignant Granulosa Cell Tumor (d)				
Overall Rates	1/50 (2%)	0/49 (0%)	17/49 (35%)	18/50 (36%)
Terminal Rates	1/30 (3%)	0/31 (0%)	7/14 (50%)	0/0
Day of First Observation	729		497	388
Logistic Regression Tests	P<0.001	P=0.493N	P<0.001	P<0.001

(a) For a complete explanation of the entries in this table, see Table D3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Survivors were killed during week 85.
(c) No P value is reported because no tumors were observed in the 2.5 mg/mouse and vehicle control groups.
(d) Historical incidence in dermal studies using acetone as a vehicle (mean): 1/97 (1%); historical incidence in untreated controls (mean ± SD): 16/1,577 (1% ± 2%)

Lung: The incidence of alveolar/bronchiolar adenomas or carcinomas (combined) in mid dose female mice was significantly greater than that in vehicle controls (Table 22).

Spleen: Hematopoietic cell proliferation was observed at increased ($P<0.01$) incidences in exposed mice (male: vehicle control, 2/49; low dose, 7/50; mid dose, 31/50; high dose, 39/50; female: 3/50; 7/50; 28/50; 30/50). The change was due primarily to hyperplasia of the myeloid elements and was considered a response to necrotizing inflammation and neoplasms of the skin.

Epididymis: Subacute inflammation was observed at increased incidences in mid ($P<0.05$) and high ($P<0.01$) dose male mice (vehicle control, 0/50; low dose, 0/50; mid dose, 6/50; high dose, 13/49).

TABLE 22. LUNG LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse (b)
Alveolar Epithelial Hyperplasia				
Overall Rates	1/50 (2%)	1/50 (2%)	0/50 (0%)	1/50 (2%)
Alveolar/Bronchiolar Adenoma				
Overall Rates	3/50 (6%)	5/50 (10%)	8/50 (16%)	6/50 (12%)
Alveolar/Bronchiolar Carcinoma				
Overall Rates	1/50 (2%)	4/50 (8%)	3/50 (6%)	1/50 (2%)
Alveolar/Bronchiolar Adenoma or Carcinoma (c)				
Overall Rates	4/50 (8%)	9/50 (18%)	11/50 (22%)	7/50 (14%)
Terminal Rates	3/30 (10%)	7/31 (23%)	4/15 (27%)	0/0
Day of First Observation	719	709	495	444
Logistic Regression Tests	P=0.033	P=0.114	P=0.032	P=0.075

(a) For a complete explanation of the entries in this table, see Table D3 (footnotes); the statistical analyses used are discussed in Section II (Statistical Methods).
(b) Survivors were killed during week 85.
(c) Historical incidence in dermal studies using acetone as a vehicle (mean): 3/98 (3%); historical incidence in untreated controls (mean ± SD): 107/1,676 (6% ± 4%)

4-Vinyl-1-cyclohexene diepoxide was mutagenic in *Salmonella typhimurium* strains TA98, TA100, and TA1535 with and without exogenous metabolic activation; the compound was equivocally mutagenic in strain TA1537 without S9 but gave a positive response in the presence of activation. 4-Vinyl-1-cyclohexene diepoxide induced resistance to trifluorothymidine in mouse L5178Y/TK cells without exogenous metabolic activation; it was not tested with activation. When tested for chromosomal effects in Chinese hamster ovary cells, 4-vinyl-1-cyclohexene diepoxide induced sister chromatid exchanges and chromosomal aberrations in the presence and absence of exogenous metabolic activation. The experimental procedures and results are presented in Appendix L.

IV. DISCUSSION AND CONCLUSIONS

Toxicity of 4-Vinyl-1-cyclohexene Diepoxide
Carcinogenicity of 4-Vinyl-1-cyclohexene Diepoxide
Possible Mechanisms of 4-Vinyl-1-cyclohexene Diepoxide-Induced Carcinogenicity
Genetic Mechanisms
Nongenetic Mechanisms
Audit
Conclusions

IV. DISCUSSION AND CONCLUSIONS

Toxicity of 4-Vinyl-1-cyclohexene Diepoxide

4-Vinyl-1-cyclohexene diepoxide is used as a chemical intermediate and as a reactive diluent for diepoxides and epoxy resins. Short-term toxicology studies were conducted by the gavage and dermal routes of exposure in F344/N rats and B6C3F$_1$ mice of each sex. The carcinogenesis studies were performed by the dermal route only, and thus the dermal studies are the primary focus of this Technical Report.

In the short-term dermal studies, compound-related skin lesions included redness, scabs, and ulcers at the application site and diffuse hyperplasia of the sebaceous gland and/or acanthosis and hyperkeratosis of the stratified squamous epithelium. Weil et al. (1963) studied 60 commercially used epoxy compounds, including 4-vinyl-1-cyclohexene diepoxide, for potential acute toxicity. Twenty-eight of those chemicals were evaluated in single-dose oral LD_{50} studies in rats, in single-dose dermal LD_{50} studies in rabbits, and in skin irritation and corneal injury studies in rabbits; no consistent correlations with chemical structures were found. 4-Vinyl-1-cyclohexene diepoxide was found to be an irritant to skin and eyes. The skin lesions and clinical signs of toxicity observed in the current short-term dermal toxicity studies corroborate findings of the Weil et al. studies with respect to the irritant properties of this chemical. This corroboration is further supported by the differences in toxicity seen in target organs for oral and dermal routes of exposure in the current studies. Compound-related inflammation of the stomach mucosal layer in the oral studies (Appendix H) and of skin in the dermal studies in rats and mice suggests that 4-vinyl-1-cyclohexene diepoxide is a direct irritant at the site of contact.

Although skin was the target organ of toxicity by the dermal route in both rats and mice, compound-related ovarian atrophy was observed only in mice by the dermal and oral routes of exposure. This suggests a species difference in the systemic toxicity of 4-vinyl-1-cyclohexene diepoxide when administered by dermal application. Earlier, Kodama et al. (1961) reported that intramuscular injections of 4-vinyl-1-cyclohexene diepoxide to Long-Evans male rats decreased the leukocyte count by 60%, decreased the number of nucleated cells in the femur marrow, and increased the ratio of myeloid to erythroid cells. In the current studies, 4-vinyl-1-cyclohexene diepoxide administered by gavage or dermal application did not have any direct effect on the hematopoietic system in rats. In contrast to the current studies, the Kodama et al. study used a single dose in a different strain of rats, resulting in a 20% reduction in body weight, which could have affected the hematopoietic system.

In the 2-year studies in rats, the survival rate of the high dose females was reduced compared with that of vehicle controls. The survival rates for male rats at the end of the study were low in all groups, including vehicle controls. There is no explanation for the low survival of male vehicle control rats. In the 2-year studies in mice, survival rates of mid and high dose groups were lower for both males and females. The lower survival rates seen in exposed groups were likely due to the high incidences of neoplasms observed in those animals. The incidences of squamous cell neoplasms of the skin in exposed rats ranged from 32% to 72% and in mice from 12% to 84%. None were seen in the vehicle controls.

Carcinogenicity of 4-Vinyl-1-cyclohexene Diepoxide

4-Vinyl-1-cyclohexene diepoxide is carcinogenic to skin at the site of application in both male and female rats and mice. Although the neoplasms were diagnosed according to the predominant cell type present, all were considered to originate primarily from the basal cells of the skin and adnexal structures, showing different degrees of differentiation to basal, squamous, or sebaceous cells. In both rats and mice, the predominant skin neoplasms seen were squamous cell carcinomas. However, basal cell adenomas and/or carcinomas were observed more frequently in rats (14 animals) than in mice (1 animal). According to Yuspa (1986), rats are more prone to develop basal cell neoplasms of the skin than are mice, and the current studies show that the predominant type of skin neoplasm related to chemical exposure is squamous cell carcinoma. In the current studies, the apparent latent period for development of these neoplasms was

longer for rats than for mice and shorter at higher doses than at lower doses. By the end of the 2-year studies, the mid and high dose groups of mice and both dosed groups of rats had skin lesions that had progressed predominantly to squamous cell carcinomas. Skin neoplasms were observed in all dosed groups of rats and mice, and the numbers of squamous cell carcinomas in both dosed groups of male rats and in the mid and high dose groups of mice were similar. Female rats showed a linear dose response. A number of studies have shown that 4-vinyl-1-cyclohexene diepoxide is a skin carcinogen in male mice (Hendry et al., 1951; Kotin and Falk, 1963; Van Duuren et al., 1963; Van Duuren and Goldschmidt, 1966; Van Duuren, 1969). None of those dermal carcinogenicity studies used male or female rats or female mice as study animals. The current studies confirm the previous results in male mice and show that 4-vinyl-1-cyclohexene diepoxide is a potent dermal carcinogen in both rats and mice of either sex.

Benign and malignant neoplasms of the ovary occurred in mid and high dose female mice. A few of these neoplasms were malignant and metastasized to the lungs. In the 15-month evaluation of female mice, tubular hyperplasia of the ovarian surface epithelium was seen in most of the animals at 5 or 10 mg/mouse but not at 2.5 mg/mouse. Two of nine animals in the high dose group and one animal in the mid dose group had granulosa cell tumors of the ovary. At the end of the study, the incidences of these neoplasms were similar in mid and high dose groups, and no ovarian neoplasms were seen in the 2.5 mg/mouse group. There was a morphologic continuum from tubular hyperplasia to benign mixed tumors in mice. No such neoplasms were observed in female rats. The occurrence of these neoplasms is uncommon in rodent chemical carcinogenicity studies. Of nearly 350 chemicals studied by the National Toxicology Program (NTP), 7 (2%) have been shown to induce ovarian neoplasms in female mice (Maronpot, 1987; Huff et al., 1989; NTP, 1989a; Table 23). There appears to be no clear structure-activity relationship among these chemicals. The exception is 4-vinylcyclohexene, which is a structural analog to and the starting material for production of 4-vinyl-1-cyclohexene diepoxide. 4-Vinylcyclohexene toxicology and carcinogenicity studies were performed by the NTP in rats and mice of each sex by the gavage route of administration (NTP, 1986a). The chemical was administered at doses of 200 or 400 mg/kg for 103 weeks. There was clear evidence of carcinogenicity for female mice, as shown by markedly increased incidences of benign and malignant ovarian granulosa cell tumors at both doses. The studies in male and female rats and male mice were considered inadequate studies of carcinogenicity because of extensive and early deaths at the high dose or at both doses. Results from the current studies suggest that the carcinogenic activity seen with 4-vinylcyclohexene may have been due to the metabolite(s) of 4-vinyl-1-cyclohexene.

The incidence of alveolar/bronchiolar adenomas or carcinomas in mid dose female mice was 22%, compared with 14% in the high dose group and 8% in vehicle controls. The historical incidence of these neoplasms in untreated control female $B6C3F_1$ mice is 6%. The high mortality and early termination of the high dose group may have been responsible for the lower incidence in the high dose group, since animals were not at risk long enough for these neoplasms to develop. Thus, it was considered that these neoplasms may have been related to chemical administration.

Possible Mechanisms of 4-Vinyl-1-cyclohexene Diepoxide-Induced Carcinogenicity

Chemical carcinogens have been divided into three classes: genotoxic carcinogens (e.g., alkylating agents, polycyclic aromatic hydrocarbons, nitrosamines), nongenotoxic carcinogens (e.g., promoters, cytotoxic agents, immunosuppressor agents, solid state agents), and unclassified carcinogens that do not fall exactly into one of the above two categories (e.g., chemicals causing peroxisome proliferation) (Williams and Weisburger, 1986). It is likely that both genetic and nongenetic mechanisms are involved in the carcinogenic effects seen in these studies. 4-Vinyl-1-cyclohexene diepoxide could function as the ultimate carcinogen by initiating neoplasm formation that could be promoted by suppression of immune surveillance or by gonadotropin or by a combination of both. This assumption is based

TABLE 23. RESULTS AND STATUS INFORMATION FOR NTP CHEMICALS HAVING OVARIAN TOXICITY (a)

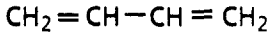
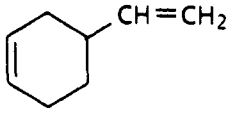
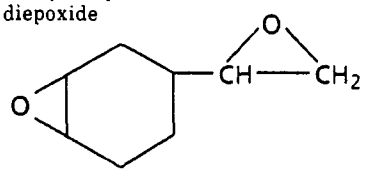
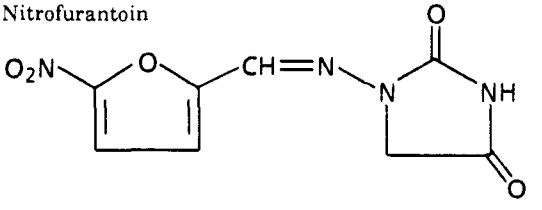
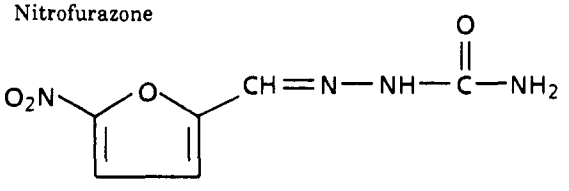
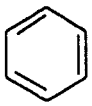
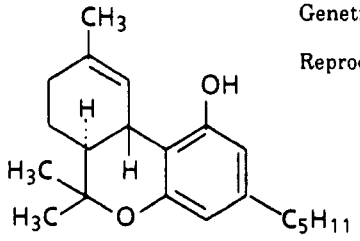
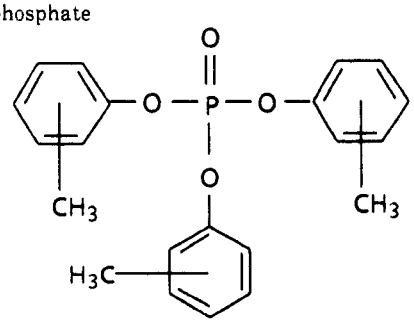
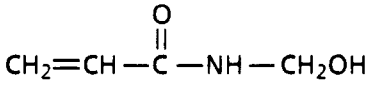
Chemical/Structure	Results/Status of Test	
1,3-Butadiene 	Sites of carcinogenicity NTP TR 288 (NTP, 1984)	Male mouse--heart, lymphomas, lung, stomach; female mouse--heart, lymphomas, lung, stomach, mammary gland, ovary
	Pharmacokinetics	Ongoing
	Genetic toxicology	SA: selected ML: – DL: – CY: on test
	Reproductive toxicology	Developmental toxicity in mice
4-Vinylcyclohexene 	Sites of carcinogenicity NTP TR 303 (NTP, 1986a)	Male rat, female rat, male mouse--inadequate studies; female mouse--ovary
	Chemical disposition	Ongoing
	Genetic toxicology	SA: – ML: + CY: +/+
	Reproductive toxicology	Continuous breeding: on test
4-Vinyl-1-cyclohexene diepoxide 	Sites of carcinogenicity NTP TR 362	Male rat--skin; female rat--skin; male mouse--skin; female mouse--skin, ovary
	Chemical disposition	Ongoing
	Immunotoxicity	+
	Genetic toxicology	SA: + ML: + CY: +/+
	Reproductive toxicology	Not selected
Nitrofurantoin 	Sites of carcinogenicity NTP TR 341 (NTP, 1989b)	Male rat--kidney; female rat--none; male mouse--none; female mouse--ovary
	Genetic toxicology	SA: + ML: + DL: – CY: +/+
	Reproductive toxicology	Continuous breeding: on test
Nitrofurazone 	Sites of carcinogenicity NTP TR 337 (NTP, 1988)	Male rat--equivocal; female rat--mammary gland; male mouse--none; female mouse--ovary
	Genetic toxicology	SA: + ML: + CY: +/+
	Reproductive toxicology	Developmental toxicity with maternal toxicity in mice and rabbits

TABLE 23. RESULTS AND STATUS INFORMATION FOR NTP CHEMICALS HAVING OVARIAN TOXICITY (Continued)

Chemical/Structure	Results/Status of Test	
Benzene 	Sites of carcinogenicity NTP TR 289 (NTP, 1986b)	Male rat--Zymbal gland, oral cavity, skin; female rat--Zymbal gland, skin; male mouse--Zymbal gland lymphomas, lung, harderian gland, preputial gland; female mouse--lymphomas, ovary, mammary gland, lung, Zymbal gland
	Pharmacokinetics	Ongoing
	Immunotoxicity	+
	Genetic toxicology	SA: – ML: – DL: – CY: –/+
	Reproductive toxicology	Developmental toxicity in rats
1-*trans*-Δ^9-Tetrahydrocannabinol 	Sites of carcinogenicity	2-y studies in progress
	Immunotoxicity	+
	Genetic toxicology	SA: – CY: –/+
	Reproductive toxicology	Ovarian and testicular toxicant in 13-wk studies
Tricresyl phosphate 	Sites of carcinogenicity	2-y studies in progress
	Genetic toxicology	SA: –, – CY: –/–
	Reproductive toxicology	Impaired fertility in mice of each sex (Chapin et al., 1988)
N-Methylolacrylamide 	Sites of carcinogenicity NTP TR 352 (NTP, 1989a)	Male rat--none; female rat--none; male mouse--harderian gland, preputial gland; female mouse--harderian gland, liver, lung, ovary
	Genetic toxicology	SA: – ML: on test CY: +/+
	Reproductive toxicology	Continuous breeding selected

(a) SA = Salmonella; ML = mouse lymphoma; DL = Drosophila; CY = cytogenetics. Results for cytogenetics presented as chromosomal aberrations/sister chromatid exchanges.

on the following information on genetic and nongenetic aspects of 4-vinyl-1-cyclohexene diepoxide toxicity.

Genetic Mechanisms

The general scheme for the metabolic fate of epoxides has been reviewed (Oesch, 1982). The covalent binding of epoxides to DNA is an important reaction that leads to mutagenicity and is strongly suspected to be a primary event that ultimately leads to the initiation of cancer. The side-chain epoxide of 4-vinyl-1-cyclohexene diepoxide should alkylate nucleophilic sites on cellular macromolecules, such as DNA and nucleoproteins, as do ethylene oxide and propylene oxide (Lawley and Jarman, 1972; Djuric et al., 1986) and other alkyl epoxides (Citti et al., 1984). Although no attempt has been made to identify such alkylation products for 4-vinyl-1-cyclohexene diepoxide, its mutagenic activity in the absence of metabolic activation is consistent with this mode of action. 4-Vinyl-1-cyclohexene diepoxide induced reverse gene mutations in both frame-shift and base-substitution strains of *Salmonella typhimurium* but was particularly effective in the base-substitution strains. 4-Vinyl-1-cyclohexene diepoxide induced cytogenetic damage in cultured Chinese hamster ovary cells, producing sister chromatid exchanges and chromosomal aberrations at relatively low doses. In addition to its side-chain epoxide, 4-vinyl-1-cyclohexene diepoxide contains a cyclohexyl epoxide, which is apparently less reactive than the side-chain epoxide (Watabe and Sawahata, 1976); the identified metabolites of 4-vinyl-1-cyclohexene diepoxide confirm that this cyclohexyl epoxide is also capable of electrophilic activity. Thus, 4-vinyl-1-cyclohexene diepoxide is potentially capable of forming interstrand or intrastrand cross-links of DNA or DNA-protein cross-links.

The concentration of epoxides at the target site could be controlled by several enzymes, most of which are located in the endoplasmic reticulum. These enzymes differ in quantity in various cell types, developmental stages, sexes, and species. Epoxide hydrase and glutathione transferase are two major enzyme systems involved in biotransformation of epoxides. These enzymes, therefore, could contribute to differences seen in susceptibility of species and sexes to the toxicity and carcinogenicity of epoxides (Oesch, 1987). Both epoxide hydrase and glutathione transferase are probably involved in the metabolism of 4-vinyl-1-cyclohexene diepoxide (Watabe and Sawahata, 1976; Giannarini et al., 1981). The species differences seen in ovarian neoplasms could be due to differences in the activities of enzymes catalyzing metabolism of 4-vinyl-1-cyclohexene diepoxide in rats and mice. Glatt and Oesch (1987) have reported that epoxide hydrase activities are lower in mice than in rats. Therefore, it is possible that mice in these studies were more susceptible than rats to 4-vinyl-1-cyclohexene diepoxide-induced ovarian carcinogenicity because of the lower rate of metabolic inactivation of 4-vinyl-1-cyclohexene diepoxide. Furthermore, the differences in epoxide hydrase activities in various organ systems could also help explain the carcinogenicity that was seen in skin and not in other tissues in spite of considerable dermal absorption of 4-vinyl-1-cyclohexene diepoxide. Rat epidermis has very low epoxide hydrase activity compared with other tissues. For example, epidermal-specific microsomal epoxide hydrase activity was only about 1% of that found in liver (Oesch, 1982). It has been reported that species and strain differences in polycyclic aromatic hydrocarbon-induced ovarian toxicity depend on the metabolism of reactive metabolites by ovarian tissue (Mattison et al., 1983). It is possible that the species differences seen in this study for ovarian toxicity/carcinogenicity may also be due to differences in the metabolism of 4-vinyl-1-cyclohexene diepoxide by ovarian tissue.

A mutated Harvey *ras* gene (*ras*^{Ha} oncogene) has been recovered from mouse skin papillomas induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) and 12-*O*-tetradecanoylphorbol-13-acetate (TPA) initiation-promotion experiments, and it was proposed that mutation of this gene may be an initiating event for some skin neoplasms (Balmin, 1985). It has been shown that benzo[*a*]pyrene diol epoxide, a skin carcinogen, can mutate and activate cloned normal *ras*^{Ha} proto-oncogene (Marshall et al., 1984). It is possible that 4-vinyl-1-cyclohexene diepoxide or its diol derivative(s) could also initiate tumor initiation events by activation of oncogene(s) present in the epidermis.

Nongenetic Mechanisms

A number of malignancies, including ovarian neoplasms, have been shown to be associated with immunosuppressive therapy in humans (Penn, 1985). Cellular immunity may be an effective mechanism for sensing and eliminating neoplastic cells. This concept was first proposed by Paul Ehrlich in 1909. Although this hypothesis has not been supported in studies of T cell-deficient nude mice (Stutman, 1979), it has gained strength from recent evidence ascribing surveillance functions to natural killer (NK) cells and macrophages (Herberman, 1985). Furthermore, there is evidence supporting the permissive role immunodeficiency plays in viral oncogenesis associated with B cell lymphomas, Kaposi's sarcoma, and squamous cell and hepatocellular carcinomas (Purtilo and Linder, 1983). Other studies have shown that the immune status of the host may not influence tumor incidence (i.e., frequency of de novo-arising tumors) but may influence tumor growth (Trutin-Ostovic et al., 1986). Many of these studies are difficult to interpret because most of the carcinogens examined were themselves immunosuppressive and the means used to produce immunodeficiency (e.g., cyclophosphamide or radiation) could also be carcinogenic or alter the ability of the host to metabolize chemicals.

The carcinogenicity observed in the present studies could be associated with the immunosuppressive effect of 4-vinyl-1-cyclohexene diepoxide. The immunotoxicity studies in mice performed at doses similar to those in the short-term toxicity studies showed that 4-vinyl-1-cyclohexene diepoxide in the 10 mg/mouse per day group, and to a lesser extent in the 5 mg/mouse per day group, produced immunosuppression. This was indicated by a decrease in the lymphoproliferative response to phytohemagglutinin and concanavalin A in the high dose group and suppression of the antibody plaque-forming-cell responses in the 5 and 10 mg/mouse groups (Appendix G). This correlated well with the observation of ovarian neoplasms in these dose groups only. The relationship between immunosuppression and ovarian tumorigenesis in mice has been previously reported. Nishizuka et al. (1976) reported that thymectomy of 3-day-old female mice in various strains resulted in acute and chronic ovarian degeneration and subsequent formation of granulosa cell tumors at a later age.

Nishizuka et al. (1976) proposed a scheme of ovarian neoplasm formation (Figure 5) resulting from oocyte depletion and subsequent possible progression stimulated by gonadotropins. Whether the ovarian atrophy and loss of oocytes observed in 4-vinyl-1-cyclohexene diepoxide-exposed mice was due to an autoimmune etiology is not clear; however, it is more likely that they were a direct effect of 4-vinyl-1-cyclohexene diepoxide. It is known that there are similarities between ionizing radiation and chemicals in their depletion of oocytes in mice (Dobson and Felton, 1983). The 4-vinyl-1-cyclohexene diepoxide-induced sequence of events in formation of ovarian neoplasms could be similar to the one proposed by Nishizuka. In retrospect, determination of serum hormone levels during the course of the current study would have tested this assumption.

Immune mechanisms may play a crucial role in the development of cutaneous neoplasms (Romerdahl and Kripke, 1986). This suggestion is based on interference with the immune system by ultraviolet radiation and subsequent formation of neoplasms. Hormonal imbalance could also play a role in the enhancement of epidermal carcinoma formation, since it was shown that long-term administration of prolactin markedly enhanced the induction of epidermal squamous cell carcinomas by 3-methylcholanthrene in male Swiss albino mice (Lupulescu, 1985).

Chemical carcinogenesis is a complex process, and it would be naïve to derive any conclusions from this discussion concerning the chronologic order of molecular events leading to 4-vinyl-1-cyclohexene diepoxide-induced neoplasia. Additional information on the metabolism, immunotoxicity, and reproductive toxicity of chemicals listed in Table 23 may provide further insight into the mechanism(s) of mouse ovarian carcinogenesis.

Audit

The experimental and tabulated data for the NTP Technical Report on 4-vinyl-1-cyclohexene

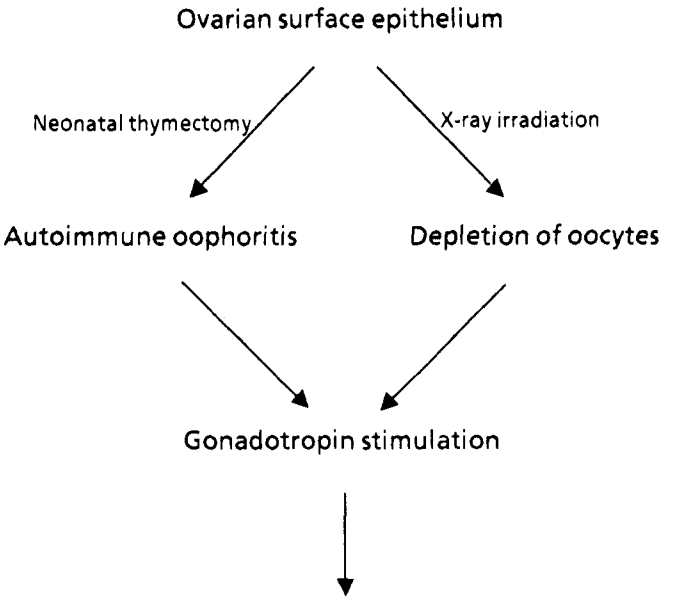


FIGURE 5. A SCHEME OF HISTOGENESIS OF OVARIAN TUMORS
(Nishizuka et al., 1976)

diepoxide were examined for accuracy, consistency, completeness, and compliance with Good Laboratory Practice regulations. As summarized in Appendix M, the audit revealed no major problems with the conduct of the studies or with collection and documentation of the experimental data. No discrepancies were found that influenced the final interpretation of the results of these studies.

Conclusions

Under the conditions of these 2-year dermal studies, there was *clear evidence of carcinogenic activity** of 4-vinyl-1-cyclohexene diepoxide for male and female F344/N rats, as shown by squamous cell and basal cell neoplasms of the skin. There was *clear evidence of carcinogenic activity* of 4-vinyl-1-cyclohexene diepoxide for male and female B6C3F$_1$ mice, as shown by squamous cell carcinomas of the skin in males and squamous cell carcinomas of the skin and ovarian neoplasms in females; increased incidences of lung neoplasms in females may also have been related to chemical application.

*Explanation of Levels of Evidence of Carcinogenic Activity is on page 7.
A summary of the Peer Review comments and the public discussion on this Technical Report appears on page 10.

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APPENDIX A

SUMMARY OF LESIONS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	15 mg/Rat	30 mg/Rat
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(45)	(48)	(40)
Leukemia mononuclear	1 (2%)		
Mesothelioma malignant			1 (3%)
Intestine large, colon	(48)	(49)	(40)
Carcinoma		1 (2%)	
Mesothelioma malignant	1 (2%)		1 (3%)
Intestine large, rectum	(48)	(48)	(44)
Carcinoma		1 (2%)	
Mesothelioma malignant	1 (2%)		1 (2%)
Intestine small, duodenum	(48)	(50)	(45)
Adenocarcinoma			1 (2%)
Leukemia mononuclear	1 (2%)		1 (2%)
Mesothelioma malignant			1 (2%)
Intestine small, ileum	(44)	(49)	(37)
Leukemia mononuclear	1 (2%)	2 (4%)	
Mesothelioma malignant			1 (3%)
Intestine small, jejunum	(46)	(49)	(42)
Leukemia mononuclear			1 (2%)
Mesothelioma malignant			1 (2%)
Liver	(50)	(50)	(50)
Carcinoma, metastatic, islets, pancreatic		1 (2%)	
Leukemia mononuclear	16 (32%)	14 (28%)	15 (30%)
Squamous cell carcinoma, metastatic, skin		1 (2%)	
Mesentery	*(50)	*(50)	*(50)
Carcinoma, metastatic, skin			1 (2%)
Carcinoma, metastatic, intestine large		1 (2%)	
Leukemia mononuclear	1 (2%)		
Mesothelioma malignant	1 (2%)	1 (2%)	1 (2%)
Squamous cell carcinoma, metastatic, skin		1 (2%)	
Pancreas	(50)	(50)	(45)
Carcinoma, metastatic, intestine large		1 (2%)	
Leukemia mononuclear	8 (16%)	1 (2%)	4 (9%)
Mesothelioma malignant	1 (2%)		1 (2%)
Squamous cell carcinoma, metastatic, skin		1 (2%)	
Pharynx	*(50)	*(50)	*(50)
Palate, papilloma squamous	1 (2%)		
Salivary glands	(50)	(50)	(50)
Carcinoma, metastatic, skin			1 (2%)
Leukemia mononuclear	1 (2%)	1 (2%)	1 (2%)
Squamous cell carcinoma, metastatic, skin		1 (2%)	
Stomach, forestomach	(50)	(50)	(47)
Leukemia mononuclear	1 (2%)	1 (2%)	1 (2%)
Mesothelioma malignant	1 (2%)		
Stomach, glandular	(50)	(50)	(48)
Leiomyosarcoma	1 (2%)		
Leukemia mononuclear			1 (2%)
Mesothelioma malignant	1 (2%)		1 (2%)
Squamous cell carcinoma, metastatic, skin		1 (2%)	
Tongue	*(50)	*(50)	*(50)
Papilloma squamous		1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Carcinoma, metastatic, skin			1 (2%)
Leukemia mononuclear	10 (20%)	5 (10%)	13 (26%)
Squamous cell carcinoma, metastatic, skin		1 (2%)	
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Leukemia mononuclear	13 (26%)	6 (12%)	11 (22%)
Medulla, squamous cell carcinoma, metastatic, skin		1 (2%)	
Adrenal gland, medulla	(50)	(50)	(50)
Leukemia mononuclear	11 (22%)	6 (12%)	9 (18%)
Pheochromocytoma malignant			2 (4%)
Pheochromocytoma benign	6 (12%)	11 (22%)	
Bilateral, pheochromocytoma benign	2 (4%)	4 (8%)	
Islets, pancreatic	(50)	(50)	(46)
Adenoma	1 (2%)	2 (4%)	3 (7%)
Carcinoma		2 (4%)	
Parathyroid gland	(49)	(45)	(45)
Adenoma		2 (4%)	1 (2%)
Pituitary gland	(50)	(50)	(48)
Leukemia mononuclear	10 (20%)	5 (10%)	10 (21%)
Pars distalis, adenoma	24 (48%)	26 (52%)	26 (54%)
Pars distalis, adenoma, multiple			1 (2%)
Pars distalis, carcinoma	2 (4%)	1 (2%)	
Thyroid gland	(48)	(50)	(43)
Leukemia mononuclear			3 (7%)
C-cell, adenoma	7 (15%)	5 (10%)	2 (5%)
C-cell, adenoma, multiple		1 (2%)	
C-cell, carcinoma	2 (4%)		
Follicular cell, adenoma	1 (2%)	3 (6%)	3 (7%)
Follicular cell, carcinoma	1 (2%)	1 (2%)	
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Epididymis	(50)	(50)	(48)
Leukemia mononuclear	1 (2%)		
Mesothelioma malignant	1 (2%)	1 (2%)	
Preputial gland	(49)	(49)	(50)
Adenoma		3 (6%)	1 (2%)
Papilloma squamous		2 (4%)	
Prostate	(49)	(50)	(50)
Leukemia mononuclear	1 (2%)	1 (2%)	2 (4%)
Testes	(50)	(50)	(50)
Leukemia mononuclear	4 (8%)	1 (2%)	3 (6%)
Mesothelioma malignant	1 (2%)	2 (4%)	1 (2%)
Bilateral, interstitial cell, adenoma	34 (68%)	35 (70%)	25 (50%)
Interstitial cell, adenoma	10 (20%)	5 (10%)	14 (28%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Leukemia mononuclear	7 (14%)	1 (2%)	2 (4%)
Bone marrow	(50)	(50)	(49)
Femoral, leukemia mononuclear	14 (28%)	14 (28%)	11 (22%)
Femoral, squamous cell carcinoma, metastatic, skin		1 (2%)	
Sternal, leukemia mononuclear	1 (2%)		
Sternal, leukemia mononuclear	1 (2%)		
Lymph node	(50)	(50)	(50)
Inguinal, leukemia mononuclear	1 (2%)		
Mediastinal, carcinoma, metastatic, skin			1 (2%)
Mediastinal, leukemia mononuclear	8 (16%)	5 (10%)	4 (8%)
Pancreatic, leukemia mononuclear	1 (2%)	1 (2%)	
Lymph node, mandibular	(50)	(49)	(50)
Leukemia mononuclear	12 (24%)	11 (22%)	10 (20%)
Lymph node, mesenteric	(7)	(10)	(3)
Carcinoma, metastatic, intestine large		1 (10%)	
Leukemia mononuclear	1 (14%)	3 (30%)	2 (67%)
Mediastinal, squamous cell carcinoma, metastatic, skin		1 (10%)	
Spleen	(50)	(50)	(49)
Leukemia mononuclear	16 (32%)	15 (30%)	15 (31%)
Mesothelioma malignant	1 (2%)		1 (2%)
Squamous cell carcinoma, metastatic, skin		1 (2%)	
Thymus	(41)	(40)	(42)
Leukemia mononuclear	7 (17%)	3 (8%)	3 (7%)
Thymoma benign	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(45)	(48)	(42)
Adenocarcinoma	1 (2%)	2 (4%)	
Fibroadenoma	1 (2%)	1 (2%)	1 (2%)
Skin	(50)	(50)	(50)
Basal cell adenoma	1 (2%)		
Basal cell carcinoma	1 (2%)	1 (2%)	
Keratoacanthoma			2 (4%)
Leukemia mononuclear			1 (2%)
Trichoepithelioma			1 (2%)
Back, keratoacanthoma		1 (2%)	
Back, squamous cell carcinoma		2 (4%)	1 (2%)
Back, subcutaneous tissue, fibroma		1 (2%)	
Back, sebaceous gland, adenoma		1 (2%)	
Scapula, basal cell adenoma			4 (8%)
Scapula, basal cell carcinoma		1 (2%)	2 (4%)
Scapula, basal cell carcinoma, multiple			1 (2%)
Scapula, basal cell carcinoma, metastatic, skin			1 (2%)
Scapula, carcinoma			1 (2%)
Scapula, keratoacanthoma		1 (2%)	1 (2%)
Scapula, papilloma squamous		3 (6%)	6 (12%)
Scapula, squamous cell carcinoma		10 (20%)	12 (24%)
Scapula, squamous cell carcinoma, multiple		22 (44%)	24 (48%)
Scapula, squamous cell carcinoma, metastatic, skin		1 (2%)	
Sebaceous gland, scapula, adenoma		1 (2%)	1 (2%)
Subcutaneous tissue, fibroma	1 (2%)	1 (2%)	
Subcutaneous tissue, hemangioma		1 (2%)	
Subcutaneous tissue, liposarcoma		1 (2%)	
Subcutaneous tissue, sarcoma	1 (2%)		
Subcutaneous tissue, scapula, fibrosarcoma			1 (2%)

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Diaphragm, carcinoma, metastatic, skin			1 (2%)
Diaphragm, intercostal, squamous cell carcinoma, metastatic, skin		1 (2%)	
NERVOUS SYSTEM			
Brain	(50)	(50)	(49)
Carcinoma, metastatic, pituitary gland	1 (2%)		
Leukemia mononuclear	5 (10%)	1 (2%)	6 (12%)
Squamous cell carcinoma, metastatic, skin		1 (2%)	
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Carcinoma, metastatic			1 (2%)
Carcinoma, metastatic, skin			1 (2%)
Chordoma	1 (2%)		
Leukemia mononuclear	16 (32%)	14 (28%)	15 (30%)
Pheochromocytoma malignant, metastatic, adrenal gland			1 (2%)
Squamous cell carcinoma, metastatic, skin		4 (8%)	1 (2%)
Squamous cell carcinoma, metastatic, uncertain primary site		1 (2%)	
Nose	(50)	(50)	(49)
Leukemia mononuclear	2 (4%)	1 (2%)	2 (4%)
Trachea	(50)	(49)	(48)
Leukemia mononuclear	1 (2%)		
SPECIAL SENSES SYSTEM			
Eye	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		1 (2%)
Zymbal gland	*(50)	*(50)	*(50)
Adenoma			1 (2%)
Carcinoma			1 (2%)
URINARY SYSTEM			
Kidney	(50)	(50)	(49)
Carcinoma, metastatic, skin			1 (2%)
Leukemia mononuclear	14 (28%)	14 (28%)	13 (27%)
Mesothelioma malignant	1 (2%)		1 (2%)
Squamous cell carcinoma, metastatic, skin		1 (2%)	
Renal tubule, adenoma			1 (2%)
Urinary bladder	(49)	(50)	(49)
Leukemia mononuclear	2 (4%)	1 (2%)	3 (6%)
Mesothelioma malignant	1 (2%)	1 (2%)	1 (2%)
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	16 (32%)	15 (30%)	15 (30%)
Mesothelioma malignant	1 (2%)	2 (4%)	1 (2%)
Hemangioma		1 (2%)	

TABLE A1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	60	60	60
Moribund	31	37	29
Dead	12	5	16
Terminal sacrifice	7	8	4
Scheduled sacrifice	10	10	10
Drowned			1
TUMOR SUMMARY			
Total animals with primary neoplasms **	50	49	49
Total primary neoplasms	117	173	156
Total animals with benign neoplasms	50	45	46
Total benign neoplasms	90	111	94
Total animals with malignant neoplasms	24	39	41
Total malignant neoplasms	27	62	62
Total animals with secondary neoplasms ***	1	7	5
Total secondary neoplasms	1	23	11
Total animals with malignant neoplasms--uncertain primary site		1	

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

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: VEHICLE CONTROL

WEEKS ON STUDY	055	066	066	068	072	073	073	075	077	078	079	079	082	084	084	084	085	086	086	086	087	087	087	089
CARCASS ID	4011	2911	3711	1111	0811	0911	1511	2311	3211	3611	4311	4711	2411	0211	4111	3411	4611	5011	4511	0511	2111	2011	2711	1311	0311
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	A	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Intestine large, colon	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant				X																					
Intestine large, rectum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Mesothelioma malignant				X																					
Intestine small	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Intestine small, ileum	+	+	+	+	A	+	+	+	A	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Intestine small, jejunum	+	+	+	+	+	+	+	A	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X							X	X		X				X			X				X	
Mesentery				+														+							
Leukemia mononuclear																									
Mesothelioma malignant				X																					
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X								X						X			X					
Mesothelioma malignant				X																					
Pharynx																+	+								
Palate, papilloma squamous																X									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X																								
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mesothelioma malignant				X																					
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leiomyosarcoma																									
Mesothelioma malignant				X																					
Tooth																									
CARDIOVASCULAR SYSTEM																									
Blood vessel																						+	+		
Heart	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X									X	X		X				X			X					
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X									X	X						X			X				X	
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X									X	X						X			X					
Pheochromocytoma benign														X											
Bilateral, pheochromocytoma benign																									X
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Parathyroid gland	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X									X	X						X			X					
Pars distalis, adenoma		X			X			X	X			X		X	X	X	X	X			X	X	X	X	
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma	X		X				X																		
C cell, carcinoma																							X		
Follicular cell, adenoma																									
Follicular cell, carcinoma														X											
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ductus deferens																						+			
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																				X					
Mesothelioma malignant				X																					
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X										X						X							X	
Mesothelioma malignant				X																					
Bilateral, interstitial cell, adenoma	X			X		X	X			X		X	X		X	X	X		X	X			X		X
Interstitial cell, adenoma			X		X						X											X		X	

+. Tissue examined microscopically
. Not examined
– Present but not examined microscopically
I Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	0 8 9	0 8 9	0 9 3	0 9 6	0 9 6	0 9 6	0 9 7	0 9 7	0 9 8	0 9 8	0 9 8	0 9 8	0 9 9	1 0 0	1 0 1	1 0 2	1 0 5	1 0 6	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	TOTAL:
CARCASS ID	4 2 1	1 2 1	2 8 1	3 0 1	3 5 1	4 9 1	0 6 1	0 7 1	0 1 1	1 9 1	2 5 1	2 6 1	3 9 1	3 8 1	3 3 1	1 7 1	1 4 1	4 4 1	0 4 1	1 0 1	1 6 1	1 8 1	2 2 1	3 1 1	4 8 1	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear					X																					1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Mesothelioma malignant																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear					X																					1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	44
Leukemia mononuclear					X																					1
Intestine small, jejunum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X	X				X	X					X							X	X	16
Mesentery				+				+	+		+				+											7
Leukemia mononuclear											X															1
Mesothelioma malignant																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X	X				X																8
Mesothelioma malignant																										1
Pharynx																										2
Palate, papilloma squamous																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																X										1
Mesothelioma malignant																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leiomyosarcoma																								X		1
Mesothelioma malignant																										1
Tooth																		+	+							2
CARDIOVASCULAR SYSTEM																										
Blood vessel				+								+	+	+		+										7
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X	X										X										10
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X	X				X	X					X							X			13
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X	X				X						X							X			11
Pheochromocytoma benign			X			X										X	X					X				6
Bilateral, pheochromocytoma benign													X													2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X	X				X						X										10
Pars distalis, adenoma		X			X		X	X	X			X	X						X	X			X			24
Pars distalis, carcinoma																								X	X	2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
C cell, adenoma							X									X	X		X							7
C cell, carcinoma									X																	2
Follicular cell, adenoma				X																						1
Follicular cell, carcinoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ductus deferens				+																						2
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Mesothelioma malignant																										1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	49
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	49
Leukemia mononuclear																X										1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										4
Mesothelioma malignant																										1
Bilateral, interstitial cell, adenoma	X	X	X	X	X	X			X		X	X	X	X	X	X	X		X	X	X	X		X	X	34
Interstitial cell, adenoma							X	X		X								X					X			10

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	05 5	06 6	06 6	06 8	07 2	07 3	07 3	07 5	07 7	07 8	07 9	07 9	07 9	08 2	08 4	08 4	08 4	08 5	08 6	08 6	08 6	08 7	08 7	08 7	08 9
CARCASS ID	40 1	29 1	37 1	11 1	08 1	09 1	15 1	23 1	32 1	36 1	43 1	47 1	24 1	02 1	41 1	34 1	46 1	50 1	45 1	05 1	21 1	20 1	27 1	13 1	03 1
HEMATOPOIETIC SYSTEM																									
Blood	+										+		+				+								
Leukemia mononuclear	X										X		X				X								
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear	X		X								X		X				X			X				X	
Sternal, leukemia mononuclear																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, leukemia mononuclear											X														
Mediastinal, leukemia mononuclear			X								X									X			X	
Pancreatic, leukemia mononuclear													X												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X									X	X		X				X			X				X	
Lymph node, mesenteric				+																					
Leukemia mononuclear																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X		X							X	X		X				X			X				X	
Mesothelioma malignant				X																					
Thymus	+	+	M	+	+	+	+	+	+	+	I	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X									X										X				X	
Thymoma benign									X																
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Basal cell carcinoma																									X
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, sarcoma												X													
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																									
Leukemia mononuclear	X		X								X						X			X					
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Chordoma																									
Leukemia mononuclear	X		X							X	X		X				X			X				X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X										X														
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																	X								
SPECIAL SENSES SYSTEM																									
Eye				+							+						+								
Leukemia mononuclear											X														
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear	X									X	X						X			X				X	
Mesothelioma malignant				X																					
Urethra																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																									
Mesothelioma malignant				X																					

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	089	089	093	096	096	096	097	097	098	098	098	098	099	099	100	101	102	105	106	107	107	107	107	107	107	107	TOTAL:
CARCASS ID	421	121	281	301	351	491	061	071	011	191	251	261	391	381	331	171	141	441	041	101	161	181	221	311	481		TISSUES TUMORS
HEMATOPOIETIC SYSTEM																											
Blood	+				+	+																					7
Leukemia mononuclear	X				X	X																					7
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear	X				X					X	X						X						X	X			14
Sternal, leukemia mononuclear						X																					1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Inguinal, leukemia mononuclear																											1
Mediastinal, leukemia mononuclear	X					X				X							X										8
Pancreatic, leukemia mononuclear																											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X	X				X							X										12
Lymph node, mesenteric					+			+	+				+		+				+								7
Leukemia mononuclear					X																						1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X	X				X	X						X							X	X		16
Mesothelioma malignant																											1
Thymus	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	I	+	M	+	+	+	M	41
Leukemia mononuclear					X	X					X																7
Thymoma benign																											1
INTEGUMENTARY SYSTEM																											
Mammary gland	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	45
Adenocarcinoma																										X	1
Fibroadenoma									X																		1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma		X																									1
Basal cell carcinoma																											1
Subcutaneous tissue, fibroma																			X								1
Subcutaneous tissue, sarcoma																											1
MUSCULOSKELETAL SYSTEM																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																										X	1
Leukemia mononuclear																											5
RESPIRATORY SYSTEM																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Chordoma							X																				1
Leukemia mononuclear	X				X	X				X	X						X						X	X			16
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																											2
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																											1
SPECIAL SENSES SYSTEM																											
Eye																	+		+				+		+		7
Leukemia mononuclear																											1
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X				X	X				X	X						X						X	X			14
Mesothelioma malignant																											1
Urethra								+																			1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+		49
Leukemia mononuclear					X												X										2
Mesothelioma malignant																											1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: 15 mg/Rat

WEEKS ON STUDY	012	054	056	056	058	061	067	070	077	077	078	082	082	083	086	087	088	088	090	092	092	092	093	095	096
CARCASS ID	12221	14771	13881	15571	15111	17551	15991	13001	12551	16331	15001	14881	12991	16441	12441	13441	13661	16881	16001	16991	12771	14551	13771	12661	12331
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma		X																							
Intestine large, rectum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma		X																							
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Intestine small, jejunum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, islets, pancreatic																									
Leukemia mononuclear					X					X				X					X					X	
Squamous cell carcinoma, metastatic, skin																									
Mesentery		+																							
Carcinoma, metastatic, intestine large		X																							
Mesothelioma malignant																									
Squamous cell carcinoma, metastatic, skin																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, intestine large		X																							
Leukemia mononuclear																									
Squamous cell carcinoma, metastatic, skin																									
Pharynx																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Squamous cell carcinoma, metastatic, skin																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, skin																									
Tongue																									
Papilloma squamous																									
Tooth												+								+					
CARDIOVASCULAR SYSTEM																									
Blood vessel	+																					+			+
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X									X										X	
Squamous cell carcinoma, metastatic, skin																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X				X										X	
Medulla, squamous cell carcinoma, metastatic, skin																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X				X										X	
Pheochromocytoma benign												X				X									X
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																						X			
Carcinoma																									
Parathyroid gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+
Adenoma																									
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X										X	
Pars distalis, adenoma				X		X	X	X		X	X					X		X		X		X			
Pars distalis, carcinoma															X										
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
C cell, adenoma										X										X					X
C cell, adenoma, multiple																							X		
Follicular cell, adenoma												X													
Follicular cell, carcinoma																									
GENERAL BODY SYSTEM																									
None																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X					X				X					X					X	
Squamous cell carcinoma, metastatic, skin																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Mesothelioma malignant																									

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 15 mg/Rat (Continued)

WEEKS ON STUDY	097	097	097	097	097	099	099	099	099	100	101	102	103	104	105	106	106	107	107	107	107	107	107	107	107	107	TOTAL TISSUES TUMORS
CARCASS ID	14411	15411	12111	13211	15211	12811	14211	15611	16211	13911	13311	13511	16711	14111	14611	14401	15311	13111	14311	14911	15511	15811	16111	16511	16611		
ALIMENTARY SYSTEM																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+		48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+		49
Carcinoma																											1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+		48
Carcinoma																											1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Leukemia mononuclear																				X							2
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma, metastatic, islets, pancreatic															X												1
Leukemia mononuclear	X	X							X	X	X		X			X			X	X							14
Squamous cell carcinoma, metastatic, skin	X																										1
Mesentery	+				+		+	+					+														6
Carcinoma, metastatic, intestine large																											1
Mesothelioma malignant							X																				1
Squamous cell carcinoma, metastatic, skin	X																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Carcinoma, metastatic, intestine large																											1
Leukemia mononuclear										X																	1
Squamous cell carcinoma, metastatic, skin	X																										1
Pharynx											+	+															2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																											1
Squamous cell carcinoma, metastatic, skin	X																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Squamous cell carcinoma, metastatic, skin	X																										1
Tongue				+																							1
Papilloma squamous				X																							1
Tooth						+	+										+										5
CARDIOVASCULAR SYSTEM																											
Blood vessel					+		+																				5
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear		X								X																	5
Squamous cell carcinoma, metastatic, skin	X																										1
ENDOCRINE SYSTEM																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear										X	X					X											6
Medulla, squamous cell carcinoma, metastatic, skin	X																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear										X	X					X											6
Pheochromocytoma benign	X	X	X	X			X					X		X	X												11
Bilateral, pheochromocytoma benign											X					X			X	X							4
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Adenoma	X																										2
Carcinoma															X							X					2
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+		45
Adenoma										X															X		2
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear									X	X			X														5
Pars distalis, adenoma			X	X	X	X	X		X		X	X		X	X			X		X	X	X		X	X		26
Pars distalis, carcinoma																											1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
C cell, adenoma				X								X															5
C cell, adenoma, multiple																											1
Follicular cell, adenoma									X												X						3
Follicular cell, carcinoma																X											1
GENERAL BODY SYSTEM																											
None																											
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear	X	X							X	X	X		X			X			X	X							14
Squamous cell carcinoma, metastatic, skin	X																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Leukemia mononuclear																											1
Mesothelioma malignant							X																				1

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 15 mg/Rat (Continued)

WEEKS ON STUDY	012	054	056	056	058	061	067	070	077	077	078	082	082	083	086	087	088	088	090	092	092	092	093	095	096
CARCASS ID	12201	14701	13801	15701	15101	17501	15901	13001	12501	16301	15001	14801	12901	16401	12401	13401	13601	16801	16001	16901	12701	14501	13701	12601	12301
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant																									
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X									X						
Papilloma squamous																X									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Seminal vesicle								+																	
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Mesothelioma malignant																			X						
Bilateral, interstitial cell, adenoma								X	X	X		X	X			X	X	X	X		X	X	X	X	X
Interstitial cell, adenoma			X	X		X														X					
HEMATOPOIETIC SYSTEM																									
Blood																								+	
Leukemia mononuclear																								X	
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear					X					X				X					X					X	
Femoral, squamous cell carcinoma, metastatic, skin																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear										X				X											
Pancreatic, leukemia mononuclear														X											
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X				X										X	
Lymph node, mesenteric		+												+										+	
Carcinoma, metastatic, intestine large		X																							
Leukemia mononuclear														X										X	
Mediastinal, squamous cell carcinoma, metastatic, skin																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X					X				X					X					X	
Squamous cell carcinoma, metastatic, skin																									
Thymus	+	M	+	+	M	M	+	+	+	+	+	+	M	M	M	I	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X														X	
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell carcinoma																									
Back, keratoacanthoma																							X		
Back, squamous cell carcinoma																		X							
Back, subcutaneous tissue, fibroma																					X				
Back, sebaceous gland, adenoma																									
Scapula, basal cell carcinoma																						X			
Scapula, keratoacanthoma																									
Scapula, papilloma squamous																									
Scapula, squamous cell carcinoma															X		X			X					
Scapula, squamous cell carcinoma, multiple																X						X	X	X	X
Scapula, squamous cell carcinoma, metastatic, skin																									
Sebaceous gland, scapula, adenoma																							X		
Subcutaneous tissue, fibroma																									
Subcutaneous tissue, hemangioma																									
Subcutaneous tissue, liposarcoma																	X								
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Diaphragm, intercostal, squamous cell carcinoma, metastatic, skin																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																								X	
Squamous cell carcinoma, metastatic, skin																									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear					X					X				X					X					X	
Squamous cell carcinoma, metastatic, skin																									
Squamous cell carcinoma, metastatic, uncertain primary site													X												
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																								X	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye										+															

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 15 mg/Rat (Continued)

WEEKS ON STUDY	0 9 7	0 9 7	0 9 7	0 9 7	0 9 7	0 9 9	0 9 9	0 9 9	0 9 9	1 0 0	1 0 1	1 0 2	1 0 3	1 0 4	1 0 5	1 0 6	1 0 6	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	TOTAL:
CARCASS ID	1 4 4 1	1 5 4 1	1 2 1 1	1 3 2 1	1 5 2 1	1 2 8 1	1 4 2 1	1 5 6 1	1 6 2 1	1 3 9 1	1 3 3 1	1 3 5 1	1 6 7 1	1 4 1 1	1 4 6 1	1 4 0 1	1 5 3 1	1 3 1 1	1 4 3 1	1 4 9 1	1 5 5 1	1 5 8 1	1 6 1 1	1 6 5 1	1 6 6 1	TISSUES / TUMORS
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant							X																		1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenoma															X										3
Papilloma squamous										X															2
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																									1
Seminal vesicle																									1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																									1
Mesothelioma malignant							X																		2
Bilateral, interstitial cell, adenoma	X	X			X	X	X	X	X	X		X	X		X	X	X	X	X	X	X	X	X	X	35
Interstitial cell, adenoma			X																						5
HEMATOPOIETIC SYSTEM																									
Blood																									1
Leukemia mononuclear																									1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear	X	X							X	X	X		X			X			X	X					14
Femoral, squamous cell carcinoma, metastatic, skin	X																								1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear		X														X				X					5
Pancreatic, leukemia mononuclear																									1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	49
Leukemia mononuclear		X							X	X	X		X						X	X		X			11
Lymph node, mesenteric	+			+	+	+		+			+	+													10
Carcinoma, metastatic, intestine large																									1
Leukemia mononuclear											X														3
Mediastinal, squamous cell carcinoma, metastatic, skin	X																								1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X							X	X	X		X			X			X	X		X			15
Squamous cell carcinoma, metastatic, skin	X																								1
Thymus	M	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	40
Leukemia mononuclear										X															3
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenocarcinoma																		X		X					2
Fibroadenoma														X											1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell carcinoma							X																		1
Back, keratoacanthoma																									1
Back, squamous cell carcinoma																	X								2
Back, subcutaneous tissue, fibroma																									1
Back, sebaceous gland, adenoma																						X			1
Scapula, basal cell carcinoma																									1
Scapula, keratoacanthoma								X																	1
Scapula, papilloma squamous						X											X						X		3
Scapula, squamous cell carcinoma	X	X		X			X						X									X	X		10
Scapula, squamous cell carcinoma, multiple			X		X	X		X	X	X		X		X	X	X	X	X	X	X	X			X	X	22
Scapula, squamous cell carcinoma, metastatic, skin	X																								1
Sebaceous gland, scapula, adenoma																									1
Subcutaneous tissue, fibroma																								X	1
Subcutaneous tissue, hemangioma																		X							1
Subcutaneous tissue, liposarcoma																									1
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle	+																								1
Diaphragm, intercostal, squamous cell carcinoma, metastatic, skin	X																								1
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																									1
Squamous cell carcinoma, metastatic, skin	X																								1
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear	X	X							X	X	X		X			X			X	X					14
Squamous cell carcinoma, metastatic, skin	X							X				X										X			4
Squamous cell carcinoma, metastatic, uncertain primary site																									1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																									1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																									
Eye			+																				+		3

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: 30 mg/Rat

WEEKS ON STUDY	0 3 5	0 5 0	0 5 7	0 6 3	0 6 9	0 7 2	0 7 8	0 7 9	0 7 9	0 7 9	0 8 0	0 8 2	0 8 2	0 8 3	0 8 5	0 8 5	0 8 5	0 8 5	0 8 5	0 8 7	0 8 7	0 8 8	0 8 8	0 8 8	0 8 8
CARCASS ID	2 6 6 1	2 5 7 1	2 5 1 1	2 4 5 1	2 8 8 1	2 5 3 1	2 7 2 1	2 8 0 1	2 6 7 1	2 7 6 1	2 7 0 1	2 5 5 1	2 8 7 1	2 4 9 1	2 5 2 1	2 6 3 1	2 8 6 1	2 4 8 1	2 6 8 1	2 4 2 1	2 5 9 1	2 4 1 1	2 5 0 1	2 7 9 1	2 7 5 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Intestine large, cecum	+	A	+	A	A	+	+	A	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+
Mesothelioma malignant									X																
Intestine large, colon	+	A	+	A	+	+	+	A	+	A	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+
Mesothelioma malignant									X																
Intestine large, rectum	+	+	+	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+
Mesothelioma malignant									X																
Intestine small	+	A	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	A	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma	X																								
Leukemia mononuclear							X																		
Mesothelioma malignant									X																
Intestine small, ileum	+	A	+	A	+	M	+	A	+	A	+	+	+	A	+	+	A	+	A	+	+	+	+	+	+
Mesothelioma malignant									X																
Intestine small, jejunum	+	A	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	A	+	+	+	+	+	+
Leukemia *mononuclear*							X																		
Mesothelioma malignant									X																
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X					X						X		X		X			X
Mesentery									+		+						+							+	
Carcinoma, metastatic, skin																	X								
Mesothelioma malignant									X																
Pancreas	+	A	+	A	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X											X		X		X			
Mesothelioma malignant									X																
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, skin																	X								
Leukemia mononuclear							X																		
Stomach	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
Stomach, glandular	+	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
Mesothelioma malignant									X																
Tongue																									
CARDIOVASCULAR SYSTEM																									
Blood vessel																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, skin																	X								
Leukemia mononuclear							X					X						X		X		X			X
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia *mononuclear*							X					X						X		X		X			X
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X					X						X				X			
Pheochromocytoma malignant		X																							
Islets, pancreatic	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																X									
Parathyroid gland	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M
Adenoma																									
Pituitary gland	+	+	+	A	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X					X						X		X		X			X
Pars distalis, adenoma			X		X	X					X		X	X	X				X	X			X		X
Pars distalis, adenoma, multiple																									
Thyroid gland	+	A	+	A	+	+	+	A	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X											X							
C cell, adenoma																			X						
Follicular cell, adenoma						X																			
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ductus deferens																									
Epididymis	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Penis																		+							
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X																		
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X											X							
Mesothelioma malignant									X																
Bilateral, interstitial cell, adenoma									X		X	X				X	X	X		X	X		X		
Interstitial cell, adenoma							X	X						X					X			X			X

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 30 mg/Rat (Continued)

WEEKS ON STUDY	089	090	090	091	092	092	095	095	095	096	096	096	096	098	098	098	099	099	099	103	104	106	107	107	107	107	TOTAL
CARCASS ID	247 1	243 1	265 1	282 1	260 1	254 1	264 1	278 1	281 1	258 1	262 1	269 1	246 1	290 1	277 1	283 1	244 1	256 1	261 1	261 1	274 1	271 1	273 1	284 1	285 1	289 1	TISSUES TUMORS
ALIMENTARY SYSTEM																											
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine large, cecum	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	40
Mesothelioma malignant																											1
Intestine large, colon	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	40
Mesothelioma malignant																											1
Intestine large, rectum	+	A	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Mesothelioma malignant																											1
Intestine small	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenocarcinoma																											1
Leukemia mononuclear																											1
Mesothelioma malignant																											1
Intestine small, ileum	+	A	A	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	37
Mesothelioma malignant																											1
Intestine small, jejunum	+	A	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Leukemia mononuclear																											1
Mesothelioma malignant																											1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear				X	X			X				X	X			X				X	X			X			15
Mesentery											+			+													6
Carcinoma, metastatic, skin																											1
Mesothelioma malignant																											1
Pancreas	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Leukemia mononuclear																											4
Mesothelioma malignant																											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, skin																											1
Leukemia mononuclear																											1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																											1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																											1
Mesothelioma malignant																											1
Tongue				+																							1
CARDIOVASCULAR SYSTEM																											
Blood vessel									+														+				2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, skin																											1
Leukemia mononuclear					X			X				X				X				X	X			X			13
ENDOCRINE SYSTEM																											
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X				X				X				X				X			11
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X				X				X				X				X			9
Pheochromocytoma malignant									X																		2
Islets, pancreatic	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma					X												X										3
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45
Adenoma																							X				1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear								X								X					X			X			10
Pars distalis, adenoma	X	X				X	X			X	X	X	X	X	X		X			X		X			X	X	26
Pars distalis, adenoma, multiple																					X						1
Thyroid gland	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	43
Leukemia mononuclear																								X			3
C cell, adenoma																							X				2
Follicular cell, adenoma		X																						X			3
GENERAL BODY SYSTEM																											
None																											
GENITAL SYSTEM																											
Ductus deferens																							+				1
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	48
Penis																											1
Preputial gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																											1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X																						2
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X																			3
Mesothelioma malignant																											1
Bilateral, interstitial cell, adenoma		X			X		X	X	X	X		X			X	X	X	X	X	X		X	X	X			25
Interstitial cell, adenoma	X		X	X		X							X	X							X					X	14

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 30 mg/Rat (Continued)

WEEKS ON STUDY	035	050	057	063	069	072	078	079	079	079	080	082	082	083	085	085	085	085	085	087	087	088	088	088	088
CARCASS ID	26611	25711	25111	24511	28811	25311	27211	28011	26711	27611	27011	25511	28711	24911	25211	26311	28611	24811	26811	24211	25911	24111	25011	27911	27511
HEMATOPOIETIC SYSTEM																									
Blood																		+							
Leukemia mononuclear																		X							
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+
Femoral, leukemia mononuclear							X					X						X		X		X			X
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, carcinoma, metastatic, skin																	X								
Mediastinal, leukemia mononuclear																						X			X
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X					X						X		X					X
Lymph node, mesenteric																						+		+	
Leukemia mononuclear																						X			
Spleen	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X					X						X		X		X			X
Mesothelioma malignant									X																
Thymus	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X							
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+
Fibroadenoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																								X	
Leukemia mononuclear							X																		
Trichoepithelioma																									
Back, squamous cell carcinoma																						X			
Scapula, basal cell adenoma																									
Scapula, basal cell carcinoma																			X						
Scapula, basal cell carcinoma, multiple																									
Scapula, basal cell carcinoma, metastatic, skin																			X						
Scapula, carcinoma																	X								
Scapula, keratoacanthoma											X														
Scapula, papilloma squamous																			X					X	X
Scapula, squamous cell carcinoma							X	X		X						X		X		X		X			
Scapula, squamous cell carcinoma, multiple																			X		X		X	X	X
Sebaceous gland, scapula, adenoma																									
Subcutaneous tissue, scapula, fibrosarcoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																	+								
Diaphragm, carcinoma, metastatic, skin																	X								
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X											X							
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic																X									
Carcinoma, metastatic, skin																	X								
Leukemia mononuclear							X					X						X		X		X			X
Pheochromocytoma malignant, metastatic, adrenal gland		X																							
Squamous cell carcinoma, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X											X							
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye																+									+
Leukemia mononuclear																									
Harderian gland			+																						
Zymbal gland																+						+			
Adenoma																						X			
Carcinoma																X									
URINARY SYSTEM																									
Kidney	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, skin																	X								
Leukemia mononuclear							X					X						X		X		X			X
Mesothelioma malignant									X																
Renal tubule, adenoma																									X
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X											X							
Mesothelioma malignant									X																

TABLE A2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE RATS: 30 mg/Rat (Continued)

WEEKS ON STUDY	089	090	090	091	092	092	095	095	096	096	096	098	098	098	099	099	099	103	104	106	107	107	107	107	TOTAL:
CARCASS ID	24711	24311	26511	28211	26011	25411	26411	27811	28111	25811	26211	26911	24611	29011	27711	28311	24411	25611	26111	27411	27111	27311	28411	28511	28911	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood					+																					2
Leukemia mononuclear					X																					2
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Femoral, leukemia mononuclear					X			X				X								X			X			11
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, carcinoma, metastatic, skin																										1
Mediastinal, leukemia mononuclear																				X			X			4
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear												X				X			X	X			X			10
Lymph node, mesenteric					+																					3
Leukemia mononuclear					X																					2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear				X	X			X				X	X			X			X	X			X			15
Mesothelioma malignant																										1
Thymus	+	+	+	+	+	+	+	+	M	+	M	+	+	+	I	+	+	+	+	+	+	+	M	+	M	42
Leukemia mononuclear								X								X										3
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	I	M	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	42
Fibroadenoma													X													1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Keratoacanthoma																								X		2
Leukemia mononuclear																										1
Trichoepithelioma				X																						1
Back, squamous cell carcinoma																										1
Scapula, basal cell adenoma											X				X	X						X				4
Scapula, basal cell carcinoma																X										2
Scapula, basal cell carcinoma, multiple														X												1
Scapula, basal cell carcinoma, metastatic, skin																										1
Scapula, carcinoma																										1
Scapula, keratoacanthoma																										1
Scapula, papilloma squamous										X						X										6
Scapula, squamous cell carcinoma					X	X		X											X	X						12
Scapula, squamous cell carcinoma, multiple	X		X	X			X		X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	24
Sebaceous gland, scapula, adenoma							X																			1
Subcutaneous tissue, scapula, fibrosarcoma																									X	1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Diaphragm, carcinoma, metastatic, skin																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear								X								X			X				X			6
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic																										1
Carcinoma, metastatic, skin																										1
Leukemia mononuclear				X	X			X				X	X			X			X	X			X			15
Pheochromocytoma malignant, metastatic, adrenal gland																										1
Squamous cell carcinoma, metastatic, skin																								X		1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										2
Trachea	+	+	A	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
SPECIAL SENSES SYSTEM																										
Eye					+			+			+								+							6
Leukemia mononuclear								X																		1
Harderian gland																										1
Zymbal gland																										2
Adenoma																										1
Carcinoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Carcinoma, metastatic, skin																										1
Leukemia mononuclear								X				X	X			X			X	X			X			13
Mesothelioma malignant																										1
Renal tubule, adenoma																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																X										3
Mesothelioma malignant																										1

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	15 mg/Rat	30 mg/Rat
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	8/50 (16%)	15/50 (30%)	0/50 (0%)
Adjusted Rates (b)	46.1%	64.7%	0.0%
Terminal Rates (c)	1/7 (14%)	2/8 (25%)	0/4 (0%)
Day of First Observation	571	569	
Life Table Tests (d)	P=0.065N	P=0.239	P=0.020N
Logistic Regression Tests (d)	P=0.021N	P=0.112	P=0.006N
Cochran-Armitage Trend Test (d)	P=0.019N		
Fisher Exact Test (d)		P=0.077	P=0.003N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	8/50 (16%)	15/50 (30%)	2/50 (4%)
Adjusted Rates (b)	46.1%	64.7%	7.8%
Terminal Rates (c)	1/7 (14%)	2/8 (25%)	0/4 (0%)
Day of First Observation	571	569	350
Life Table Tests (d)	P=0.187N	P=0.239	P=0.126N
Logistic Regression Tests (d)	P=0.080N	P=0.112	P=0.052N
Cochran-Armitage Trend Test (d)	P=0.070N		
Fisher Exact Test (d)		P=0.077	P=0.046N
Preputial Gland: Adenoma			
Overall Rates (a)	0/49 (0%)	3/49 (6%)	1/50 (2%)
Adjusted Rates (b)	0.0%	14.0%	2.6%
Terminal Rates (c)	0/6 (0%)	0/8 (0%)	0/4 (0%)
Day of First Observation		538	568
Life Table Tests (d)	P=0.349	P=0.158	P=0.511
Logistic Regression Tests (d)	P=0.385	P=0.121	P=0.519
Cochran-Armitage Trend Test (d)	P=0.385		
Fisher Exact Test (d)		P=0.121	P=0.505
Preputial Gland: Adenoma or Squamous Papilloma			
Overall Rates (a)	0/49 (0%)	5/49 (10%)	1/50 (2%)
Adjusted Rates (b)	0.0%	21.7%	2.6%
Terminal Rates (c)	0/6 (0%)	0/8 (0%)	0/4 (0%)
Day of First Observation		538	568
Life Table Tests (d)	P=0.357	P=0.061	P=0.511
Logistic Regression Tests (d)	P=0.404	P=0.034	P=0.519
Cochran-Armitage Trend Test (d)	P=0.407		
Fisher Exact Test (d)		P=0.028	P=0.505
Pancreatic Islets: Adenoma			
Overall Rates (a)	1/50 (2%)	2/50 (4%)	3/46 (7%)
Adjusted Rates (b)	2.5%	7.2%	16.7%
Terminal Rates (c)	0/7 (0%)	0/8 (0%)	0/4 (0%)
Day of First Observation	548	642	591
Life Table Tests (d)	P=0.188	P=0.572	P=0.287
Logistic Regression Tests (d)	P=0.196	P=0.500	P=0.276
Cochran-Armitage Trend Test (d)	P=0.196		
Fisher Exact Test (d)		P=0.500	P=0.278
Pancreatic Islets: Adenoma or Carcinoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	3/46 (7%)
Adjusted Rates (b)	2.5%	26.2%	16.7%
Terminal Rates (c)	0/7 (0%)	1/8 (13%)	0/4 (0%)
Day of First Observation	548	642	591
Life Table Tests (d)	P=0.178	P=0.246	P=0.287
Logistic Regression Tests (d)	P=0.216	P=0.195	P=0.276
Cochran-Armitage Trend Test (d)	P=0.220		
Fisher Exact Test (d)		P=0.181	P=0.278

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (e)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	19.3%	31.3%	7.7%
Terminal Rates (c)	1/7 (14%)	2/8 (25%)	0/4 (0%)
Day of First Observation	682	722	684
Life Table Tests (d)	P=0.541N	P=0.579	P=0.603N
Logistic Regression Tests (d)	P=0.495N	P=0.616	P=0.571N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.500	P=0.500N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	24/50 (48%)	26/50 (52%)	27/48 (56%)
Adjusted Rates (b)	74.8%	89.8%	90.4%
Terminal Rates (c)	3/7 (43%)	6/8 (75%)	2/4 (50%)
Day of First Observation	458	389	394
Life Table Tests (d)	P=0.167	P=0.453N	P=0.223
Logistic Regression Tests (d)	P=0.226	P=0.421	P=0.261
Cochran-Armitage Trend Test (d)	P=0.237		
Fisher Exact Test (d)		P=0.421	P=0.269
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	26/50 (52%)	27/50 (54%)	27/48 (56%)
Adjusted Rates (b)	87.4%	90.1%	90.4%
Terminal Rates (c)	5/7 (71%)	6/8 (75%)	2/4 (50%)
Day of First Observation	458	389	394
Life Table Tests (d)	P=0.240	P=0.383N	P=0.290
Logistic Regression Tests (d)	P=0.358	P=0.502	P=0.397
Cochran-Armitage Trend Test (d)	P=0.374		
Fisher Exact Test (d)		P=0.500	P=0.413
Skin (Application Site): Basal Cell Adenoma			
Overall Rates (a)	0/50 (0%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	0.0%	0.0%	42.5%
Terminal Rates (c)	0/7 (0%)	0/8 (0%)	1/4 (25%)
Day of First Observation			668
Life Table Tests (d)	P=0.005	(f)	P=0.033
Logistic Regression Tests (d)	P=0.008	(f)	P=0.040
Cochran-Armitage Trend Test (d)	P=0.015		
Fisher Exact Test (d)		(f)	P=0.059
Skin (Application Site): Basal Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	3.3%	20.1%
Terminal Rates (c)	0/7 (0%)	0/8 (0%)	0/4 (0%)
Day of First Observation		642	595
Life Table Tests (d)	P=0.041	P=0.553	P=0.100
Logistic Regression Tests (d)	P=0.055	P=0.502	P=0.110
Cochran-Armitage Trend Test (d)	P=0.060		
Fisher Exact Test (d)		P=0.500	P=0.121
Skin (Application Site): Basal Cell Adenoma or Basal Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	1/50 (2%)	6/50 (12%)
Adjusted Rates (b)	0.0%	3.3%	48.9%
Terminal Rates (c)	0/7 (0%)	0/8 (0%)	1/4 (25%)
Day of First Observation		642	595
Life Table Tests (d)	P=0.001	P=0.553	P=0.009
Logistic Regression Tests (d)	P=0.003	P=0.502	P=0.011
Cochran-Armitage Trend Test (d)	P=0.005		
Fisher Exact Test (d)		P=0.500	P=0.013

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
Skin (Application Site): Basal Cell Adenoma or Sebaceous Gland Adenoma			
Overall Rates (a)	0/50 (0%)	2/50 (4%)	5/50 (10%)
Adjusted Rates (b)	0.0%	15.6%	45.5%
Terminal Rates (c)	0/7 (0%)	1/8 (13%)	1/4 (25%)
Day of First Observation		647	659
Life Table Tests (d)	P=0.005	P=0.277	P=0.017
Logistic Regression Tests (d)	P=0.009	P=0.269	P=0.020
Cochran-Armitage Trend Test (d)	P=0.016		
Fisher Exact Test (d)		P=0.247	P=0.028
Skin (Application Site): Basal Cell Adenoma, Sebaceous Gland Adenoma, or Basal Cell Carcinoma			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	7/50 (14%)
Adjusted Rates (b)	0.0%	18.4%	51.6%
Terminal Rates (c)	0/7 (0%)	1/8 (13%)	1/4 (25%)
Day of First Observation		642	595
Life Table Tests (d)	P=0.001	P=0.161	P=0.005
Logistic Regression Tests (d)	P=0.003	P=0.134	P=0.006
Cochran-Armitage Trend Test (d)	P=0.005		
Fisher Exact Test (d)		P=0.121	P=0.006
Skin (All Sites): Basal Cell Adenoma			
Overall Rates (e)	1/50 (2%)	0/50 (0%)	4/50 (8%)
Adjusted Rates (b)	4.2%	0.0%	42.5%
Terminal Rates (c)	0/7 (0%)	0/8 (0%)	1/4 (25%)
Day of First Observation	620		668
Life Table Tests (d)	P=0.044	P=0.443N	P=0.118
Logistic Regression Tests (d)	P=0.063	P=0.500N	P=0.143
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.500N	P=0.181
Skin (All Sites): Basal Cell Carcinoma			
Overall Rates (e)	1/50 (2%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	3.8%	8.4%	20.1%
Terminal Rates (c)	0/7 (0%)	0/8 (0%)	0/4 (0%)
Day of First Observation	619	642	595
Life Table Tests (d)	P=0.170	P=0.597	P=0.266
Logistic Regression Tests (d)	P=0.209	P=0.500	P=0.309
Cochran-Armitage Trend Test (d)	P=0.222		
Fisher Exact Test (d)		P=0.500	P=0.309
Skin (All Sites): Basal Cell Adenoma or Carcinoma			
Overall Rates (e)	2/50 (4%)	2/50 (4%)	6/50 (12%)
Adjusted Rates (b)	7.9%	8.4%	48.9%
Terminal Rates (c)	0/7 (0%)	0/8 (0%)	1/4 (25%)
Day of First Observation	619	642	595
Life Table Tests (d)	P=0.045	P=0.587N	P=0.091
Logistic Regression Tests (d)	P=0.067	P=0.691N	P=0.112
Cochran-Armitage Trend Test (d)	P=0.080		
Fisher Exact Test (d)		P=0.691	P=0.134
Skin (All Sites): Trichoepithelioma, Basal Cell Adenoma, or Sebaceous Gland Adenona			
Overall Rates (e)	1/50 (2%)	2/50 (4%)	6/50 (12%)
Adjusted Rates (b)	4.2%	15.6%	48.0%
Terminal Rates (c)	0/7 (0%)	1/8 (13%)	1/4 (25%)
Day of First Observation	620	647	635
Life Table Tests (d)	P=0.012	P=0.571	P=0.036
Logistic Regression Tests (d)	P=0.020	P=0.524	P=0.043
Cochran-Armitage Trend Test (d)	P=0.029		
Fisher Exact Test (d)		P=0.500	P=0.056

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
Skin (All Sites): Trichoepithelioma, Basal Cell Adenoma, Sebaceous Gland Adenoma, or Basal Cell Carcinoma			
Overall Rates (e)	2/50 (4%)	4/50 (8%)	8/50 (16%)
Adjusted Rates (b)	7.9%	22.7%	53.8%
Terminal Rates (c)	0/7 (0%)	1/8 (13%)	1/4 (25%)
Day of First Observation	619	642	595
Life Table Tests (d)	P=0.013	P=0.456	P=0.032
Logistic Regression Tests (d)	P=0.021	P=0.355	P=0.037
Cochran-Armitage Trend Test (d)	P=0.029		
Fisher Exact Test (d)		P=0.339	P=0.046
Skin (All Sites): Keratoacanthoma			
Overall Rates (e)	0/50 (0%)	2/50 (4%)	3/50 (6%)
Adjusted Rates (b)	0.0%	8.6%	29.4%
Terminal Rates (c)	0/7 (0%)	0/8 (0%)	1/4 (25%)
Day of First Observation		647	558
Life Table Tests (d)	P=0.055	P=0.305	P=0.101
Logistic Regression Tests (d)	P=0.075	P=0.250	P=0.116
Cochran-Armitage Trend Test (d)	P=0.082		
Fisher Exact Test (d)		P=0.247	P=0.121
Skin (Application Site): Squamous Cell Papilloma (g,h)			
Overall Rates (e)	0/50 (0%)	3/50 (6%)	6/50 (12%)
Adjusted Rates (b)	0.0%	25.2%	39.3%
Terminal Rates (c)	0/7 (0%)	1/8 (13%)	0/4 (0%)
Day of First Observation		688	595
Life Table Tests (d)	P=0.004	P=0.174	P=0.014
Logistic Regression Tests (d)	P=0.006	P=0.159	P=0.015
Cochran-Armitage Trend Test (d)	P=0.010		
Fisher Exact Test (d)		P=0.121	P=0.013
Skin (Application Site): Squamous Cell Carcinoma (h)			
Overall Rates (e)	0/50 (0%)	33/50 (66%)	36/50 (72%)
Adjusted Rates (b)	0.0%	100.0%	100.0%
Terminal Rates (c)	0/7 (0%)	8/8 (100%)	4/4 (100%)
Day of First Observation		596	543
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Testis: Interstitial Cell Adenoma			
Overall Rates (a)	44/50 (88%)	40/50 (80%)	39/50 (78%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	7/7 (100%)	8/8 (100%)	4/4 (100%)
Day of First Observation	379	387	543
Life Table Tests (d)	P=0.430	P=0.116N	P=0.449
Logistic Regression Tests (d)	P=0.139N	P=0.248N	P=0.143N
Cochran-Armitage Trend Test (d)	P=0.121N		
Fisher Exact Test (d)		P=0.207N	P=0.143N
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	7/48 (15%)	6/50 (12%)	2/43 (5%)
Adjusted Rates (b)	39.0%	22.4%	27.3%
Terminal Rates (c)	1/7 (14%)	0/8 (0%)	1/4 (25%)
Day of First Observation	379	538	595
Life Table Tests (d)	P=0.122N	P=0.388N	P=0.174N
Logistic Regression Tests (d)	P=0.089N	P=0.468N	P=0.108N
Cochran-Armitage Trend Test (d)	P=0.088N		
Fisher Exact Test (d)		P=0.468N	P=0.108N

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	9/48 (19%)	6/50 (12%)	2/43 (5%)
Adjusted Rates (b)	44.6%	22.4%	27.3%
Terminal Rates (c)	1/7 (14%)	0/8 (0%)	1/4 (25%)
Day of First Observation	379	538	595
Life Table Tests (d)	P=0.044N	P=0.203N	P=0.076N
Logistic Regression Tests (d)	P=0.029N	P=0.259N	P=0.041N
Cochran-Armitage Trend Test (d)	P=0.029N		
Fisher Exact Test (d)		P=0.259N	P=0.038N
Thyroid Gland: Follicular Cell Adenoma			
Overall Rates (a)	1/48 (2%)	3/50 (6%)	3/43 (7%)
Adjusted Rates (b)	4.5%	19.2%	29.7%
Terminal Rates (c)	0/7 (0%)	1/8 (13%)	1/4 (25%)
Day of First Observation	667	569	503
Life Table Tests (d)	P=0.161	P=0.374	P=0.236
Logistic Regression Tests (d)	P=0.196	P=0.333	P=0.265
Cochran-Armitage Trend Test (d)	P=0.199		
Fisher Exact Test (d)		P=0.324	P=0.268
Thyroid Gland: Follicular Cell Adenoma or Carcinoma			
Overall Rates (a)	2/48 (4%)	4/50 (8%)	3/43 (7%)
Adjusted Rates (b)	7.1%	27.3%	29.7%
Terminal Rates (c)	0/7 (0%)	1/8 (13%)	1/4 (25%)
Day of First Observation	571	569	503
Life Table Tests (d)	P=0.312	P=0.417	P=0.425
Logistic Regression Tests (d)	P=0.359	P=0.369	P=0.450
Cochran-Armitage Trend Test (d)	P=0.363		
Fisher Exact Test (d)		P=0.359	P=0.447
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (e)	16/50 (32%)	15/50 (30%)	15/50 (30%)
Adjusted Rates (b)	60.3%	65.7%	70.3%
Terminal Rates (c)	2/7 (29%)	3/8 (38%)	1/4 (25%)
Day of First Observation	379	404	543
Life Table Tests (d)	P=0.428	P=0.322N	P=0.488
Logistic Regression Tests (d)	P=0.483N	P=0.495N	P=0.519N
Cochran-Armitage Trend Test (d)	P=0.457N		
Fisher Exact Test (d)		P=0.500N	P=0.500N
All Sites: Benign Tumors			
Overall Rates (e)	50/50 (100%)	45/50 (90%)	46/50 (92%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	7/7 (100%)	8/8 (100%)	4/4 (100%)
Week of First Observation	379	387	394
Life Table Tests (d)	P=0.378	P=0.101N	P=0.411
Logistic Regression Tests (d)	P=0.093N	P=0.072N	P=0.116N
Cochran-Armitage Trend Test (d)	P=0.070N		
Fisher Exact Test (d)		P=0.028N	P=0.059N
All Sites: Malignant Tumors			
Overall Rates (e)	24/50 (48%)	40/50 (80%)	41/50 (82%)
Adjusted Rates (b)	75.9%	100.0%	100.0%
Terminal Rates (c)	3/7 (43%)	8/8 (100%)	4/4 (100%)
Week of First Observation	379	373	242
Life Table Tests (d)	P=0.001	P=0.105	P=0.004
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001

TABLE A3. ANALYSIS OF PRIMARY TUMORS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
All Sites: All Tumors			
Overall Rates (e)	50/50 (100%)	49/50 (98%)	49/50 (98%)
Adjusted Rates (b)	100.0%	100.0%	100.0%
Terminal Rates (c)	7/7 (100%)	8/8 (100%)	4/4 (100%)
Week of First Observation	379	373	242
Life Table Tests (d)	P=0.261	P=0.210N	P=0.295
Logistic Regression Tests (d)	P=0.437N	P=1.000	P=0.626N
Cochran-Armitage Trend Test (d)	P=0.331N		
Fisher Exact Test (d)		P=0.500N	P=0.500N

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(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 a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined grossly at the site
(f) No P value is reported because no tumors were observed in the dosed and control groups.
(g) All squamous papillomas were observed in animals also bearing a squamous cell carcinoma.
(h) All squamous cell tumors were observed at the site of application.

TABLE A4a. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM BASAL CELL TUMORS IN MALE F344/N RATS (a)

	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
No 2-year dermal studies using acetone as a vehicle are included in the historical data base.			
Overall Historical Incidence for Untreated Controls			
TOTAL	(b) 20/1,596 (1.3%)	(c) 10/1,596 (0.6%)	(d) 30/1,596 (1.9%)
SD (e)	1.82%	1.07%	2.16%
Range (f)			
High	3/50	2/50	4/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes 4 trichoepitheliomas, 1 adnexal adenoma, 4 sebaceous gland adenomas, and 11 basal cell tumors
(c) Basal cell carcinomas; one adenocarcinoma, NOS, was also observed.
(d) Includes 4 trichoepitheliomas, 1 adnexal adenoma, 4 sebaceous gland adenomas, 1 adenocarcinoma, 11 basal cell tumors, and 9 basal cell carcinomas
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE A4b. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN MALE F344/N RATS (a)

	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
No 2-year dermal studies using acetone as a vehicle are included in the historical data base.			
Overall Historical Incidence for Untreated Controls			
TOTAL	(b) 21/1,596 (1.3%)	10/1,596 (0.6%)	(b) 31/1,596 (1.9%)
SD (c)	1.50%	1.08%	1.81%
Range (d)			
High	2/49	2/49	3/49
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes one papilloma, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	15 mg/Rat	30 mg/Rat
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Esophagus	(50)	(50)	(49)
Inflammation, necrotizing, acute			1 (2%)
Intestine large, cecum	(45)	(48)	(40)
Inflammation, suppurative	1 (2%)		1 (3%)
Parasite metazoan	1 (2%)	1 (2%)	1 (3%)
Thrombus	1 (2%)		
Intestine large, colon	(48)	(49)	(40)
Mineralization	5 (10%)	3 (6%)	
Parasite metazoan	2 (4%)	2 (4%)	
Intestine large, rectum	(48)	(48)	(44)
Inflammation, suppurative	1 (2%)		
Mineralization	2 (4%)	2 (4%)	
Parasite metazoan	4 (8%)		1 (2%)
Intestine small, duodenum	(48)	(50)	(45)
Inflammation, necrotizing, acute	4 (8%)	5 (10%)	1 (2%)
Mineralization		1 (2%)	
Thrombus	1 (2%)		
Intestine small, ileum	(44)	(49)	(37)
Inflammation, necrotizing, acute	1 (2%)	1 (2%)	
Liver	(50)	(50)	(50)
Basophilic focus	15 (30%)	15 (30%)	10 (20%)
Degeneration, cystic	7 (14%)	7 (14%)	3 (6%)
Eosinophilic focus		1 (2%)	
Fatty change	5 (10%)	6 (12%)	2 (4%)
Hepatodiaphragmatic nodule	1 (2%)	1 (2%)	1 (2%)
Inflammation, chronic active	1 (2%)		
Inflammation, necrotizing, acute		3 (6%)	2 (4%)
Thrombus		1 (2%)	
Bile duct, cyst			1 (2%)
Bile duct, hyperplasia	20 (40%)	39 (78%)	19 (38%)
Centrilobular, necrosis	11 (22%)	9 (18%)	8 (16%)
Hepatocyte, regeneration		1 (2%)	
Mesentery	(7)	(6)	(6)
Inflammation, chronic active	2 (29%)		1 (17%)
Inflammation, necrotizing, acute	1 (14%)		2 (33%)
Artery, mineralization	4 (57%)	3 (50%)	1 (17%)
Pancreas	(50)	(50)	(45)
Inflammation, acute			1 (2%)
Inflammation, chronic active	1 (2%)		1 (2%)
Acinus, atrophy	23 (46%)	24 (48%)	19 (42%)
Acinus, hyperplasia	2 (4%)		1 (2%)
Artery, mineralization	1 (2%)		
Pharynx	(2)	(2)	
Inflammation, suppurative	1 (50%)	2 (100%)	
Salivary glands	(50)	(50)	(50)
Inflammation, suppurative	1 (2%)		
Necrosis		1 (2%)	
Artery, mineralization	2 (4%)		
Stomach, forestomach	(50)	(50)	(47)
Inflammation, chronic active	1 (2%)	10 (20%)	2 (4%)
Mineralization	6 (12%)	3 (6%)	1 (2%)
Ulcer	8 (16%)	6 (12%)	8 (17%)
Epithelium, hyperplasia	6 (12%)	10 (20%)	2 (4%)
Stomach, glandular	(50)	(50)	(48)
Inflammation, necrotizing, acute	11 (22%)	3 (6%)	5 (10%)
Mineralization	10 (20%)	11 (22%)	4 (8%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
ALIMENTARY SYSTEM (Continued)			
Tooth	(2)	(5)	
Dysplasia		1 (20%)	
Peridontal tissue, inflammation, suppurative	2 (100%)	4 (80%)	
CARDIOVASCULAR SYSTEM			
Blood vessel	(7)	(5)	(2)
Aneurysm		1 (20%)	
Aorta, mineralization	7 (100%)	4 (80%)	2 (100%)
Heart	(50)	(50)	(50)
Degeneration, chronic	45 (90%)	42 (84%)	48 (96%)
Inflammation, suppurative		2 (4%)	3 (6%)
Mineralization	9 (18%)	7 (14%)	3 (6%)
Atrium, thrombus	4 (8%)	3 (6%)	2 (4%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(50)	(50)
Hyperplasia	23 (46%)	24 (48%)	31 (62%)
Hypertrophy	1 (2%)		
Necrosis		3 (6%)	2 (4%)
Vacuolization cytoplasmic		1 (2%)	
Adrenal gland, medulla	(50)	(50)	(50)
Hyperplasia	28 (56%)	28 (56%)	20 (40%)
Islets, pancreatic	(50)	(50)	(46)
Hyperplasia	2 (4%)	1 (2%)	5 (11%)
Parathyroid gland	(49)	(45)	(45)
Hyperplasia	14 (29%)	14 (31%)	4 (9%)
Hypertrophy		1 (2%)	
Pituitary gland	(50)	(50)	(48)
Pars distalis, cyst	1 (2%)		
Pars distalis, hyperplasia	23 (46%)	10 (20%)	11 (23%)
Pars distalis, mineralization	2 (4%)	1 (2%)	
Pars distalis, necrosis		1 (2%)	
Thyroid gland	(48)	(50)	(43)
Mineralization	1 (2%)	1 (2%)	
Pigmentation, lipofuscin		1 (2%)	
C-cell, hyperplasia	28 (58%)	30 (60%)	22 (51%)
Follicular cell, hyperplasia		2 (4%)	1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Ductus deferens	(2)		(1)
Mineralization	2 (100%)		1 (100%)
Epididymis	(50)	(50)	(48)
Mineralization			1 (2%)
Penis			(1)
Inflammation, necrotizing, acute			1 (100%)
Preputial gland	(49)	(49)	(50)
Hyperplasia	1 (2%)		3 (6%)
Inflammation, chronic active	11 (22%)	16 (33%)	9 (18%)
Duct, hyperplasia		1 (2%)	1 (2%)
Prostate	(49)	(50)	(50)
Inflammation, chronic active	34 (69%)	32 (64%)	41 (82%)
Epithelium, hyperplasia			1 (2%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
GENITAL SYSTEM (Continued)			
Testes	(50)	(50)	(50)
Cyst		1 (2%)	
Thrombus	1 (2%)		
Interstitial cell, hyperplasia	9 (18%)	7 (14%)	14 (28%)
Seminiferous tubule, atrophy	9 (18%)	2 (4%)	4 (8%)
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(50)	(49)
Femoral, myelofibrosis	3 (6%)	1 (2%)	4 (8%)
Lymph node, mandibular	(50)	(49)	(50)
Edema			2 (4%)
Inflammation, necrotizing, acute		1 (2%)	
Lymph node, mesenteric	(7)	(10)	(3)
Edema	1 (14%)	4 (40%)	
Hemorrhage		1 (10%)	
Inflammation, necrotizing, acute		1 (10%)	
Spleen	(50)	(50)	(49)
Abscess			1 (2%)
Amyloid deposition			1 (2%)
Fibrosis	8 (16%)	8 (16%)	7 (14%)
Hematopoietic cell proliferation	1 (2%)	1 (2%)	1 (2%)
Hemorrhage, chronic		1 (2%)	
Necrosis		3 (6%)	3 (6%)
Thymus	(41)	(40)	(42)
Cyst	1 (2%)		
Inflammation, necrotizing, acute		1 (3%)	
INTEGUMENTARY SYSTEM			
Mammary gland	(45)	(48)	(42)
Hyperplasia, cystic	34 (76%)	25 (52%)	36 (86%)
Mineralization	1 (2%)		
Skin	(50)	(50)	(50)
Abscess	2 (4%)		
Acanthosis		2 (4%)	1 (2%)
Cyst epithelial inclusion, multiple			1 (2%)
Inflammation, necrotizing, acute	3 (6%)	1 (2%)	2 (4%)
Mineralization	1 (2%)		
Back, acanthosis		6 (12%)	8 (16%)
Back, inflammation, necrotizing, acute		1 (2%)	
Back, sebaceous gland, hypertrophy		4 (8%)	8 (16%)
Scapula, acanthosis		39 (78%)	40 (80%)
Scapula, cyst epithelial inclusion		1 (2%)	1 (2%)
Scapula, hypertrophy		2 (4%)	
Scapula, inflammation, necrotizing, acute	1 (2%)		1 (2%)
Sebaceous gland, hypertrophy		1 (2%)	1 (2%)
Sebaceous gland, scapula, hypertrophy		28 (56%)	39 (78%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Cranium, fibrous osteodystrophy	13 (26%)	12 (24%)	4 (8%)
Femur, fibrous osteodystrophy	13 (26%)	12 (24%)	4 (8%)
NERVOUS SYSTEM			
Brain	(50)	(50)	(49)
Compression	7 (14%)	7 (14%)	11 (22%)
Infarct	4 (8%)	2 (4%)	3 (6%)

TABLE A5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Infarct		1 (2%)	1 (2%)
Inflammation, chronic active	11 (22%)	15 (30%)	1 (2%)
Mineralization	9 (18%)	7 (14%)	2 (4%)
Thrombus	1 (2%)		1 (2%)
Alveolar epithelium, hyperplasia		3 (6%)	
Artery, mediastinum, mineralization	3 (6%)	6 (12%)	
Mediastinum, inflammation, chronic active		1 (2%)	
Pleura, inflammation, suppurative			2 (4%)
Nose	(50)	(50)	(49)
Mucosa, inflammation, suppurative	21 (42%)	12 (24%)	13 (27%)
Mucosa, thrombus	1 (2%)	1 (2%)	3 (6%)
Nasolacrimal duct, inflammation, suppurative	3 (6%)	2 (4%)	4 (8%)
Septum, necrosis	1 (2%)		1 (2%)
Trachea	(50)	(49)	(48)
Inflammation, chronic active		1 (2%)	
SPECIAL SENSES SYSTEM			
Eye	(7)	(3)	(6)
Degeneration	3 (43%)	2 (67%)	6 (100%)
URINARY SYSTEM			
Kidney	(50)	(50)	(49)
Hydronephrosis		1 (2%)	
Mineralization	9 (18%)	7 (14%)	5 (10%)
Nephropathy, chronic	50 (100%)	49 (98%)	49 (100%)
Pelvis, inflammation, suppurative	2 (4%)	5 (10%)	4 (8%)
Renal tubule, cytoplasmic alteration	2 (4%)		
Renal tubule, hyperplasia	2 (4%)	6 (12%)	4 (8%)
Renal tubule, necrosis	1 (2%)		
Urethra	(1)		
Inflammation, suppurative	1 (100%)		
Urinary bladder	(49)	(50)	(49)
Hemorrhage	1 (2%)	1 (2%)	
Inflammation, suppurative	2 (4%)		
Mineralization	2 (4%)		

APPENDIX B

SUMMARY OF LESIONS IN FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	15 mg/Rat	30 mg/Rat
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Liver	(50)	(50)	(50)
Leukemia mononuclear	11 (22%)	11 (22%)	9 (18%)
Neoplastic nodule			1 (2%)
Mesentery	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		
Lipoma		1 (2%)	
Pancreas	(48)	(47)	(48)
Leukemia mononuclear	2 (4%)	1 (2%)	3 (6%)
Pharynx	*(50)	*(50)	*(50)
Palate, squamous cell carcinoma		1 (2%)	
Stomach, forestomach	(50)	(48)	(50)
Leukemia mononuclear	2 (4%)		
Stomach, glandular	(50)	(48)	(50)
Leukemia mononuclear	1 (2%)		
Tongue	*(50)	*(50)	*(50)
Leukemia mononuclear	1 (2%)		
Papilloma squamous	1 (2%)	1 (2%)	1 (2%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Leukemia mononuclear	7 (14%)	1 (2%)	7 (14%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(48)	(50)
Adenoma	1 (2%)	1 (2%)	
Leukemia mononuclear	8 (16%)	1 (2%)	5 (10%)
Adrenal gland, medulla	(50)	(48)	(50)
Leukemia mononuclear	7 (14%)	1 (2%)	4 (8%)
Pheochromocytoma malignant	1 (2%)		
Pheochromocytoma benign	2 (4%)	2 (4%)	1 (2%)
Bilateral, pheochromocytoma benign		1 (2%)	
Islets, pancreatic	(48)	(48)	(48)
Adenoma		1 (2%)	1 (2%)
Parathyroid gland	(47)	(43)	(48)
Adenoma	1 (2%)	1 (2%)	
Pituitary gland	(47)	(49)	(48)
Leukemia mononuclear	7 (15%)	3 (6%)	7 (15%)
Pars distalis, adenoma	19 (40%)	14 (29%)	17 (35%)
Pars distalis, carcinoma	14 (30%)	15 (31%)	11 (23%)
Thyroid gland	(46)	(48)	(49)
Bilateral, C-cell, adenoma	1 (2%)	2 (4%)	
C-cell, adenoma	4 (9%)	12 (25%)	9 (18%)
C-cell, adenoma, multiple	1 (2%)		
C-cell, carcinoma		3 (6%)	1 (2%)
Follicular cell, adenoma	2 (4%)		1 (2%)
GENERAL BODY SYSTEM			
None			

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
GENITAL SYSTEM			
Clitoral gland	(45)	(50)	(49)
Adenoma	2 (4%)	7 (14%)	3 (6%)
Carcinoma	1 (2%)		
Sarcoma			1 (2%)
Ovary	(50)	(49)	(50)
Granulosa cell tumor benign	1 (2%)		
Leukemia mononuclear	3 (6%)	1 (2%)	2 (4%)
Luteoma		1 (2%)	
Uterus	(50)	(50)	(50)
Carcinoma		1 (2%)	
Leukemia mononuclear	1 (2%)		2 (4%)
Polyp stromal	3 (6%)	7 (14%)	6 (12%)
Polyp stromal, multiple		1 (2%)	
Sarcoma stromal		1 (2%)	
HEMATOPOIETIC SYSTEM			
Blood	*(50)	*(50)	*(50)
Leukemia mononuclear	3 (6%)		1 (2%)
Bone marrow	(50)	(49)	(49)
Femoral, leukemia mononuclear	6 (12%)	6 (12%)	5 (10%)
Femoral, lymphoma malignant histiocytic	1 (2%)		
Lymph node	(50)	(50)	(50)
Axillary, squamous cell carcinoma, metastatic, skin			1 (2%)
Inguinal, leukemia mononuclear	1 (2%)		1 (2%)
Mediastinal, leukemia mononuclear	3 (6%)	3 (6%)	5 (10%)
Pancreatic, leukemia mononuclear		2 (4%)	2 (4%)
Lymph node, mandibular	(50)	(50)	(50)
Leukemia mononuclear	7 (14%)	7 (14%)	7 (14%)
Lymph node, mesenteric	(3)		(2)
Hemangiosarcoma			1 (50%)
Leukemia mononuclear	2 (67%)		
Spleen	(50)	(50)	(49)
Leukemia mononuclear	12 (24%)	17 (34%)	13 (27%)
Thymus	(44)	(43)	(41)
Leukemia mononuclear	4 (9%)	2 (5%)	
Thymoma benign			1 (2%)
Thymoma malignant	1 (2%)		
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(49)	(50)
Adenocarcinoma	2 (4%)	3 (6%)	1 (2%)
Fibroadenoma	14 (28%)	11 (22%)	8 (16%)
Fibroadenoma, multiple	6 (12%)		
Leukemia mononuclear	1 (2%)		
Skin	(50)	(50)	(50)
Basal cell adenoma	1 (2%)	1 (2%)	
Back, squamous cell carcinoma			1 (2%)
Back, sebaceous gland, adenoma	1 (2%)		
Scapula, basal cell carcinoma		3 (6%)	4 (8%)
Scapula, papilloma squamous			1 (2%)
Scapula, squamous cell carcinoma		8 (16%)	12 (24%)
Scapula, squamous cell carcinoma, multiple		8 (16%)	22 (44%)
Sebaceous gland, scapula, adenoma		1 (2%)	1 (2%)
Subcutaneous tissue, fibroma	2 (4%)		
Subcutaneous tissue, lipoma			1 (2%)

TABLE B1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
MUSCULOSKELETAL SYSTEM			
Skeletal muscle	*(50)	*(50)	*(50)
Abdominal, rhabdomyosarcoma	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Carcinoma, metastatic, pituitary gland	3 (6%)	3 (6%)	3 (6%)
Leukemia mononuclear	2 (4%)		1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Leukemia mononuclear	11 (22%)	13 (26%)	10 (20%)
Squamous cell carcinoma, metastatic, skin			3 (6%)
Nose	(49)	(50)	(49)
Leukemia mononuclear	1 (2%)		
SPECIAL SENSES SYSTEM			
None			
URINARY SYSTEM			
Kidney	(50)	(50)	(49)
Leukemia mononuclear	8 (16%)	7 (14%)	6 (12%)
Nephroblastoma malignant		1 (2%)	
Urinary bladder	(50)	(50)	(48)
Leukemia mononuclear	1 (2%)		
Transitional epithelium, papilloma		2 (4%)	
SYSTEMIC LESIONS			
Multiple organs	*(50)	*(50)	*(50)
Leukemia mononuclear	12 (24%)	17 (34%)	13 (26%)
Lymphoma malignant histiocytic	1 (2%)		
Hemangiosarcoma			1 (2%)
ANIMAL DISPOSITION SUMMARY			
Animals initially in study	60	60	60
Terminal sacrifice	27	23	15
Dead	8	13	21
Moribund	15	14	14
Scheduled sacrifice	10	10	10
TUMOR SUMMARY			
Total animals with primary neoplasms **	43	47	44
Total primary neoplasms	95	128	119
Total animals with benign neoplasms	39	40	32
Total benign neoplasms	62	67	52
Total animals with malignant neoplasms	25	38	39
Total malignant neoplasms	33	61	67
Total animals with secondary neoplasms ***	3	3	6
Total secondary neoplasms	3	3	7

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

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: VEHICLE CONTROL

WEEKS ON STUDY	033	055	061	084	086	087	087	087	090	091	093	095	097	100	100	102	103	103	103	104	104	105	106	107	107
CARCASS ID	10311	07611	09211	09811	10911	10711	08111	10211	08911	10511	11011	06511	06711	09911	10411	09111	08411	09611	07711	08611	09411	07011	06211	06111	06311
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine large, cecum	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	A	+	+	A	+	+	+
Intestine large, colon	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	A	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X						X			X		X	X		X		X		X	X		
Mesentery									+					+									+		
Leukemia mononuclear																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	A	I	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X												X									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																		X					X		
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X																					
Tongue				+																					
Leukemia mononuclear				X																					
Papilloma squamous				X																					
Tooth																						+			
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
Leukemia mononuclear				X									X			X		X				X	X		
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma															X										
Leukemia mononuclear				X						X			X			X		X				X	X		
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X						X			X			X						X	X		
Pheochromocytoma malignant																									
Pheochromocytoma benign															X										
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	A	I	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma												X													
Pituitary gland	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	-	-	+	+	+	+	+
Leukemia mononuclear				X						X			X			X		X					X		
Pars distalis, adenoma				X		X						X				X		X			X		X	X	
Pars distalis, carcinoma									X		X			X	X				X	X		X			X
Thyroid gland	+	+	+	+	+	A	+	+	+	+	+	A	+	+	+	A	A	+	+	-	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma																							X		X
C-cell, adenoma, multiple																									
Follicular cell, adenoma																								X	
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	-	+	+	+	+	+
Adenoma															X										
Carcinoma																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	-	+
Granulosa cell tumor benign																									
Leukemia mononuclear				X												X							X		
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+
Leukemia mononuclear																X									
Polyp stromal									X						X		X								
Vagina											+									+	+				

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	TOTAL TISSUES TUMORS
CARCASS ID	06401	06611	06811	06911	07111	07211	07311	07411	07511	07811	07911	08011	08211	08311	08511	08711	08811	09011	09311	09511	09711	10011	10111	10611	10811	
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, rectum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																		X			X					11
Mesentery																		+								4
Leukemia mononuclear																		X								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																										2
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										2
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Tongue																										1
Leukemia mononuclear																										1
Papilloma squamous																										1
Tooth												+														2
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																		X								7
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
Leukemia mononuclear																		X								6
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																		X								7
Pheochromocytoma malignant										X																1
Pheochromocytoma benign																			X							2
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Adenoma																										1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																		X								7
Pars distalis, adenoma		X	X			X	X	X		X	X	X	X			X				X						19
Pars distalis, carcinoma				X													Y				X		Y	Y	Y	14
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Bilateral, C cell, adenoma				X																						1
C cell, adenoma						X											X									4
C cell, adenoma, multiple																									X	1
Follicular cell, adenoma																							X			2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma			X			X																				2
Carcinoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor benign												X														1
Leukemia mononuclear																										3
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
Polyp stromal																										3
Vagina																										3

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	033	055	061	084	086	087	087	087	090	091	093	095	097	100	100	102	103	103	103	104	104	105	106	107	107
CARCASS ID	10331	07611	09211	09811	10911	10711	08111	10211	08911	10511	11011	06511	06711	09911	10411	09111	08411	09611	07711	08611	09411	07011	06211	06111	06331
HEMATOPOIETIC SYSTEM																									
Blood				+						+			+												
Leukemia mononuclear				X						X			X												
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear													X			X		X				X	X		
Femoral, lymphoma malignant histiocytic																									
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Inguinal, leukemia mononuclear																									
Mediastinal, leukemia mononuclear										X			X												
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X						X			X		X			X					X		
Lymph node, mesenteric										+			+												
Leukemia mononuclear										X			X												
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X						X			X		X	X		X	X	X		X	X		
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	M	+	M
Leukemia mononuclear				X						X						X		X							
Thymoma malignant																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Fibroadenoma			X		X		X	X		X	X			X				X							
Fibroadenoma, multiple																									X
Leukemia mononuclear																		X							
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Back, sebaceous gland, adenoma																									
Subcutaneous tissue, fibroma										X															
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									+
Abdominal, rhabdomyosarcoma																									X
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland											X														
Leukemia mononuclear																X							X		
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X						X			X			X		X	X	X		X	X		
Nose	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X															
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye				+						+										+					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear				X						X			X			X		X				X	X		
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																X									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	TOTAL:
CARCASS ID	0641	0661	0681	0691	0711	0721	0731	0741	0751	0781	0791	0801	0821	0831	0851	0871	0881	0901	0931	0951	0971	1001	1011	1061	1081	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										3
Leukemia mononuclear																										3
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, leukemia mononuclear																		X								6
Femoral, lymphoma malignant histiocytic																			X							1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Inguinal, leukemia mononuclear																		X								1
Mediastinal, leukemia mononuclear																		X								3
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																					X					7
Lymph node, mesenteric																							+			3
Leukemia mononuclear																										2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																		X			X					12
Thymus	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	44
Leukemia mononuclear																										4
Thymoma malignant						X																				1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																X	X									2
Fibroadenoma				X			X	X					X											X	X	14
Fibroadenoma, multiple											X			X		X		X			X					6
Leukemia mononuclear																										1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																X										1
Back, sebaceous gland, adenoma						X																				1
Subcutaneous tissue, fibroma																		X								2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Abdominal, rhabdomyosarcoma																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland				X																			X			3
Leukemia mononuclear																										2
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																		X			X					11
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye											+								+							5
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																		X								8
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: 15 mg/Rat

WEEKS ON STUDY	024	059	068	070	077	078	082	082	084	085	086	086	087	087	088	088	089	090	091	092	094	095	096	097
CARCASS ID	22771	19311	21441	21221	22551	21111	18111	19881	19001	22991	21771	18331	20221	19111	22331	18881	20551	22881	18991	19711	20441	22441	19661	18771	19991
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	M	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	M	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	A	+	A	+	A	M	+	+	+	+	+	+	A	+	+	A	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X					X				X					X
Mesentery																+								
Lipoma																X								
Pancreas	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Leukemia mononuclear																									X
Pharynx																									
Palate, squamous cell carcinoma																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue			+																						
Papilloma squamous			X																						
Tooth																		+							
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear										X															
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Adenoma																						X			
Leukemia mononuclear																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pheochromocytoma benign																									
Bilateral, pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	A	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	+	+	+	M	+	M	+	+	M	+	+	+	+	+	+	+	+	M	+	+	M	+	+	+	+
Adenoma																									
Pituitary gland	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X								X										
Pars distalis, adenoma					X			X		X			X			X		X							
Pars distalis, carcinoma									X								X		X		X	X	X	X	
Thyroid gland	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+
Bilateral, C-cell, adenoma																									
C-cell, adenoma			X			X			X														X	X	
C-cell, carcinoma						X			X																
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma					X																				
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear															X										
Luteoma																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma																									
Polyp stromal											X														
Polyp stromal, multiple																									
Sarcoma stromal					X																				
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, leukemia mononuclear															X										
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mediastinal, leukemia mononuclear										X															
Pancreatic, leukemia mononuclear																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X									X						
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X					X				X						X
Thymus	+	+	M	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	+	+	M	+	M	+
Leukemia mononuclear										X															

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 15 mg/Rat (Continued)

WEEKS ON STUDY	103	106	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	TOTAL:
CARCASS ID	18401	19501	18201	18501	18601	19201	19401	20001	20111	20031	20061	20071	20081	20091	21001	21131	21151	21161	21181	21191	22001	22111	22122	22261	23001	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X			X							X		X					X	X			11
Mesentery									+																	2
Lipoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
Leukemia mononuclear																										1
Pharynx																								+		1
Palate, squamous cell carcinoma																								X		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Tongue																										1
Papilloma squamous																										1
Tooth																										1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Leukemia mononuclear																	X									1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear																	X									1
Pheochromocytoma benign				X																		X				2
Bilateral, pheochromocytoma benign																				X						1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																								X		1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	M	●	+	+	+	+	+	+	+	43
Adenoma		X																								1
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear					X																					3
Pars distalis, adenoma		X		X	X	X				X	X					X									X	14
Pars distalis, carcinoma	X		X											X			X				X	X	X	X		15
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Bilateral, C-cell, adenoma						X														X						2
C-cell, adenoma		X	X	X			X		X				X				X									12
C-cell, carcinoma																									X	3
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma	X	X						X					X					X						X			7
Ovary	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear																										1
Luteoma					X																					1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma																				X						1
Polyp stromal	X											X		X			X		X			X				7
Polyp stromal, multiple									X																	1
Sarcoma stromal																										1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Femoral, leukemia mononuclear					X			X					X							X				X			6
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mediastinal, leukemia mononuclear					X																			X		3
Pancreatic, leukemia mononuclear					X						X															2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X		X										X								X			7
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X		X			X			X		X	X	X	X	X			X		X	X			17
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	43
Leukemia mononuclear					X																					2

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 15 mg/Rat (Continued)

WEEKS ON STUDY	024	059	068	070	077	078	082	082	084	085	086	086	087	087	088	088	089	089	090	091	092	094	095	096	097
CARCASS ID	22771	19131	21411	21221	22251	21111	18111	19881	19001	22911	21711	18311	20211	19111	22311	18881	20511	22881	18911	19711	20411	22411	19611	18711	19911
INTEGUMENTARY SYSTEM																									
Mammary gland	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																			X						
Fibroadenoma						X						X		X						X					
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basal cell adenoma																									
Scapula, basal cell carcinoma																									
Scapula, squamous cell carcinoma																			X						
Scapula, squamous cell carcinoma, multiple																									
Sebaceous gland, scapula, adenoma																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland																	X								
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X					X					X						X
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye			+						+			+													
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear							X			X					X					X						X
Nephroblastoma malignant																									
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Transitional epithelium, papilloma																									X

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 15 mg/Rat (Continued)

WEEKS ON STUDY	103	106	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	107	TOTAL: TISSUES TUMORS
CARCASS ID	18401	19501	18201	18501	18601	19201	19401	20001	20111	20031	20061	20071	20081	20091	21101	21131	21151	21161	21181	21191	22201	22111	22211	22261	23011	
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adenocarcinoma					X													X								3
Fibroadenoma						X		X			X					X	X			X				X		11
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basal cell adenoma																					X					1
Scapula, basal cell carcinoma		X									X		X													3
Scapula, squamous cell carcinoma	X			X			X				X	X				X							X			8
Scapula, squamous cell carcinoma, multiple			X		X	X			X				X								X	X		X		8
Sebaceous gland, scapula, adenoma																									X	1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland																					X	X				3
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear			X		X			X					X	X	X							X	X			13
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Eye																										3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear					X																		X			7
Nephroblastoma malignant																			X							1
Urinary bladder	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Transitional epithelium, papilloma									X																	2

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: 30 mg/Rat

WEEKS ON STUDY	057	058	058	059	066	071	073	075	076	078	081	083	086	088	089	089	089	091	092	093	093	094	095	096	097
CARCASS ID	31001	31801	34001	33401	30901	35001	30301	31701	30601	30501	32501	33301	32001	33201	32301	31201	34501	34101	31901	32101	32901	30801	31301	34401	34901
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	A	A	A	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	A	A	A	A	+	+	+	A	+	+	+	+	+	+	A	+	A	+
Intestine small, jejunum	+	+	+	+	+	+	+	A	+	A	+	+	+	M	A	+	+	+	A	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X	X										X	
Neoplastic nodule																									
Pancreas	+	+	+	+	+	+	+	+	+	A	+	+	+	+	A	+	+	–	+	+	+	+	–	+	–
Leukemia mononuclear														X										X	
Pharynx																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	–
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tongue																	+								
Papilloma squamous																	X								
Tooth																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X	X										X	
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	–
Adrenal gland, cortex	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	–	+	+	+	+	+	–
Leukemia mononuclear													X											X	
Adrenal gland, medulla	+	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Leukemia mononuclear																									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	–	+	+	+	+	+	–	A	+	+	+	+	A	+	+	–	+	+	+	+	+	+	–
Adenoma																									
Parathyroid gland	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
Pituitary gland	+	+	+	+	I	+	+	+	+	+	+	+	+	+	A	+	+	+	–	+	+	+	+	+	–
Leukemia mononuclear													X	X										X	
Pars distalis, adenoma								X	X										X	X					
Pars distalis, carcinoma	X					X				X		X					X				X				X
Thyroid gland	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–
C-cell, adenoma			X										X				X								
C-cell, carcinoma																									
Follicular cell, adenoma																								X	
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Sarcoma																									X
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear														X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear																								X	
Polyp stromal			X						X																
HEMATOPOIETIC SYSTEM																									
Blood																									
Leukemia mononuclear																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	–	+	+	+	+	+	–
Femoral, leukemia mononuclear													X	X											
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	–	+	+
Axillary, squamous cell carcinoma, metastatic, skin																									
Inguinal, leukemia mononuclear													X												
Mediastinal, leukemia mononuclear													X	X										X	
Pancreatic, leukemia mononuclear																									
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+
Leukemia mononuclear													X	X										X	
Lymph node, mesenteric						+																			
Hemangiosarcoma						X																			
Spleen	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X	X				X		X				X	
Thymus	+	+	+	+	+	+	+	+	+	A	+	+	M	+	+	+	M	+	I	+	+	+	+	+	+
Thymoma benign																									

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 30 mg/Rat
(Continued)

WEEKS ON STUDY	0 9 7	0 9 8	0 9 8	0 9 9	0 9 9	0 9 9	1 0 0	1 0 0	1 0 0	1 0 0	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	1 0 7	TOTAL:
CARCASS ID	3 2 7 1	3 1 5 1	3 0 4 1	3 3 5 1	3 4 6 1	3 1 1 1	3 0 7 1	3 3 9 1	3 2 6 1	3 2 8 1	3 0 1 1	3 0 2 1	3 1 4 1	3 1 6 1	3 2 2 1	3 3 2 4 1	3 3 0 1	3 3 1 1	3 3 6 1	3 3 7 1	3 3 8 1	3 4 2 1	3 4 3 1	3 4 7 1	3 4 8 1	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Intestine large, colon	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	42
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X						X			X				X		X	X							9
Neoplastic nodule															X										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear											X															3
Pharynx								+																		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Tongue																										1
Papilloma squamous																										1
Tooth																	+	+								2
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear						X		X			X				X											7
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X						X			X															5
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X				X		X			X															4
Pheochromocytoma benign			X																							1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																									X	1
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Leukemia mononuclear		X						X			X						X									7
Pars distalis, adenoma	X			X	X			X	X				X		X	X		X		X			X	X	X	17
Pars distalis, carcinoma		X	X								X			X												11
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
C-cell, adenoma		X								X			X		X				X						X	9
C-cell, carcinoma																					X					1
Follicular cell, adenoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Clitoral gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Adenoma			X		X																					3
Sarcoma																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X																		2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear											X															2
Polyp stromal						X				X													X		X	6
HEMATOPOIETIC SYSTEM																										
Blood								+																		1
Leukemia mononuclear								X																		1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Femoral, leukemia mononuclear								X			X							X								5
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Axillary, squamous cell carcinoma, metastatic, skin	X																									1
Inguinal, leukemia mononuclear																										1
Mediastinal, leukemia mononuclear								X										X								5
Pancreatic, leukemia mononuclear								X							X											2
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear								X							X		X	X								7
Lymph node, mesenteric	+																									2
Hemangiosarcoma																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear		X			X			X			X				X	X	X	X								13
Thymus	+	+	+	+	M	M	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	41
Thymoma benign			X																							1

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 30 mg/Rat (Continued)

WEEKS ON STUDY	057	058	058	059	066	071	073	075	075	078	081	081	086	088	089	089	089	091	092	093	093	094	095	096	097
CARCASS ID	31011	31811	34011	33411	30911	35011	30311	31711	30611	30511	32511	33311	32011	33211	32311	31211	34511	34111	31911	32111	32911	30811	31311	34411	34911
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																						X			
Fibroadenoma																									X
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Back, squamous cell carcinoma																									
Scapula, basal cell carcinoma																						X			
Scapula, papilloma squamous																									
Scapula, squamous cell carcinoma													X				X						X		
Scapula, squamous cell carcinoma, multiple																		X		X	X	X		X	X
Sebaceous gland, scapula, adenoma															X										
Subcutaneous tissue, lipoma																								X	
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carcinoma, metastatic, pituitary gland												X													X
Leukemia mononuclear																									
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X	X										X	
Squamous cell carcinoma, metastatic, skin																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Eye									+									+				+			
Harderian gland			+																						
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia mononuclear													X											X	
Urinary bladder	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE B2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE RATS: 30 mg/Rat (Continued)

WEEKS ON STUDY	097	098	098	099	099	099	100	100	100	100	107	107	107	107	107	107	107	107	107	107	107	107	107	107	TOTAL: TISSUES TUMORS
CARCASS ID	32711	31511	30411	33511	34611	31111	30711	33911	32611	32811	30111	30211	31411	31611	32211	32411	33011	33111	33611	33711	33811	34211	34311	34711	34811	
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma																										1
Fibroadenoma					X		X			X	X	X												X	X	8
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Back, squamous cell carcinoma									X																	1
Scapula, basal cell carcinoma			X																	X	X					4
Scapula, papilloma squamous					X																					1
Scapula, squamous cell carcinoma		X				X		X			X	X						X	X	X			X			12
Scapula, squamous cell carcinoma, multiple	X		X	X	X		X		X	X			X	X	X	X					X	X	X		X	X	22
Sebaceous gland, scapula, adenoma																										1
Subcutaneous tissue, lipoma																										1
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoma, metastatic, pituitary gland											X															3
Leukemia mononuclear											X															1
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia mononuclear		X					X				X				X	X	X	X								10
Squamous cell carcinoma, metastatic, skin	X																X		X							3
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																									
Eye																										3
Harderian gland				+																						2
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Leukemia mononuclear						X		X			X						X									6
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	48

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	15 mg/Rat	30 mg/Rat
Adrenal Medulla: Pheochromocytoma			
Overall Rates (a)	2/50 (4%)	3/48 (6%)	1/50 (2%)
Adjusted Rates (b)	6.3%	13.0%	4.3%
Terminal Rates (c)	1/27 (4%)	3/23 (13%)	0/15 (0%)
Day of First Observation	698	743	684
Life Table Tests (d)	P=0.568	P=0.406	P=0.711N
Logistic Regression Tests (d)	P=0.577N	P=0.379	P=0.594N
Cochran-Armitage Trend Test (d)	P=0.400N		
Fisher Exact Test (d)		P=0.480	P=0.500N
Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma			
Overall Rates (a)	3/50 (6%)	3/48 (6%)	1/50 (2%)
Adjusted Rates (b)	9.9%	13.0%	4.3%
Terminal Rates (c)	2/27 (7%)	3/23 (13%)	0/15 (0%)
Day of First Observation	698	743	684
Life Table Tests (d)	P=0.472N	P=0.569	P=0.542N
Logistic Regression Tests (d)	P=0.418N	P=0.535	P=0.431N
Cochran-Armitage Trend Test (d)	P=0.240N		
Fisher Exact Test (d)		P=0.641	P=0.309N
Clitoral Gland: Adenoma			
Overall Rates (a)	2/45 (4%)	7/50 (14%)	3/49 (6%)
Adjusted Rates (b)	8.0%	25.7%	12.2%
Terminal Rates (c)	2/25 (8%)	4/23 (17%)	0/14 (0%)
Day of First Observation	743	534	675
Life Table Tests (d)	P=0.174	P=0.061	P=0.283
Logistic Regression Tests (d)	P=0.305	P=0.059	P=0.411
Cochran-Armitage Trend Test (d)	P=0.475		
Fisher Exact Test (d)		P=0.107	P=0.541
Clitoral Gland: Adenoma or Carcinoma			
Overall Rates (a)	3/45 (7%)	7/50 (14%)	3/49 (6%)
Adjusted Rates (b)	10.6%	25.7%	12.2%
Terminal Rates (c)	2/25 (8%)	4/23 (17%)	0/14 (0%)
Day of First Observation	698	534	675
Life Table Tests (d)	P=0.263	P=0.116	P=0.395
Logistic Regression Tests (d)	P=0.447	P=0.127	P=0.586
Cochran-Armitage Trend Test (d)	P=0.520N		
Fisher Exact Test (d)		P=0.205	P=0.620N
Mammary Gland: Fibroadenoma			
Overall Rates (e)	20/50 (40%)	11/50 (22%)	8/50 (16%)
Adjusted Rates (b)	54.4%	37.6%	40.2%
Terminal Rates (c)	12/27 (44%)	7/23 (30%)	4/15 (27%)
Day of First Observation	425	542	675
Life Table Tests (d)	P=0.117N	P=0.140N	P=0.191N
Logistic Regression Tests (d)	P=0.014N	P=0.057N	P=0.023N
Cochran-Armitage Trend Test (d)	P=0.004N		
Fisher Exact Test (d)		P=0.041N	P=0.007N
Mammary Gland: Adenocarcinoma			
Overall Rates (e)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	7.4%	11.5%	3.2%
Terminal Rates (c)	2/27 (7%)	2/23 (9%)	0/15 (0%)
Day of First Observation	743	625	648
Life Table Tests (d)	P=0.583N	P=0.417	P=0.660N
Logistic Regression Tests (d)	P=0.506N	P=0.414	P=0.604N
Cochran-Armitage Trend Test (d)	P=0.399N		
Fisher Exact Test (d)		P=0.500	P=0.500N

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
Mammary Gland: Fibroadenoma or Adenocarcinoma			
Overall Rates (e)	21/50 (42%)	14/50 (28%)	9/50 (18%)
Adjusted Rates (b)	57.5%	47.1%	42.1%
Terminal Rates (c)	13/27 (48%)	9/23 (39%)	4/15 (27%)
Day of First Observation	425	542	648
Life Table Tests (d)	P=0.162N	P=0.283N	P=0.223N
Logistic Regression Tests (d)	P=0.021N	P=0.147N	P=0.027N
Cochran-Armitage Trend Test (d)	P=0.006N		
Fisher Exact Test (d)		P=0.104N	P=0.008N
Pituitary Gland/Pars Distalis: Adenoma			
Overall Rates (a)	19/47 (40%)	14/49 (29%)	17/48 (35%)
Adjusted Rates (b)	55.9%	43.0%	67.6%
Terminal Rates (c)	12/26 (46%)	7/23 (30%)	8/15 (53%)
Day of First Observation	586	534	519
Life Table Tests (d)	P=0.153	P=0.382N	P=0.116
Logistic Regression Tests (d)	P=0.514	P=0.229N	P=0.471
Cochran-Armitage Trend Test (d)	P=0.345N		
Fisher Exact Test (d)		P=0.157N	P=0.385N
Pituitary Gland/Pars Distalis: Carcinoma			
Overall Rates (a)	14/47 (30%)	15/49 (31%)	11/48 (23%)
Adjusted Rates (b)	40.4%	46.9%	34.6%
Terminal Rates (c)	7/26 (27%)	7/23 (30%)	2/15 (13%)
Day of First Observation	626	584	396
Life Table Tests (d)	P=0.323	P=0.275	P=0.375
Logistic Regression Tests (d)	P=0.317N	P=0.428	P=0.302N
Cochran-Armitage Trend Test (d)	P=0.262N		
Fisher Exact Test (d)		P=0.554	P=0.299N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma			
Overall Rates (a)	33/47 (70%)	29/49 (59%)	28/48 (58%)
Adjusted Rates (b)	82.0%	75.5%	82.6%
Terminal Rates (c)	19/26 (73%)	14/23 (61%)	10/15 (67%)
Day of First Observation	586	534	396
Life Table Tests (d)	P=0.107	P=0.471	P=0.086
Logistic Regression Tests (d)	P=0.320N	P=0.341N	P=0.360N
Cochran-Armitage Trend Test (d)	P=0.139N		
Fisher Exact Test (d)		P=0.180N	P=0.160N
Skin (Application Site): Basal Cell Carcinoma (f)			
Overall Rates (a)	0/50 (0%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	0.0%	12.5%	20.0%
Terminal Rates (c)	0/27 (0%)	2/23 (9%)	2/15 (13%)
Day of First Observation		739	654
Life Table Tests (d)	P=0.012	P=0.098	P=0.020
Logistic Regression Tests (d)	P=0.015	P=0.081	P=0.032
Cochran-Armitage Trend Test (d)	P=0.049		
Fisher Exact Test (d)		P=0.121	P=0.059
Skin (Application Site): Sebaceous Gland Adenoma, or Basal Cell Carcinoma			
Overall Rates (a)	1/50 (2%)	4/50 (8%)	5/50 (10%)
Adjusted Rates (b)	3.7%	16.7%	22.2%
Terminal Rates (c)	1/27 (4%)	3/23 (13%)	2/15 (13%)
Day of First Observation	743	739	619
Life Table Tests (d)	P=0.019	P=0.137	P=0.033
Logistic Regression Tests (d)	P=0.028	P=0.119	P=0.061
Cochran-Armitage Trend Test (d)	P=0.080		
Fisher Exact Test (d)		P=0.181	P=0.102

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
Skin (All Sites): Basal Cell Adenoma or Carcinoma			
Overall Rates (e)	1/50 (2%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	3.7%	16.7%	20.0%
Terminal Rates (c)	1/27 (4%)	3/23 (13%)	2/15 (13%)
Day of First Observation	743	739	654
Life Table Tests (d)	P=0.040	P=0.137	P=0.064
Logistic Regression Tests (d)	P=0.047	P=0.105	P=0.091
Cochran-Armitage Trend Test (d)	P=0.146		
Fisher Exact Test (d)		P=0.181	P=0.181
Skin (All Sites): Sebaceous Gland Adenoma, Basal Cell Adenoma, or Basal Cell Carcinoma			
Overall Rates (e)	2/50 (4%)	5/50 (10%)	5/50 (10%)
Adjusted Rates (b)	7.4%	20.8%	22.2%
Terminal Rates (c)	2/27 (7%)	4/23 (17%)	2/15 (13%)
Day of First Observation	743	739	619
Life Table Tests (d)	P=0.046	P=0.157	P=0.076
Logistic Regression Tests (d)	P=0.063	P=0.140	P=0.127
Cochran-Armitage Trend Test (d)	P=0.178		
Fisher Exact Test (d)		P=0.218	P=0.218
Skin (Application Site): Squamous Cell Carcinoma (f)			
Overall Rates (e)	0/50 (0%)	16/50 (32%)	(g) 34/50 (68%)
Adjusted Rates (b)	0.0%	63.6%	100.0%
Terminal Rates (c)	0/27 (0%)	14/23 (61%)	15/15 (100%)
Day of First Observation		625	601
Life Table Tests (d)	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001		
Fisher Exact Test (d)		P<0.001	P<0.001
Thyroid Gland: C-Cell Adenoma			
Overall Rates (a)	6/46 (13%)	14/48 (29%)	9/49 (18%)
Adjusted Rates (b)	21.4%	45.8%	39.0%
Terminal Rates (c)	5/27 (19%)	8/23 (35%)	4/15 (27%)
Day of First Observation	736	471	404
Life Table Tests (d)	P=0.040	P=0.018	P=0.053
Logistic Regression Tests (d)	P=0.208	P=0.027	P=0.223
Cochran-Armitage Trend Test (d)	P=0.315		
Fisher Exact Test (d)		P=0.048	P=0.335
Thyroid Gland: C-Cell Carcinoma			
Overall Rates (a)	0/46 (0%)	3/48 (6%)	1/49 (2%)
Adjusted Rates (b)	0.0%	8.7%	6.7%
Terminal Rates (c)	0/27 (0%)	1/23 (4%)	1/15 (7%)
Day of First Observation		542	743
Life Table Tests (d)	P=0.268	P=0.106	P=0.383
Logistic Regression Tests (d)	P=0.411	P=0.144	P=0.383
Cochran-Armitage Trend Test (d)	P=0.398		
Fisher Exact Test (d)		P=0.129	P=0.516
Thyroid Gland: C-Cell Adenoma or Carcinoma			
Overall Rates (a)	6/46 (13%)	15/48 (31%)	10/49 (20%)
Adjusted Rates (b)	21.4%	49.4%	44.5%
Terminal Rates (c)	5/27 (19%)	9/23 (39%)	5/15 (33%)
Day of First Observation	736	471	404
Life Table Tests (d)	P=0.020	P=0.010	P=0.026
Logistic Regression Tests (d)	P=0.131	P=0.015	P=0.137
Cochran-Armitage Trend Test (d)	P=0.239		
Fisher Exact Test (d)		P=0.030	P=0.248

TABLE B3. ANALYSIS OF PRIMARY TUMORS IN FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
Uterus: Stromal Polyp			
Overall Rates (e)	3/50 (6%)	8/50 (16%)	6/50 (12%)
Adjusted Rates (b)	7.8%	30.8%	26.2%
Terminal Rates (c)	0/27 (0%)	6/23 (26%)	2/15 (13%)
Day of First Observation	626	600	404
Life Table Tests (d)	P=0.044	P=0.053	P=0.070
Logistic Regression Tests (d)	P=0.163	P=0.060	P=0.272
Cochran-Armitage Trend Test (d)	P=0.215		
Fisher Exact Test (d)		P=0.100	P=0.243
Hematopoietic System: Mononuclear Leukemia			
Overall Rates (e)	12/50 (24%)	17/50 (34%)	13/50 (26%)
Adjusted Rates (b)	31.1%	58.7%	50.9%
Terminal Rates (c)	2/27 (7%)	12/23 (52%)	5/15 (33%)
Day of First Observation	586	571	601
Life Table Tests (d)	P=0.064	P=0.081	P=0.089
Logistic Regression Tests (d)	P=0.226	P=0.103	P=0.324
Cochran-Armitage Trend Test (d)	P=0.456		
Fisher Exact Test (d)		P=0.189	P=0.500
All Sites: Benign Tumors			
Overall Rates (e)	39/50 (78%)	40/50 (80%)	32/50 (64%)
Adjusted Rates (b)	88.2%	95.1%	88.4%
Terminal Rates (c)	22/27 (81%)	21/23 (91%)	11/15 (73%)
Week of First Observation	425	471	404
Life Table Tests (d)	P=0.078	P=0.130	P=0.083
Logistic Regression Tests (d)	P=0.227N	P=0.332	P=0.274N
Cochran-Armitage Trend Test (d)	P=0.069N		
Fisher Exact Test (d)		P=0.500	P=0.093N
All Sites: Malignant Tumors			
Overall Rates (e)	25/50 (50%)	38/50 (76%)	39/50 (78%)
Adjusted Rates (b)	61.8%	97.4%	100.0%
Terminal Rates (c)	12/27 (44%)	22/23 (96%)	15/15 (100%)
Week of First Observation	586	534	396
Life Table Tests (d)	P<0.001	P=0.002	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P=0.002		
Fisher Exact Test (d)		P=0.006	P=0.003
All Sites: All Tumors			
Overall Rates (e)	43/50 (86%)	47/50 (94%)	44/50 (88%)
Adjusted Rates (b)	89.6%	100.0%	100.0%
Terminal Rates (c)	22/27 (81%)	23/23 (100%)	15/15 (100%)
Week of First Observation	425	471	396
Life Table Tests (d)	P=0.003	P=0.050	P=0.003
Logistic Regression Tests (d)	P=0.159	P=0.060	P=0.233
Cochran-Armitage Trend Test (d)	P=0.436		
Fisher Exact Test (d)		P=0.159	P=0.500

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(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 a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined grossly at the site
(f) All tumors were observed at the site of application.
(g) A squamous papilloma was observed in an animal also bearing a squamous cell carcinoma.

TABLE B4a. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM BASAL CELL TUMORS IN FEMALE F344/N RATS (a)

	Incidence in Controls		
	Benign	Malignant	Benign or Malignant
No 2-year dermal studies using acetone as a vehicle are included in the historical data base.			
Overall Historical Incidence for Untreated Controls			
TOTAL	(b) 3/1,643 (0.2%)	(c) 4/1,643 (0.2%)	(d) 7/1,643 (0.4%)
SD (e)	0.58%	0.66%	0.83%
Range (f)			
High	1/50	1/50	1/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes one trichoepithelioma
(c) All basal cell carcinomas
(d) Includes one trichoepithelioma, two basal cell tumors, and four basal cell carcinomas
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE B4b. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN FEMALE F344/N RATS (a)

	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
No 2-year dermal studies using acetone as a vehicle are included in the historical data base.			
Overall Historical Incidence for Untreated Controls			
TOTAL	(b) 4/1,643 (0.2%)	3/1,643 (0.2%)	(b) 7/1,643 (0.4%)
SD (c)	0.66%	0.59%	0.83%
Range (d)			
High	1/50	1/49	1/49
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes two papillomas, NOS
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B4c. HISTORICAL INCIDENCE OF URINARY BLADDER TRANSITIONAL CELL TUMORS IN FEMALE F344/N RATS (a)

	Incidence of Papillomas or Carcinomas in Controls
No 2-year dermal studies using acetone as a vehicle are included in the historical data base.	
Overall Historical Incidence for Untreated Controls	
TOTAL	(b) 3/1,602 (0.2%)
SD (c)	0.59%
Range (d)	
High	1/49
Low	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Includes one papilloma, NOS, one transitional cell papilloma, and one transitional cell carcinoma; one transitional cell carcinoma of the urinary bladder mucosa was also observed.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	15 mg/Rat	30 mg/Rat
Animals initially in study	60	60	60
Animals removed	60	60	60
Animals examined histopathologically	50	50	50
ALIMENTARY SYSTEM			
Intestine large, cecum	(46)	(47)	(45)
Parasite metazoan		1 (2%)	1 (2%)
Intestine large, colon	(47)	(50)	(48)
Inflammation, suppurative	1 (2%)		
Parasite metazoan		1 (2%)	3 (6%)
Intestine large, rectum	(48)	(48)	(48)
Inflammation, suppurative	1 (2%)		
Parasite metazoan	5 (10%)	7 (15%)	4 (8%)
Intestine small, duodenum	(50)	(49)	(49)
Inflammation, necrotizing, acute	1 (2%)		
Intestine small, ileum	(47)	(44)	(42)
Inflammation, necrotizing, acute			1 (2%)
Liver	(50)	(50)	(50)
Angiectasis			1 (2%)
Basophilic focus	38 (76%)	32 (64%)	35 (70%)
Clear cell focus		2 (4%)	
Degeneration, cystic		1 (2%)	
Eosinophilic focus		1 (2%)	
Fatty change	9 (18%)	5 (10%)	1 (2%)
Hepatodiaphragmatic nodule	3 (6%)	2 (4%)	3 (6%)
Hyperplasia, focal		1 (2%)	
Inflammation, chronic active		4 (8%)	2 (4%)
Inflammation, necrotizing, acute	1 (2%)	1 (2%)	2 (4%)
Bile duct, hyperplasia	7 (14%)	10 (20%)	14 (28%)
Centrilobular, necrosis	5 (10%)	5 (10%)	1 (2%)
Hepatocyte, regeneration	1 (2%)		
Mesentery	(4)	(2)	
Inflammation, chronic active	3 (75%)		
Inflammation, necrotizing, acute	1 (25%)		
Artery, inflammation, chronic active		1 (50%)	
Pancreas	(48)	(47)	(48)
Focal cellular change		1 (2%)	
Inflammation, acute			1 (2%)
Inflammation, chronic active	2 (4%)	1 (2%)	
Metaplasia	1 (2%)		
Acinus, atrophy	19 (40%)	17 (36%)	17 (35%)
Acinus, hyperplasia	1 (2%)		
Pharynx		(1)	(1)
Inflammation, suppurative			1 (100%)
Salivary glands	(50)	(50)	(50)
Atrophy	1 (2%)		1 (2%)
Focal cellular change		1 (2%)	
Inflammation, suppurative	1 (2%)		
Necrosis	1 (2%)		
Duct, inflammation, chronic active			1 (2%)
Stomach, forestomach	(50)	(48)	(50)
Inflammation, chronic active	2 (4%)	3 (6%)	
Ulcer	5 (10%)		
Epithelium, hyperplasia	5 (10%)	4 (8%)	
Stomach, glandular	(50)	(48)	(50)
Inflammation, chronic active	2 (4%)		
Inflammation, necrotizing, acute	4 (8%)	2 (4%)	1 (2%)
Mineralization	1 (2%)		

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
ALIMENTARY SYSTEM (Continued)			
Tooth	(2)	(1)	(2)
Dysplasia	1 (50%)		
Gingiva, hyperplasia, squamous			1 (50%)
Peridontal tissue, inflammation, suppurative	1 (50%)	1 (100%)	1 (50%)
CARDIOVASCULAR SYSTEM			
Heart	(50)	(50)	(50)
Degeneration, chronic	45 (90%)	40 (80%)	35 (70%)
Inflammation, suppurative	1 (2%)		
Mineralization	1 (2%)		
Atrium, thrombus	2 (4%)	1 (2%)	1 (2%)
ENDOCRINE SYSTEM			
Adrenal gland, cortex	(50)	(48)	(50)
Hyperplasia	38 (76%)	29 (60%)	34 (68%)
Hypertrophy	4 (8%)	1 (2%)	2 (4%)
Necrosis	1 (2%)		1 (2%)
Vacuolization cytoplasmic	1 (2%)	1 (2%)	1 (2%)
Adrenal gland, medulla	(50)	(48)	(50)
Hyperplasia	9 (18%)	10 (21%)	6 (12%)
Islets, pancreatic	(48)	(48)	(48)
Hyperplasia	2 (4%)		
Parathyroid gland	(47)	(43)	(48)
Hyperplasia	1 (2%)		
Pituitary gland	(47)	(49)	(48)
Cyst	1 (2%)		
Pars distalis, degeneration, focal			1 (2%)
Pars distalis, hyperplasia	19 (40%)	20 (41%)	15 (31%)
Thyroid gland	(46)	(48)	(49)
Inflammation, chronic active	1 (2%)	1 (2%)	
C-cell, hyperplasia	37 (80%)	33 (69%)	23 (47%)
Follicular cell, hyperplasia	2 (4%)	2 (4%)	1 (2%)
GENERAL BODY SYSTEM			
None			
GENITAL SYSTEM			
Clitoral gland	(45)	(50)	(49)
Hyperplasia	6 (13%)	3 (6%)	4 (8%)
Inflammation, chronic active	8 (18%)	2 (4%)	5 (10%)
Inflammation, necrotizing, acute		1 (2%)	2 (4%)
Duct, hyperplasia		1 (2%)	2 (4%)
Ovary	(50)	(49)	(50)
Cyst	4 (8%)	5 (10%)	9 (18%)
Uterus	(50)	(50)	(50)
Dilatation		1 (2%)	
Inflammation, chronic active		2 (4%)	
Prolapse		1 (2%)	1 (2%)
Vagina	(3)		
Inflammation, suppurative	3 (100%)		
HEMATOPOIETIC SYSTEM			
Bone marrow	(50)	(49)	(49)
Femoral, hyperplasia, reticulum cell	4 (8%)	5 (10%)	6 (12%)
Femoral, myelofibrosis	3 (6%)	1 (2%)	
Femoral, necrosis	1 (2%)		1 (2%)
Femoral, myeloid cell, hyperplasia			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
HEMATOPOIETIC SYSTEM (Continued)			
Lymph node	(50)	(50)	(50)
Mediastinal, hematopoietic cell proliferation			1 (2%)
Lymph node, mandibular	(50)	(50)	(50)
Hematopoietic cell proliferation			1 (2%)
Inflammation, necrotizing, acute		1 (2%)	
Lymph node, mesenteric	(3)		(2)
Edema	1 (33%)		1 (50%)
Spleen	(50)	(50)	(49)
Fibrosis	2 (4%)	2 (4%)	1 (2%)
Hematopoietic cell proliferation			3 (6%)
Hemorrhage, chronic			1 (2%)
INTEGUMENTARY SYSTEM			
Mammary gland	(50)	(49)	(50)
Hyperplasia, cystic	41 (82%)	20 (41%)	37 (74%)
Skin	(50)	(50)	(50)
Inflammation, chronic active			1 (2%)
Inflammation, necrotizing, acute	1 (2%)		
Back, acanthosis	1 (2%)	4 (8%)	11 (22%)
Back, sebaceous gland, hypertrophy			15 (30%)
Hair follicle, inflammation, chronic	1 (2%)		
Scapula, acanthosis	4 (8%)	33 (66%)	42 (84%)
Scapula, cyst epithelial inclusion		1 (2%)	
Scapula, inflammation, chronic active		1 (2%)	
Scapula, inflammation, necrotizing, acute	1 (2%)	1 (2%)	1 (2%)
Sebaceous gland, scapula, hypertrophy	1 (2%)	20 (40%)	43 (86%)
MUSCULOSKELETAL SYSTEM			
Bone	(50)	(50)	(50)
Cranium, fibrous osteodystrophy	1 (2%)		
Femur, fibrous osteodystrophy	1 (2%)		
Mandible, fibrous osteodystrophy	1 (2%)		
Tarsal, hyperostosis	1 (2%)		
Tarsal, inflammation, chronic active	1 (2%)		
NERVOUS SYSTEM			
Brain	(50)	(50)	(50)
Compression	12 (24%)	7 (14%)	5 (10%)
Infarct	1 (2%)		1 (2%)
RESPIRATORY SYSTEM			
Lung	(50)	(50)	(50)
Inflammation, chronic active	4 (8%)	4 (8%)	6 (12%)
Mineralization	1 (2%)		
Alveolar epithelium, hyperplasia		2 (4%)	
Mediastinum, inflammation, chronic active			1 (2%)
Nose	(49)	(50)	(49)
Hyperplasia, squamous			1 (2%)
Mucosa, inflammation, suppurative		2 (4%)	3 (6%)
Mucosa, thrombus	2 (4%)		
Nasolacrimal duct, inflammation, suppurative	2 (4%)	2 (4%)	3 (6%)
Trachea	(50)	(50)	(49)
Inflammation, chronic active			1 (2%)
Metaplasia, squamous			1 (2%)

TABLE B5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	15 mg/Rat	30 mg/Rat
SPECIAL SENSES SYSTEM			
Eye	(5)	(3)	(3)
Degeneration	4 (80%)	2 (67%)	2 (67%)
Harderian gland			(2)
Inflammation, chronic			2 (100%)
URINARY SYSTEM			
Kidney	(50)	(50)	(49)
Amyloid deposition		1 (2%)	
Bacterium	1 (2%)		
Inflammation, suppurative	1 (2%)		
Mineralization	1 (2%)		
Nephropathy, chronic	47 (94%)	45 (90%)	46 (94%)
Cortex, atrophy, focal		1 (2%)	
Pelvis, inflammation, suppurative		1 (2%)	
Renal tubule, hyperplasia	6 (12%)		
Urinary bladder	(50)	(50)	(48)
Transitional epithelium, hyperplasia		1 (2%)	1 (2%)

APPENDIX C

SUMMARY OF LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Animals initially in study	60	60	60	60
Animals removed	60	60	60	60
Animals examined histopathologically	50	50	50	50
ALIMENTARY SYSTEM				
Intestine small	(50)	(50)	(50)	(50)
Mesothelioma malignant				1 (2%)
Pheochromocytoma complex, metastatic, diffuse				1 (2%)
Intestine small, duodenum	(49)	(50)	(48)	(50)
Polyp adenomatous	1 (2%)			
Intestine small, ileum	(50)	(50)	(46)	(50)
Adenoma			1 (2%)	
Intestine small, jejunum	(50)	(50)	(49)	(50)
Lymphoma malignant undifferentiated cell type	1 (2%)	1 (2%)		
Liver	(50)	(50)	(50)	(50)
Basosquamous tumor malignant, metastatic, skin				2 (4%)
Hemangioma	1 (2%)	4 (8%)		
Hemangioma, multiple		1 (2%)		
Hemangiosarcoma	2 (4%)		1 (2%)	
Hemangiosarcoma, multiple		2 (4%)		
Hepatocellular carcinoma	5 (10%)	5 (10%)	4 (8%)	4 (8%)
Hepatocellular carcinoma, multiple	1 (2%)			
Hepatocellular adenoma	14 (28%)	6 (12%)	10 (20%)	1 (2%)
Hepatocellular adenoma, multiple	4 (8%)	2 (4%)	1 (2%)	
Lymphoma malignant histiocytic				1 (2%)
Lymphoma malignant lymphocytic			1 (2%)	
Lymphoma malignant mixed		1 (2%)		
Squamous cell carcinoma, metastatic, skin				2 (4%)
Mesentery	*(50)	*(50)	*(50)	*(50)
Lipoma	1 (2%)			
Lymphoma malignant mixed		1 (2%)		
Pancreas	(49)	(50)	(50)	(49)
Lymphoma malignant mixed		1 (2%)		
Salivary glands	(50)	(50)	(50)	(50)
Submandibular gland, lymphoma malignant lymphocytic			1 (2%)	
Stomach, forestomach	(50)	(50)	(50)	(50)
Papilloma squamous	1 (2%)	1 (2%)	1 (2%)	
Stomach, glandular	(50)	(50)	(48)	(50)
Carcinoid tumor malignant	1 (2%)			
Lymphoma malignant mixed		1 (2%)		
Squamous cell carcinoma, metastatic, skin				1 (2%)
Tooth	*(50)	*(50)	*(50)	*(50)
Odontoma	1 (2%)			
CARDIOVASCULAR SYSTEM				
Heart	(50)	(50)	(50)	(50)
Lymphoma malignant lymphocytic			1 (2%)	
Lymphoma malignant mixed		1 (2%)		
Squamous cell carcinoma, metastatic, skin			3 (6%)	4 (8%)
ENDOCRINE SYSTEM				
Adrenal gland	(50)	(50)	(49)	(50)
Lymphoma malignant lymphocytic			1 (2%)	
Capsule, adenoma	5 (10%)	5 (10%)	3 (6%)	1 (2%)
Capsule, lymphoma malignant mixed		1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
ENDOCRINE SYSTEM (Continued)				
Adrenal gland, cortex	(50)	(49)	(49)	(50)
Medulla, squamous cell carcinoma, metastatic, skin			1 (2%)	1 (2%)
Islets, pancreatic	(48)	(50)	(47)	(48)
Adenoma	1 (2%)			
Pituitary gland	(43)	(47)	(42)	(38)
Pars distalis, adenoma	1 (2%)			
Pars intermedia, adenoma	1 (2%)			
Thyroid gland	(49)	(50)	(49)	(48)
Follicular cell, adenoma			1 (2%)	
GENERAL BODY SYSTEM				
Tissue, NOS	*(50)	*(50)	*(50)	*(50)
Squamous cell carcinoma, metastatic, skin			1 (2%)	
GENITAL SYSTEM				
Epididymis	(50)	(50)	(50)	(49)
Lymphoma malignant lymphocytic			1 (2%)	
Lymphoma malignant lymphocytic, subacute, mild			1 (2%)	
Prostate	(50)	(50)	(50)	(50)
Lymphoma malignant mixed	1 (2%)			
Testes	(50)	(50)	(50)	(50)
Hemangiosarcoma	1 (2%)			
Interstitial cell, adenoma		1 (2%)	1 (2%)	1 (2%)
HEMATOPOIETIC SYSTEM				
Bone marrow	(49)	(50)	(49)	(49)
Femoral, hemangioma	1 (2%)			
Lymph node	(49)	(49)	(45)	(46)
Squamous cell carcinoma, metastatic, skin			1 (2%)	1 (2%)
Axillary, deep cervical, mediastinal, squamous cell carcinoma, metastatic, skin		1 (2%)		
Axillary, mediastinal, squamous cell carcinoma, metastatic, skin				1 (2%)
Deep cervical, lymphoma malignant lymphocytic			1 (2%)	
Inguinal, mediastinal, squamous cell carcinoma, metastatic, skin				1 (2%)
Mediastinal, lymphoma malignant mixed		2 (4%)		
Mediastinal, squamous cell carcinoma, metastatic			1 (2%)	
Mediastinal, squamous cell carcinoma, metastatic, skin		1 (2%)	1 (2%)	1 (2%)
Pancreatic, lymphoma malignant mixed		1 (2%)		
Renal, lymphoma malignant mixed		1 (2%)		
Lymph node, mandibular	(48)	(46)	(43)	(44)
Lymphoma malignant lymphocytic			1 (2%)	
Squamous cell carcinoma, metastatic, skin			2 (5%)	3 (7%)
Axillary, squamous cell carcinoma, metastatic, skin				1 (2%)
Deep cervical, squamous cell carcinoma, metastatic, skin				1 (2%)
Mediastinal, squamous cell carcinoma, metastatic, skin				1 (2%)

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
HEMATOPOIETIC SYSTEM (Continued)				
Lymph node, mesenteric	(5)	(8)	(13)	(9)
Lymphoma malignant histiocytic		1 (13%)		
Lymphoma malignant mixed		3 (38%)		
Lymphoma malignant undifferentiated cell type	1 (20%)	1 (13%)		
Spleen	(49)	(50)	(50)	(50)
Hemangioma		1 (2%)	1 (2%)	
Hemangiosarcoma	3 (6%)		1 (2%)	
Lymphoma malignant lymphocytic		1 (2%)		
Lymphoma malignant mixed	2 (4%)	4 (8%)		
Lymphoma malignant undifferentiated cell type		1 (2%)		
INTEGUMENTARY SYSTEM				
Skin	(50)	(50)	(50)	(50)
Keratoacanthoma			1 (2%)	
Lymphoma malignant lymphocytic			1 (2%)	
Squamous cell carcinoma		1 (2%)	2 (4%)	3 (6%)
Squamous cell carcinoma, multiple			1 (2%)	
Squamous cell carcinoma, metastatic, skin				1 (2%)
Back, lymphoma malignant lymphocytic			1 (2%)	
Back, squamous cell carcinoma		4 (8%)		
Scapula, basal cell carcinoma			1 (2%)	
Scapula, basosquamous tumor malignant		2 (4%)		3 (6%)
Scapula, lymphoma malignant lymphocytic			1 (2%)	
Scapula, squamous cell carcinoma		10 (20%)	27 (54%)	37 (74%)
Scapula, squamous cell carcinoma, multiple		2 (4%)	12 (24%)	5 (10%)
MUSCULOSKELETAL SYSTEM				
Skeletal muscle	*(50)	*(50)	*(50)	*(50)
Diaphragm, squamous cell carcinoma, metastatic, skin			1 (2%)	
Hindlimb, hemangiosarcoma		1 (2%)		
NERVOUS SYSTEM				
None				
RESPIRATORY SYSTEM				
Lung	(50)	(50)	(50)	(50)
Alveolar/bronchiolar adenoma	7 (14%)	8 (16%)	8 (16%)	2 (4%)
Alveolar/bronchiolar adenoma, multiple	1 (2%)	1 (2%)		
Alveolar/bronchiolar carcinoma	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar carcinoma, multiple		1 (2%)		
Basosquamous tumor malignant, metastatic, skin				3 (6%)
Hepatocellular carcinoma, metastatic, liver	2 (4%)			
Lymphoma malignant histiocytic		1 (2%)		1 (2%)
Lymphoma malignant mixed	1 (2%)	1 (2%)		
Squamous cell carcinoma, metastatic, skin		2 (4%)	16 (32%)	20 (40%)
SPECIAL SENSES SYSTEM				
Harderian gland	*(50)	*(50)	*(50)	*(50)
Adenoma	3 (6%)	6 (12%)	3 (6%)	4 (8%)
Carcinoma			1 (2%)	
Lymphoma malignant lymphocytic			1 (2%)	
Bilateral, adenoma		1 (2%)		

TABLE C1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
URINARY SYSTEM				
Kidney	(50)	(50)	(50)	(50)
Basosquamous tumor malignant, metastatic, skin				2 (4%)
Lymphoma malignant lymphocytic			1 (2%)	
Lymphoma malignant mixed		1 (2%)		
Squamous cell carcinoma, metastatic			1 (2%)	
Squamous cell carcinoma, metastatic, skin		2 (4%)	3 (6%)	5 (10%)
Urinary bladder	(50)	(48)	(49)	(48)
Hemangiosarcoma	1 (2%)			
SYSTEMIC LESIONS				
Multiple organs	*(50)	*(50)	*(50)	*(50)
Lymphoma malignant mixed	2 (4%)	4 (8%)		
Hemangiosarcoma	4 (8%)	3 (6%)	1 (2%)	
Hemangioma	2 (4%)	6 (12%)	1 (2%)	
Lymphoma malignant undifferentiated cell	1 (2%)	1 (2%)		
Lymphoma malignant histiocytic		1 (2%)		1 (2%)
Lymphoma malignant lymphocytic		1 (2%)	2 (4%)	
Mesothelioma malignant				1 (2%)
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	60	60	60	60
Terminal sacrifice	38	35	4	
Moribund	3	4	27	30
Dead	6	11	17	20
Drowned	3		2	
Scheduled sacrifice	10	10	10	10
TUMOR SUMMARY				
Total animals with primary neoplasms **	35	40	42	47
Total primary neoplasms	59	73	83	64
Total animals with benign neoplasms	31	26	23	7
Total benign neoplasms	43	37	31	9
Total animals with malignant neoplasms	16	26	40	47
Total malignant neoplasms	16	36	52	55
Total animals with secondary neoplasms ***	2	2	17	26
Total secondary neoplasms	2	6	31	52

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

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: VEHICLE CONTROL

WEEKS ON STUDY	0 0 1	0 0 1	0 3 1	0 6 3	0 7 1	0 8 2	0 8 4	0 8 6	0 8 8	0 9 0	0 9 0	0 9 2	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5
CARCASS ID	4 8 -	4 1 1	0 2 1	1 3 1	4 2 1	2 5 1	0 3 1	2 2 1	3 1 1	1 1 1	1 5 1	3 3 1	0 1 1	0 4 1	0 5 1	0 6 1	0 7 1	0 8 1	0 9 1	1 0 1	1 2 1	1 4 1	1 6 1	1 7 1	1 8 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Polyp adenomatous																									
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Hemangioma																									
Hemangiosarcoma								X	X																
Hepatocellular carcinoma							X			X									X						
Hepatocellular carcinoma, multiple															X										
Hepatocellular adenoma						X			X			X			X	X						X			
Hepatocellular adenoma, multiple																									
Mesentery								+																	
Lipoma								X																	
Pancreas	+	M	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+	+	+	+
Carcinoid tumor malignant																									
Tooth														−											
Odontoma																									
CARDIOVASCULAR SYSTEM																									
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma													X												X
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	−	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma														X											
Parathyroid gland	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+
Pituitary gland	+	I	M	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+
Pars distalis, adenoma																									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
Tissue, NOS																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland							+	+											+				+		+
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Seminal vesicle																									
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Hemangiosarcoma								X																	
HEMATOPOIETIC SYSTEM																									
Blood															−										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+
Femoral, hemangioma																									
Lymph node	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mandibular	+	+	+	+	+	+	+	−	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymph node, mesenteric									+																
Lymphoma malignant undifferentiated cell type																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I
Hemangiosarcoma								X	X																
Lymphoma malignant mixed																X									
Thymus	I	+	M	+	M	+	+	+	M	+	+	+	+	I	M	+	+	+	M	+	+	+	+	+	+
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	M	M	+	M	M	M	M	+	M	M	+	M	M	M	M	M	+	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

+: Tissue examined microscopically
: Not examined
−: Present but not examined microscopically
I: Insufficient tissue

M: Missing
A: Autolysis precludes examination
X: Incidence of listed morphology

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

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	TOTAL:
CARCASS ID	191	201	211	231	241	261	271	281	291	301	321	341	351	361	371	381	391	401	431	441	451	461	471	491	501	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Polyp adenomatous													X													1
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant undifferentiated cell type									X																	1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma							X																			1
Hemangiosarcoma																										2
Hepatocellular carcinoma		X	X																							5
Hepatocellular carcinoma, multiple																										1
Hepatocellular adenoma					X	X	X			X							X						X	X	X	14
Hepatocellular adenoma, multiple													X		X					X	X					4
Mesentery																										1
Lipoma																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																			X							1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Carcinoid tumor malignant								X																		1
Tooth											+				+										+	4
Odontoma															X											1
CARDIOVASCULAR SYSTEM																										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma										X									X						X	5
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Adenoma																										1
Parathyroid gland	+	+	+	I	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	M	+	43
Pars distalis, adenoma																							X			1
Pars intermedia, adenoma		X																								1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	49
GENERAL BODY SYSTEM																										
Tissue, NOS															+											1
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland			+				+				+						+			+						10
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																						X				1
Seminal vesicle																									+	1
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	49
Femoral, hemangioma																				X						1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	48
Lymph node, mesenteric						+		+	+														+			5
Lymphoma malignant undifferentiated cell type									X																	1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Hemangiosarcoma																									X	3
Lymphoma malignant mixed																						X				2
Thymus	+	+	M	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	40
INTEGUMENTARY SYSTEM																										
Mammary gland	M	+	M	M	M	+	+	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	+	9
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	001	001	031	063	071	082	084	086	088	090	090	092	105	105	105	105	105	105	105	105	105	105	105	105	105	105
CARCASS ID	481	411	021	131	421	251	031	221	311	111	151	331	011	041	051	061	071	081	091	101	121	141	161	171	181	
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Alveolar/bronchiolar adenoma							X					X	X				X		X				X			
Alveolar/bronchiolar adenoma, multiple																					X					
Alveolar/bronchiolar carcinoma																										
Hepatocellular carcinoma, metastatic, liver																			X							
Lymphoma malignant mixed																										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
SPECIAL SENSES SYSTEM																										
Harderian gland	+	+	+	+	+	+	M	+	M	+	+	M	+	+	+	+	M	+	+	+	+	M	+	+	M	
Adenoma					X					X																
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	
Hemangiosarcoma																										

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: VEHICLE CONTROL (Continued)

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	TOTAL:
CARCASS ID	191	201	211	231	241	261	271	281	291	301	321	341	351	361	371	381	391	401	431	441	451	461	471	491	501	TISSUES TUMORS
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																						X				7
Alveolar/bronchiolar adenoma, multiple																							X			1
Alveolar/bronchiolar carcinoma						X																				2
Hepatocellular carcinoma, metastatic, liver		X																								2
Lymphoma malignant mixed																						X				1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland	+	+	M	+	+	M	+	M	+	+	+	+	+	+	+	M	I	+	+	+	+	+	+	+	+	39
Adenoma																									X	3
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																				X						1

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: 2.5 mg/Mouse

WEEKS ON STUDY	002	005	006	055	068	069	075	085	087	094	094	097	100	100	103	105	105	105	105	105	105	105	105	105	105
CARCASS ID	12711	13411	15211	14551	16221	14491	14441	13811	16911	14221	13551	14661	12661	13711	16511	12111	12211	12311	12441	12551	12881	12991	13011	13111	13211
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma														X					X					X	
Hemangioma, multiple																									
Hemangiosarcoma, multiple					X																				
Hepatocellular carcinoma								X		X		X													
Hepatocellular adenoma							X									X		X					X		
Hepatocellular adenoma, multiple																									
Lymphoma malignant mixed									X																
Mesentery									+																
Lymphoma malignant mixed									X																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed									X																
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed									X																
Tooth													+									+			
CARDIOVASCULAR SYSTEM																									
Blood vessel				+																					
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed									X																
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																							X		
Capsule, lymphoma malignant mixed									X																
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	+	M	M	+	M	+	+	+	M	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
Tissue, NOS																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland																									
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	-	+	+	-	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Axillary, deep cervical, mediastinal, squamous cell carcinoma, metastatic, skin												X													
Mediastinal, lymphoma malignant mixed									X					X											
Mediastinal, squamous cell carcinoma, metastatic, skin							X																		
Pancreatic, lymphoma malignant mixed									X																
Renal, lymphoma malignant mixed														X											
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Lymph node, mesenteric									+	+				+						+					
Lymphoma malignant histiocytic																				X					
Lymphoma malignant mixed									X					X											
Lymphoma malignant undifferentiated cell type																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																									
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed									X					X											
Lymphoma malignant undifferentiated cell type																									
Thymus	+	M	+	+	+	+	+	M	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 2.5 mg/Mouse (Continued)

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	TOTAL:
CARCASS ID	13331	13361	13391	14401	14411	14431	14471	14881	15001	15111	15331	15441	15551	15661	15771	15881	15991	16001	16111	16331	16441	16661	16771	16881	17001	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant undifferentiated cell type																							X			1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma	X																									4
Hemangioma, multiple																									X	1
Hemangiosarcoma, multiple																	X									2
Hepatocellular carcinoma																		X		X						5
Hepatocellular adenoma											X							X								6
Hepatocellular adenoma, multiple													X		X											2
Lymphoma malignant mixed																										1
Mesentery																										1
Lymphoma malignant mixed																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous	X																									1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Tooth											+															3
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma				X																X				X	X	5
Capsule, lymphoma malignant mixed																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	47
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GENERAL BODY SYSTEM																										
Tissue, NOS																						+				1
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Preputial gland														+	+						+	+				4
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																				X						1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Axillary, deep cervical, mediastinal, squamous cell carcinoma, metastatic, skin																										1
Mediastinal, lymphoma malig mixed																										2
Mediastinal, squamous cell carcinoma, metastatic, skin																										1
Pancreatic, lymphoma malignant mixed																										1
Renal, lymphoma malignant mixed																										1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	46
Lymph node, mesenteric			+						+								+						+			8
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed									X																	3
Lymphoma malignant undifferentiated cell type																							X			1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma												X														1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed									X				X													4
Lymphoma malignant undifferentiated cell type																							X			1
Thymus	+	+	+	+	M	+	+	+	M	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	42

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 2.5 mg/Mouse (Continued)

WEEKS ON STUDY	002	005	006	055	068	069	075	085	087	094	094	097	100	100	103	105	105	105	105	105	105	105	105	105	105
CARCASS ID	12711	13411	15211	14511	16211	14911	14411	13811	16911	14211	13511	14611	12611	13711	16511	12111	12211	12311	12411	12511	12811	12911	13011	13111	13211
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	+	M	M	M	M	M	M	M	M	M	M	+	M	M	+	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma							X																		
Back, squamous cell carcinoma							X							X											
Scapula, basosquamous tumor malignant																	X								
Scapula, squamous cell carcinoma												X			X					X					
Scapula, squamous cell carcinoma, multiple																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle																									
Hindlimb, hemangiosarcoma																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma														X	X					X	X	X			X
Alveolar/bronchiolar adenoma, multiple																									
Alveolar/bronchiolar carcinoma																									
Alveolar/bronchiolar carcinoma, multiple																									
Lymphoma malignant histiocytic																				X					
Lymphoma malignant mixed									X																
Squamous cell carcinoma, metastatic, skin							X					X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+		+	+	+	+	M	+
Adenoma												X										X			
Bilateral, adenoma																	X								
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed									X																
Squamous cell carcinoma, metastatic, skin							X					X													
Urinary bladder	+	+	+	+	+	+	+	+		+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 2.5 mg/Mouse (Continued)

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	TOTAL
CARCASS ID	13311	13361	13391	14001	14111	14311	14711	14811	15011	15111	15311	15411	15511	15611	15711	15811	15911	16011	16111	16311	16411	16611	16711	16811	17011	TISSUES TUMORS
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	+	+	M	M	M	+	+	+	M	M	M	+	M	M	M	+	M	M	M	M	M	M	11
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																										1
Back, squamous cell carcinoma				X											X											4
Scapula, basosquamous tumor malig		X																								2
Scapula, squamous cell carcinoma			X	X				X			X				X	X				X						10
Scapula, squamous cell carcinoma, multiple						X																		X		2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle											+															1
Hindlimb, hemangiosarcoma											X															1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma	X																				X					8
Alveolar/bronchiolar adenoma, multiple														X												1
Alveolar/bronchiolar carcinoma				X																						1
Alveolar/bronchiolar carcinoma, multiple								X																		1
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed																										1
Squamous cell carcinoma, metastatic, skin																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M		+	+	+	+	42
Adenoma	X				X								X											X		6
Bilateral, adenoma																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed																										1
Squamous cell carcinoma, metastatic, skin																										2
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: 5 mg/Mouse

WEEKS ON STUDY	001	001	001	001	005	006	032	035	059	063	063	075	075	076	078	081	082	085	087	088	088	090	090	090	090
CARCASS ID	25911	26511	26811	29211	28811	27111	29411	28911	24411	29111	25111	27311	28511	25211	26711	24111	28211	28001	25551	26441	26661	27701	27221	27441	27781
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									X
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma																									
Hepatocellular carcinoma															X					X		X		X	
Hepatocellular adenoma										X	X	X				X							X		
Hepatocellular adenoma, multiple																									
Lymphoma malignant lymphocytic																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Submandibular gland, lymphoma malignant lymphocytic																									
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
CARDIOVASCULAR SYSTEM																									
Blood vessel								+																	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Squamous cell carcinoma, metastatic, skin																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Capsule, adenoma												X													
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Medulla, squamous cell carcinoma, metastatic, skin																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	M
Pituitary gland	M	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	M	+	+	+	+	+
Thyroid gland	+	-	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS																+									
Squamous cell carcinoma, metastatic, skin																X									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Lymphoma malignant lymphocytic subacute, mild																									
Preputial gland										+					+				+	+					
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Lymph node	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, skin																									
Deep cervical, lymphoma malignant lymphocytic																									
Mediastinal, squamous cell carcinoma, metastatic																									
Mediastinal, squamous cell carcinoma, metastatic, skin																									
Lymph node, mandibular	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Squamous cell carcinoma, metastatic, skin																					X				
Lymph node, mesenteric						+						+						+	+	+		+	+	+	
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																				X					
Hemangiosarcoma																									
Thymus	+	+	+	M	M	+	+	+	+	M	M	+	M	+	M	M	M	M	M	+	+	M	M	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 5 mg/Mouse (Continued)

WEEKS ON STUDY	090	091	092	094	096	097	098	099	099	099	099	099	100	100	100	101	102	102	102	104	104	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	28331	25501	25411	24451	26061	25661	26691	24421	25771	28841	26631	24991	25881	24331	26221	26611	27515	24661	25331	27661	24881	24471	27711	27791	28111	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	M	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small, ileum	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Adenoma																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma					X																					1
Hepatocellular carcinoma																										4
Hepatocellular adenoma											X			X				X	X	X						10
Hepatocellular adenoma, multiple	X																									1
Lymphoma malignant lymphocytic		X																								1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Submandibular gland, lymphoma malignant lymphocytic		X																								1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																							X			1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	A	+	+	+	+	+	+	+	+	48
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic		X																								1
Squamous cell carcinoma, metastatic, skin							X							X				X								3
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic		X																								1
Capsule, adenoma											X														X	3
Adrenal gland, cortex	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Medulla, squamous cell carcinoma, metastatic, skin														X												1
Adrenal gland, medulla	+	+	+	M	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	47
Parathyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	M	+	+	42
Pituitary gland	+	+	+	M	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	42
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma												X														1
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
Squamous cell carcinoma, metastatic, skin																										1
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic		X																								1
Lymphoma malignant lymphocytic, subacute, mild													X													1
Preputial gland	+														+											6
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma										X																1
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	45
Squamous cell carcinoma, metastatic, skin													X													1
Deep cervical, lymphoma malignant lymphocytic		X																								1
Mediastinal, squamous cell carcinoma, metastatic																		X								1
Mediastinal, squamous cell carcinoma, metastatic, skin															X											1
Lymph node, mandibular	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+		43
Lymphoma malignant lymphocytic		X																								1
Squamous cell carcinoma, metastatic, skin																			X							2
Lymph node, mesenteric	+						+										+	+			+					13
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma					X																					1
Thymus	M	+	M	+	M	+	M	+	+	+	+	M	+	I	+	M	+	M	M	M	M	+	+	+	+	27

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 5 mg/Mouse (Continued)

WEEKS ON STUDY	001	001	001	001	005	006	032	035	059	063	063	075	075	076	078	081	082	085	087	088	088	090	090	090	090
CARCASS ID	25991	26511	26881	29211	28811	27111	29411	28911	24411	29111	25111	27311	28511	25211	26711	24111	28211	28011	25551	26441	26661	27001	27221	27411	27781
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	+	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Keratoacanthoma																			X						
Lymphoma malignant lymphocytic																									
Squamous cell carcinoma																									
Squamous cell carcinoma, multiple																									
Back, lymphoma malignant lymphocytic																									
Scapula, basal cell carcinoma																									
Scapula, lymphoma malignant lymphocytic																									
Scapula, squamous cell carcinoma									X			X	X	X	X	X	X	X			X	X	X		X
Scapula, squamous cell carcinoma, multiple																			X	X				X	
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+
Skeletal muscle																									
Diaphragm, squamous cell carcinoma, metastatic, skin																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																	X						X		
Alveolar/bronchiolar carcinoma																				X					
Squamous cell carcinoma, metastatic, skin									X			X				X							X	X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+
Adenoma												X													
Carcinoma																									
Lymphoma malignant lymphocytic																									
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic																									
Squamous cell carcinoma, metastatic									X																
Squamous cell carcinoma, metastatic, skin																									
Urinary bladder	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 5 mg/Mouse (Continued)

WEEKS ON STUDY	090	091	092	094	096	097	098	099	099	099	099	099	100	100	100	101	101	102	102	102	104	104	105	105	105	105	TOTAL: TISSUES TUMORS
CARCASS ID	28331	25001	25441	24451	26061	25661	26691	24221	25711	28441	26631	24491	25881	24331	26221	26111	27551	24461	25531	27661	24881	24471	27771	27791	28111		
INTEGUMENTARY SYSTEM																											
Mammary gland	M	M	M	M	M	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M		5
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Keratoacanthoma																											1
Lymphoma malignant lymphocytic		X																									1
Squamous cell carcinoma										X		X															2
Squamous cell carcinoma, multiple								X																			1
Back, lymphoma malignant lymphocytic		X																									1
Scapula, basal cell carcinoma																	X										1
Scapula, lymphoma malignant lymphocytic		X																									1
Scapula, squamous cell carcinoma	X	X	X			X	X		X	X					X		X	X	X	X	X	X		X			27
Scapula, squamous cell carcinoma, multiple				X	X						X	X	X	X		X							X		X		12
MUSCULOSKELETAL SYSTEM																											
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
Skeletal muscle															+												1
Diaphragm, squamous cell carcinoma, metastatic, skin															X												1
NERVOUS SYSTEM																											
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
RESPIRATORY SYSTEM																											
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Alveolar/bronchiolar adenoma														X					X		X		X	X	X		8
Alveolar/bronchiolar carcinoma																											1
Squamous cell carcinoma, metastatic, skin	X						X	X	X		X		X		X		X	X	X		X						16
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49
SPECIAL SENSES SYSTEM																											
Harderian gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		48
Adenoma																	X							X			3
Carcinoma								X																			1
Lymphoma malignant lymphocytic		X																									1
URINARY SYSTEM																											
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		50
Lymphoma malignant lymphocytic		X																									1
Squamous cell carcinoma, metastatic																											1
Squamous cell carcinoma, metastatic, skin								X							X				X								3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		49

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: 10 mg/Mouse

WEEKS ON STUDY	0 0 5	0 3 0	0 3 0	0 4 5	0 5 4	0 5 4	0 6 0	0 6 0	0 6 2	0 6 5	0 6 5	0 6 5	0 6 5	0 6 5	0 6 5	0 6 7	0 6 9	0 6 9	0 7 0	0 7 1	0 7 1	0 7 2	0 7 2	0 7 3	0 7 3
CARCASS ID	3 6 8 1	4 1 6 1	4 1 7 1	3 8 6 1	3 7 6 1	4 0 1 1	3 6 1 1	3 7 3 1	3 7 9 1	4 1 0 1	3 6 6 1	3 7 4 1	4 1 2 1	4 1 4 1	4 1 8 1	3 6 9 1	3 8 4 1	3 9 3 1	3 6 7 1	3 7 1 1	3 9 2 1	3 8 0 1	3 8 8 1	3 9 0 1	3 7 5 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Mesothelioma malignant						X																			
Pheochromocytoma complex, metastatic, diffuse						X																			
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant, metastatic, skin																									
Hepatocellular carcinoma															X										
Hepatocellular adenoma																									
Lymphoma malignant histiocytic				X																					
Squamous cell carcinoma, metastatic, skin																				X					
Mesentery																									
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, skin							X																		
Tooth																			+						
CARDIOVASCULAR SYSTEM																									
Blood vessel											+														
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, skin												X													
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																								X	
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Medulla, squamous cell carcinoma, metastatic, skin																				X					
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+
Islets, *pancreatic*	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	I	+	+	+
Parathyroid gland	M	+	M	M	M	+	+	+	+	M	M	+	+	+	+	+	M	+	+	M	+	M	+	+	+
Pituitary gland	+	+	+	M	M	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Thyroid gland	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
Tissue, NOS																									
GENITAL SYSTEM																									
Epididymis	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Preputial gland												+													
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Interstitial cell, adenoma																									
HEMATOPOIETIC SYSTEM																									
Blood																			+						
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic skin																									
Axillary, mediastinal, squamous cell carcinoma, metastatic, skin																				X					
Inguinal, mediastinal, squamous cell carcinoma, metastatic, skin																X									
Mediastinal, squamous cell carcinoma, metastatic, skin												X													
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic, skin																									
Axillary, squamous cell carcinoma, metastatic, skin													X												
Deep cervical, squamous cell carcinoma, metastatic, skin																									
Mediastinal, squamous cell carcinoma, metastatic, skin							X																		
Lymph node, mesenteric																					+				
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thymus	+	+	+	M	+	+	+	M	+	M	+	M	+	+	M	+	M	+	+	M	M	M	M	+	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 10 mg/Mouse (Continued)

WEEKS ON STUDY	073	073	073	074	074	074	074	075	075	075	077	077	078	079	080	081	081	081	082	082	083	083	083	083	083	TOTAL
CARCASS ID	394 1	400 1	383 1	387 1	363 1	391 1	398 1	396 1	377 1	397 1	399 1	385 1	378 1	382 1	411 1	389 1	402 1	404 1	370 1	395 1	365 1	372 1	362 1	364 1	400 1	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Mesothelioma malignant																										1
Pheochromocytoma complex, metastatic, diffuse																										1
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor malignant, metastatic, skin	X																X									2
Hepatocellular carcinoma						X					X								X							4
Hepatocellular adenoma																			X							1
Lymphoma malignant histiocytic																										1
Squamous cell carcinoma, metastatic, skin					X																					2
Mesentery						+																				1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, skin																										1
Tooth																										1
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic, skin							X									X					X					4
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Medulla, squamous cell carcinoma, metastatic, skin																										1
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	47
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Parathyroid gland	+	+	+	M	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	48
Pituitary gland	+	+	+	I	+	+	+	+	+	+	M	M	M	+	M	+	+	+	+	+	M	+	+	+	+	48
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
GENERAL BODY SYSTEM																										
Tissue, NOS																						+				1
GENITAL SYSTEM																										
Epididymis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Preputial gland																										1
Prostate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Testes	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Interstitial cell, adenoma																						X				1
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymph node	+	+	M	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	46
Squamous cell carcinoma, metastatic, skin																					X					1
Axillary, mediastinal, squamous cell carcinoma, metastatic, skin																										1
Inguinal, mediastinal, squamous cell carcinoma, metastatic, skin																										1
Mediastinal, squamous cell carcinoma, metastatic, skin																										1
Lymph node, mandibular	+	+	M	+	+	+	+	+	+	+	M	M	+	+	M	+	+	+	+	+	+	+	+	+	+	44
Squamous cell carcinoma, metastatic, skin					X	X	X																			3
Axillary, squamous cell carcinoma, metastatic, skin																										1
Deep cervical, squamous cell carcinoma, metastatic, skin				X																						1
Mediastinal, squamous cell carcinoma, metastatic, skin																										1
Lymph node, mesenteric					+			+			+			+	+		+		+						+	9
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Thymus	M	M	M	+	M	M	M	+	+	+	M	+	+	+	M	M	+	+	+	M	M	+	M	+	M	27

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 10 mg/Mouse (Continued)

WEEKS ON STUDY	005	030	030	045	054	054	060	060	062	065	065	065	065	065	065	067	069	069	070	071	071	072	072	073	073
CARCASS ID	36801	41611	41711	38611	37611	40111	36111	37311	37791	41011	36611	37411	41211	41411	41811	36991	38411	39311	36711	37111	39211	38801	38811	39011	37511
INTEGUMENTARY SYSTEM																									
Mammary gland	M	M	M	M	+	M	M	M	M	+	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma								X								X									
Squamous cell carcinoma, metastatic, skin																									
Scapula, basosquamous tumor malignant																			X						
Scapula, squamous cell carcinoma					X	X	X		X	X	X	X	X	X	X		X	X		X	X		X	X	X
Scapula, squamous cell carcinoma, multiple																X						X			
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																									
Basosquamous tumor malignant, metastatic, skin																			X						
Lymphoma malignant histiocytic				X																					
Squamous cell carcinoma, metastatic, skin					X		X		X			X			X	X				X				X	
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	+	+	+	+	M	M	+	+	+	M	+	M	+	+	+	+	+	+	+	+	I	M	+	+	+
Adenoma																			X						
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Basosquamous tumor malignant, metastatic, skin																									
Squamous cell carcinoma, metastatic, skin							X					X								X					
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	A	+

TABLE C2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF MALE MICE: 10 mg/Mouse (Continued)

WEEKS ON STUDY	073	073	073	074	074	074	074	075	075	075	077	077	078	079	080	081	081	081	082	082	083	083	083	083	083	TOTAL TISSUES TUMORS
CARCASS ID	3941	4031	3831	3871	3631	3911	3981	3961	3771	3991	3991	3851	3781	3821	3811	3891	4021	4041	3701	3951	3651	3721	3621	3641	4001	
INTEGUMENTARY SYSTEM																										
Mammary gland	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	+	M	M	M	+	M	4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma																				X						3
Squamous cell carcinoma, metastatic, skin																X										1
Scapula, basosquamous tumor malig	X																X									3
Scapula, squamous cell carcinoma		X	X	X	X			X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		37
Scapula, squamous cell carcinoma, multiple						X	X																		X	5
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma																			X				X			2
Alveolar/bronchiolar carcinoma			X																							1
Basosquamous tumor malignant, metastatic, skin	X																X									3
Lymphoma malignant histiocytic																										1
Squamous cell carcinoma, metastatic, skin				X	X	X		X					X		X	X		X		X	X	X			X	20
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland	+	+	+	+	+	+	+	+	M	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	42
Adenoma													X			X									X	4
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Basosquamous tumor malignant, metastatic, skin	X																X									2
Squamous cell carcinoma, metastatic, skin						X										X										5
Urinary bladder	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Adrenal Gland Capsule: Adenoma				
Overall Rates (a)	5/50 (10%)	5/50 (10%)	3/49 (6%)	1/50 (2%)
Adjusted Rates (b)	13.2%	14.3%	32.1%	3.7%
Terminal Rates (c)	5/38 (13%)	5/35 (14%)	1/4 (25%)	0/0
Day of First Observation	729	729	520	505
Life Table Tests (d)	P=0.055	P=0.579	P=0.104	P=0.398
Logistic Regression Tests (d)	P=0.626N	P=0.579	P=0.636N	P=0.829
Cochran-Armitage Trend Test (d)	P=0.056N			
Fisher Exact Test (d)		P=0.630N	P=0.369N	P=0.102N
Harderian Gland: Adenoma				
Overall Rates (e)	3/50 (6%)	7/50 (14%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	7.1%	19.3%	34.2%	46.3%
Terminal Rates (c)	1/38 (3%)	6/35 (17%)	1/4 (25%)	0/0
Day of First Observation	495	673	520	486
Life Table Tests (d)	P<0.001	P=0.141	P=0.230	P=0.008
Logistic Regression Tests (d)	P=0.260	P=0.155	P=0.627	P=0.484
Cochran-Armitage Trend Test (d)	P=0.517N			
Fisher Exact Test (d)		P=0.159	P=0.661N	P=0.500
Harderian Gland: Adenoma or Carcinoma				
Overall Rates (e)	3/50 (6%)	7/50 (14%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	7.1%	19.3%	37.9%	46.3%
Terminal Rates (c)	1/38 (3%)	6/35 (17%)	1/4 (25%)	0/0
Day of First Observation	495	673	520	486
Life Table Tests (d)	P<0.001	P=0.141	P=0.102	P=0.008
Logistic Regression Tests (d)	P=0.212	P=0.155	P=0.435	P=0.484
Cochran-Armitage Trend Test (d)	P=0.533N			
Fisher Exact Test (d)		P=0.159	P=0.500	P=0.500
Liver: Hepatocellular Adenoma				
Overall Rates (a)	18/50 (36%)	8/50 (16%)	11/50 (22%)	1/50 (2%)
Adjusted Rates (b)	43.7%	21.8%	55.8%	14.3%
Terminal Rates (c)	15/38 (39%)	7/35 (20%)	0/4 (0%)	0/0
Day of First Observation	574	525	435	572
Life Table Tests (d)	P=0.153	P=0.034N	P=0.016	P=0.280
Logistic Regression Tests (d)	P=0.006N	P=0.020N	P=0.264N	P=0.188N
Cochran-Armitage Trend Test (d)	P<0.001N			
Fisher Exact Test (d)		P=0.020N	P=0.093N	P<0.001N
Liver: Hepatocellular Carcinoma				
Overall Rates (a)	6/50 (12%)	5/50 (10%)	4/50 (8%)	4/50 (8%)
Adjusted Rates (b)	14.7%	12.5%	12.4%	25.9%
Terminal Rates (c)	4/38 (11%)	2/35 (6%)	0/4 (0%)	0/0
Day of First Observation	587	590	543	452
Life Table Tests (d)	P=0.002	P=0.525N	P=0.341	P=0.004
Logistic Regression Tests (d)	P=0.503N	P=0.504N	P=0.470N	P=0.671
Cochran-Armitage Trend Test (d)	P=0.298N			
Fisher Exact Test (d)		P=0.500N	P=0.370N	P=0.370N
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (a)	23/50 (46%)	12/50 (24%)	15/50 (30%)	4/50 (8%)
Adjusted Rates (b)	53.3%	30.0%	61.5%	25.9%
Terminal Rates (c)	18/38 (47%)	8/35 (23%)	0/4 (0%)	0/0
Day of First Observation	574	525	435	452
Life Table Tests (d)	P=0.008	P=0.039N	P=0.010	P=0.008
Logistic Regression Tests (d)	P=0.006N	P=0.018N	P=0.232N	P=0.085N
Cochran-Armitage Trend Test (d)	P<0.001N			
Fisher Exact Test (d)		P=0.018N	P=0.074N	P<0.001N

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	8/50 (16%)	9/50 (18%)	8/50 (16%)	2/50 (4%)
Adjusted Rates (b)	19.8%	24.3%	85.0%	42.9%
Terminal Rates (c)	6/38 (16%)	7/35 (20%)	3/4 (75%)	0/0
Day of First Observation	587	698	572	572
Life Table Tests (d)	P<0.001	P=0.442	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.215	P=0.489	P=0.250	P=0.724N
Cochran-Armitage Trend Test (d)	P=0.032N			
Fisher Exact Test (d)		P=0.500	P=0.607N	P=0.046N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	10/50 (20%)	11/50 (22%)	9/50 (18%)	3/50 (6%)
Adjusted Rates (b)	24.8%	29.7%	85.5%	45.3%
Terminal Rates (c)	8/38 (21%)	9/35 (26%)	3/4 (75%)	0/0
Day of First Observation	587	698	572	510
Life Table Tests (d)	P<0.001	P=0.431	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.237	P=0.487	P=0.312	P=0.747
Cochran-Armitage Trend Test (d)	P=0.021N			
Fisher Exact Test (d)		P=0.500	P=0.500N	P=0.036N
Skin (Application Site): Basosquamous Tumor Malignant				
Overall Rates (e)	0/50 (0%)	2/50 (4%)	0/50 (0%)	3/50 (6%)
Adjusted Rates (b)	0.0%	5.7%	0.0%	16.3%
Terminal Rates (c)	0/38 (0%)	2/35 (6%)	0/4 (0%)	0/0
Day of First Observation		729		486
Life Table Tests (d)	P<0.001	P=0.220	(f)	P=0.024
Logistic Regression Tests (d)	P=0.060	P=0.220	(f)	P=0.154
Cochran-Armitage Trend Test (d)	P=0.097			
Fisher Exact Test (d)		P=0.247	(f)	P=0.121
Skin (Application Site): Basosquamous Tumor Malignant or Basal Cell Carcinoma				
Overall Rates (e)	0/50 (0%)	2/50 (4%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	0.0%	5.7%	10.0%	16.3%
Terminal Rates (c)	0/38 (0%)	2/35 (6%)	0/4 (0%)	0/0
Day of First Observation		729	707	486
Life Table Tests (d)	P<0.001	P=0.220	P=0.236	P=0.024
Logistic Regression Tests (d)	P=0.042	P=0.220	P=0.367	P=0.154
Cochran-Armitage Trend Test (d)	P=0.104			
Fisher Exact Test (d)		P=0.247	P=0.500	P=0.121
Skin (Application Site): Squamous Cell Carcinoma				
Overall Rates (e)	0/50 (0%)	14/50 (28%)	39/50 (78%)	42/50 (84%)
Adjusted Rates (b)	0.0%	35.7%	100.0%	100.0%
Terminal Rates (c)	0/38 (0%)	10/35 (29%)	4/4 (100%)	0/0
Day of First Observation		525	411	376
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P<0.001	P<0.001	P<0.001
Skin (All Sites): Squamous Cell Carcinoma				
Overall Rates (e)	0/50 (0%)	14/50 (28%)	40/50 (80%)	43/50 (86%)
Adjusted Rates (b)	0.0%	35.7%	100.0%	100.0%
Terminal Rates (c)	0/38 (0%)	10/35 (29%)	4/4 (100%)	0/0
Day of First Observation		525	411	376
Life Table Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P<0.001	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P<0.001	P<0.001	P<0.001

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Circulatory System: Hemangioma				
Overall Rates (e)	2/50 (4%)	6/50 (12%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	5.3%	16.6%	3.2%	0.0%
Terminal Rates (c)	2/38 (5%)	5/35 (14%)	0/4 (0%)	0/0
Day of First Observation	729	698	613	
Life Table Tests (d)	P=0.208	P=0.113	P=0.575	(g)
Logistic Regression Tests (d)	P=0.660	P=0.126	P=0.638N	(g)
Cochran-Armitage Trend Test (d)	P=0.060N			
Fisher Exact Test (d)		P=0.134	P=0.500N	P=0.247N
Circulatory System: Hemangiosarcoma				
Overall Rates (e)	4/50 (8%)	3/50 (6%)	1/50 (2%)	0/50 (0%)
Adjusted Rates (b)	9.7%	7.8%	4.8%	0.0%
Terminal Rates (c)	2/38 (5%)	2/35 (6%)	0/4 (0%)	0/0
Day of First Observation	600	470	672	
Life Table Tests (d)	P=0.423N	P=0.529N	P=0.543N	(g)
Logistic Regression Tests (d)	P=0.039N	P=0.500N	P=0.243N	P=0.145N
Cochran-Armitage Trend Test (d)	P=0.025N			
Fisher Exact Test (d)		P=0.500N	P=0.181N	P=0.059N
Circulatory System: Hemangioma or Hemangiosarcoma				
Overall Rates (e)	5/50 (10%)	9/50 (18%)	2/50 (4%)	0/50 (0%)
Adjusted Rates (b)	12.2%	23.9%	7.8%	0.0%
Terminal Rates (c)	3/38 (8%)	7/35 (20%)	0/4 (0%)	0/0
Day of First Observation	600	470	613	
Life Table Tests (d)	P=0.415	P=0.167	P=0.650	(g)
Logistic Regression Tests (d)	P=0.072N	P=0.189	P=0.309N	P=0.136N
Cochran-Armitage Trend Test (d)	P=0.007N			
Fisher Exact Test (d)		P=0.194	P=0.218N	P=0.028N
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (e)	3/50 (6%)	6/50 (12%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	7.9%	15.8%	11.5%	2.1%
Terminal Rates (c)	3/38 (8%)	4/35 (11%)	0/4 (0%)	0/0
Day of First Observation	729	609	635	315
Life Table Tests (d)	P=0.054	P=0.215	P=0.240	P=0.500
Logistic Regression Tests (d)	P=0.411N	P=0.235	P=0.643	P=0.492N
Cochran-Armitage Trend Test (d)	P=0.114N			
Fisher Exact Test (d)		P=0.243	P=0.500N	P=0.309N
All Sites: Benign Tumors				
Overall Rates (e)	31/50 (62%)	26/50 (52%)	23/50 (46%)	7/50 (14%)
Adjusted Rates (b)	68.8%	66.5%	94.5%	77.9%
Terminal Rates (c)	24/38 (63%)	22/35 (63%)	3/4 (75%)	0/0
Day of First Observation	495	525	435	486
Life Table Tests (d)	P<0.001	P=0.352N	P<0.001	P<0.001
Logistic Regression Tests (d)	P=0.059N	P=0.216N	P=0.408N	P=0.083N
Cochran-Armitage Trend Test (d)	P<0.001N			
Fisher Exact Test (d)		P=0.210N	P=0.080N	P<0.001N
All Sites: Malignant Tumors				
Overall Rates (e)	16/50 (32%)	26/50 (52%)	40/50 (80%)	47/50 (94%)
Adjusted Rates (b)	37.8%	59.0%	100.0%	100.0%
Terminal Rates (c)	12/38 (32%)	17/35 (49%)	4/4 (100%)	0/0
Day of First Observation	587	470	411	315
Life Table Tests (d)	P<0.001	P=0.032	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.029	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.034	P<0.001	P<0.001

TABLE C3. ANALYSIS OF PRIMARY TUMORS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
All Sites: All Tumors				
Overall Rates (e)	35/50 (70%)	40/50 (80%)	42/50 (84%)	47/50 (94%)
Adjusted Rates (b)	77.7%	90.9%	100.0%	100.0%
Terminal Rates (c)	28/38 (74%)	31/35 (89%)	4/4 (100%)	0/0
Day of First Observation	495	470	411	315
Life Table Tests (d)	P<0.001	P=0.108	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.124	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P=0.001			
Fisher Exact Test (d)		P=0.178	P=0.077	P=0.002

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(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 a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined grossly at the site
(f) No P value is reported because no tumors were observed in the 5 mg/mouse and vehicle control groups.
(g) No P value is reported because all high dose animals died before the first tumor was observed in the vehicle control group.

TABLE C4. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN MALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence in Dermal Studies Using Acetone as a Vehicle (b)			
JP-5 navy fuel	0/50	0/50	0/50
Marine diesel fuel	1/50	0/50	1/50
TOTAL	1/100 (1.0%)	0/100	1/100 (1.0%)
Overall Historical Incidence for Untreated Controls			
TOTAL	(c) 4/1,692 (0.2%)	5/1,692 (0.3%)	(c) 9/1,692 (0.5%)
SD (d)	0.82%	0.72%	1.02%
Range (e)			
High	2/50	1/49	2/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Studies conducted at Litton Bionetics, Inc.
(c) Includes one papilloma, NOS
(d) Standard deviation
(e) Range and SD are presented for groups of 35 or more animals.

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Animals initially in study	60	60	60	60
Animals removed	60	60	60	60
Animals examined histopathologically	50	50	50	50
ALIMENTARY SYSTEM				
Intestine large, cecum	(50)	(50)	(50)	(49)
Inflammation, necrotizing				1 (2%)
Parasite metazoan		1 (2%)		
Intestine large, colon	(50)	(50)	(50)	(50)
Parasite metazoan	1 (2%)	1 (2%)		1 (2%)
Intestine large, rectum	(50)	(48)	(49)	(48)
Parasite metazoan	2 (4%)	1 (2%)	1 (2%)	1 (2%)
Liver	(50)	(50)	(50)	(50)
Amyloid deposition			1 (2%)	
Basophilic focus			2 (4%)	
Cyst	3 (6%)	3 (6%)	4 (8%)	
Cytomegaly, multifocal	2 (4%)			
Hematopoietic cell proliferation				1 (2%)
Inclusion body intracytoplasmic	1 (2%)	1 (2%)	2 (4%)	
Inflammation, chronic active, multifocal	1 (2%)		6 (12%)	7 (14%)
Inflammation, subacute, diffuse				1 (2%)
Necrosis, coagulative, focal		1 (2%)	1 (2%)	1 (2%)
Necrosis, coagulative, multifocal	1 (2%)	4 (8%)	5 (10%)	6 (12%)
Thrombus	6 (12%)	2 (4%)	1 (2%)	2 (4%)
Sinusoid, centrilobular, dilatation				1 (2%)
Vein, dilatation, focal		1 (2%)		
Mesentery	(1)	(1)		(1)
Inflammation, chronic	1 (100%)			
Inflammation, subacute				1 (100%)
Pancreas	(49)	(50)	(50)	(49)
Hyperplasia, nodular	1 (2%)			
Acinus, atrophy	1 (2%)	2 (4%)	2 (4%)	2 (4%)
Duct, ectasia				1 (2%)
Salivary glands	(50)	(50)	(50)	(50)
Inflammation, necrotizing, multifocal				1 (2%)
Inflammation, subacute, multifocal			3 (6%)	1 (2%)
Artery, inflammation, chronic	1 (2%)			
Stomach, forestomach	(50)	(50)	(50)	(50)
Acanthosis	2 (4%)			1 (2%)
Hyperkeratosis	2 (4%)			1 (2%)
Ulcer	3 (6%)			
Lamina propria, infiltration cellular, histiocytic, focal	1 (2%)			
Stomach, glandular	(50)	(50)	(48)	(50)
Hyperplasia				2 (4%)
Inflammation, acute				3 (6%)
Inflammation, necrotizing	1 (2%)			1 (2%)
Ulcer				4 (8%)
Serosa, granuloma	1 (2%)			
Tooth	(4)	(3)		(1)
Peridontal tissue, incisor, inflammation, chronic		2 (67%)		
Peridontal tissue, molar, abscess	1 (25%)			
Peridontal tissue, molar, inflammation, chronic		1 (33%)		1 (100%)
Pulp, molar, inflammation, chronic	2 (50%)			
CARDIOVASCULAR SYSTEM				
Blood vessel		(1)	(1)	(1)
Aorta, bacterium			1 (100%)	1 (100%)
Aorta, inflammation, chronic active			1 (100%)	1 (100%)

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
CARDIOVASCULAR SYSTEM				
Blood vessel (Continued)		(1)	(1)	(1)
Aorta, thrombus			1 (100%)	1 (100%)
Renal artery, inflammation, chronic		1 (100%)		
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy				1 (2%)
Dilatation				1 (2%)
Artery, thrombus		1 (2%)		
Atrium left, dilatation		1 (2%)		
Atrium left, thrombus		1 (2%)		
Coronary artery, inflammation, chronic	1 (2%)	2 (4%)		
Myocardium, inflammation, chronic, focal	1 (2%)			3 (6%)
Myocardium, inflammation, chronic, multifocal		1 (2%)		
Myocardium, inflammation, subacute, focal		1 (2%)		1 (2%)
Myocardium, mineralization, multifocal	1 (2%)		1 (2%)	
Pericardium, ectopic thyroid	1 (2%)			
Valve, bacterium			2 (4%)	1 (2%)
Valve, inflammation, subacute		1 (2%)	2 (4%)	1 (2%)
Valve, thrombus		1 (2%)	3 (6%)	1 (2%)
ENDOCRINE SYSTEM				
Adrenal gland	(50)	(50)	(49)	(50)
Capsule, hyperplasia	44 (88%)	42 (84%)	38 (78%)	44 (88%)
Adrenal gland, cortex	(50)	(49)	(49)	(50)
Hyperplasia, nodular	27 (54%)	30 (61%)	5 (10%)	5 (10%)
Hyperplasia, nodular, focal			1 (2%)	
Necrosis, liquifactive			1 (2%)	
Adrenal gland, medulla	(50)	(49)	(48)	(47)
Hyperplasia	1 (2%)			
Necrosis, liquifactive			1 (2%)	
Islets, pancreatic	(48)	(50)	(47)	(48)
Cytoplasmic alteration		1 (2%)		
Hyperplasia	22 (46%)	5 (10%)	3 (6%)	4 (8%)
Pituitary gland	(43)	(47)	(42)	(38)
Pars distalis, hyperplasia		1 (2%)		
Pars distalis, hyperplasia, nodular	1 (2%)	1 (2%)		
Thyroid gland	(49)	(50)	(49)	(48)
Hyperplasia, nodular		1 (2%)	1 (2%)	
Inflammation, chronic		1 (2%)		
Follicle, hyperplasia, nodular	12 (24%)	9 (18%)	2 (4%)	
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Epididymis	(50)	(50)	(50)	(49)
Granuloma sperm		1 (2%)		
Inflammation, subacute			6 (12%)	13 (27%)
Preputial gland	(10)	(4)	(6)	(1)
Abscess	6 (60%)	3 (75%)	2 (33%)	
Inflammation, chronic	1 (10%)	1 (25%)	1 (17%)	
Duct, dilatation	4 (40%)	1 (25%)	5 (83%)	1 (100%)
Prostate	(50)	(50)	(50)	(50)
Inflammation, chronic active	1 (2%)	1 (2%)	5 (10%)	6 (12%)
Seminal vesicle	(1)			
Dilatation	1 (100%)			

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
GENITAL SYSTEM (Continued)				
Testes	(50)	(50)	(50)	(50)
Infarct	1 (2%)			
Inflammation, chronic, focal		1 (2%)		
Seminiferous tubule, atrophy			1 (2%)	
HEMATOPOIETIC SYSTEM				
Blood	(1)			(1)
Polychromasia	1 (100%)			
Bone marrow	(49)	(50)	(49)	(49)
Femoral, necrosis, caseous				1 (2%)
Femoral, thrombus	1 (2%)			
Myeloid cell, hyperplasia				1 (2%)
Lymph node	(49)	(49)	(45)	(46)
Hyperplasia, lymphoid		1 (2%)		
Bronchial, infiltration cellular, polymorphonuclear			1 (2%)	
Deep cervical, infiltration cellular, polymorphonuclear				1 (2%)
Mediastinal, infiltration cellular, polymorphonuclear			2 (4%)	2 (4%)
Mediastinal, infiltration cellular, histiocytic				2 (4%)
Renal, hyperplasia, plasma cell			1 (2%)	
Renal, infiltration cellular, polymorphonuclear			1 (2%)	
Lymph node, mandibular	(48)	(46)	(43)	(44)
Hematopoietic cell proliferation	1 (2%)			
Infiltration cellular, polymorphonuclear	1 (2%)		3 (7%)	5 (11%)
Infiltration cellular, histiocytic	1 (2%)			
Lymph node, mesenteric	(5)	(8)	(13)	(9)
Hematopoietic cell proliferation	1 (20%)	1 (13%)	1 (8%)	1 (11%)
Infiltration cellular, polymorphonuclear	1 (20%)	1 (13%)	10 (77%)	6 (67%)
Sinus, ectasia	2 (40%)	1 (13%)	4 (31%)	3 (33%)
Spleen	(49)	(50)	(50)	(50)
Amyloid deposition		1 (2%)		
Depletion lymphoid	4 (8%)	2 (4%)	8 (16%)	2 (4%)
Fibrosis			1 (2%)	
Fibrosis, focal	1 (2%)	1 (2%)		
Hematopoietic cell proliferation	2 (4%)	7 (14%)	31 (62%)	39 (78%)
Necrosis, coagulative			1 (2%)	
Thrombus	1 (2%)			
Subcapsular, infiltration cellular, histiocytic, multifocal	1 (2%)			
Thymus	(40)	(42)	(27)	(27)
Ectopic parathyroid gland		1 (2%)		
Necrosis				1 (4%)
INTEGUMENTARY SYSTEM				
Skin	(50)	(50)	(50)	(50)
Abscess	1 (2%)		1 (2%)	
Acanthosis		5 (10%)	6 (12%)	5 (10%)
Cyst epithelial inclusion				1 (2%)
Edema		1 (2%)	1 (2%)	
Hyperkeratosis		1 (2%)	2 (4%)	
Inflammation, acute			1 (2%)	1 (2%)
Inflammation, chronic	1 (2%)			1 (2%)
Inflammation, necrotizing			6 (12%)	1 (2%)
Back, acanthosis		6 (12%)	6 (12%)	2 (4%)
Back, hyperkeratosis		1 (2%)	4 (8%)	4 (8%)
Back, inflammation, necrotizing				1 (2%)
Back, parasite metazoan	1 (2%)			

TABLE C5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
INTEGUMENTARY SYSTEM				
Skin (Continued)	(50)	(50)	(50)	(50)
Lymphatic, dilatation				1 (2%)
Scapula, acanthosis	1 (2%)	35 (70%)	38 (76%)	35 (70%)
Scapula, hyperkeratosis	1 (2%)	12 (24%)	14 (28%)	21 (42%)
Scapula, inflammation, chronic		1 (2%)		
Scapula, inflammation, chronic active			1 (2%)	
Scapula, inflammation, necrotizing	1 (2%)	4 (8%)	12 (24%)	15 (30%)
MUSCULOSKELETAL SYSTEM				
Bone	(50)	(50)	(49)	(50)
Artery, femur, thrombus				1 (2%)
Cranium, proliferation	1 (2%)			
Tibia, inflammation, acute				1 (2%)
NERVOUS SYSTEM				
Brain	(50)	(50)	(50)	(50)
Autolysis				1 (2%)
Hemorrhage, multifocal	1 (2%)			1 (2%)
Mineralization, multifocal	21 (42%)	30 (60%)	25 (50%)	22 (44%)
Hypothalamus, compression	1 (2%)			
RESPIRATORY SYSTEM				
Lung	(50)	(50)	(50)	(50)
Congestion, diffuse	3 (6%)			
Hemorrhage, focal	2 (4%)		2 (4%)	3 (6%)
Hemorrhage, multifocal	2 (4%)		2 (4%)	1 (2%)
Inflammation, suppurative, focal	1 (2%)			
Thrombus			1 (2%)	1 (2%)
Alveolar epithelium, hyperplasia				1 (2%)
Alveolus, infiltration cellular, histiocytic		1 (2%)		1 (2%)
Bronchiole, edema, diffuse	1 (2%)			
Interstitium, inflammation, chronic		2 (4%)	1 (2%)	1 (2%)
SPECIAL SENSES SYSTEM				
Harderian gland	(39)	(42)	(48)	(42)
Hyperplasia, nodular	2 (5%)	1 (2%)	1 (2%)	
Inflammation, chronic, focal	1 (3%)			1 (2%)
Inflammation, subacute			4 (8%)	5 (12%)
URINARY SYSTEM				
Kidney	(50)	(50)	(50)	(50)
Ectopic tissue	1 (2%)			
Hemorrhage, multifocal	1 (2%)			
Hydronephrosis	1 (2%)			
Infarct		2 (4%)	1 (2%)	
Inflammation, necrotizing	1 (2%)		1 (2%)	1 (2%)
Inflammation, subacute, multifocal			2 (4%)	3 (6%)
Fat, infiltration cellular, histiocytic, focal	1 (2%)			
Glomerulus, inflammation, proliferative	1 (2%)			
Renal tubule, bacterium	1 (2%)		1 (2%)	
Renal tubule, casts protein, multifocal	1 (2%)			
Renal tubule, cyst	1 (2%)		1 (2%)	
Urinary bladder	(50)	(48)	(49)	(48)
Ectasia			1 (2%)	
Thrombus	1 (2%)			

APPENDIX D

SUMMARY OF LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Animals initially in study	60	60	60	60
Animals removed	60	60	60	60
Animals examined histopathologically	50	50	50	50
ALIMENTARY SYSTEM				
Gallbladder	(48)	(49)	(48)	(49)
Lymphoma malignant histiocytic			2 (4%)	
Lymphoma malignant mixed		1 (2%)		
Sarcoma, metastatic			1 (2%)	
Intestine large, cecum	(50)	(48)	(49)	(50)
Lymphoma malignant lymphocytic				1 (2%)
Intestine large, colon	(50)	(50)	(50)	(50)
Lymphoma malignant lymphocytic				1 (2%)
Sarcoma, metastatic		1 (2%)		
Intestine large, rectum	(50)	(49)	(50)	(50)
Lymphoma malignant lymphocytic				1 (2%)
Intestine small, ileum	(48)	(50)	(50)	(50)
Lymphoma malignant lymphocytic				1 (2%)
Lymphoma malignant mixed	1 (2%)			
Intestine small, jejunum	(50)	(50)	(50)	(50)
Lymphoma malignant lymphocytic	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Hemangioma			1 (2%)	1 (2%)
Hemangiosarcoma			1 (2%)	
Hepatocellular carcinoma	2 (4%)	3 (6%)	3 (6%)	2 (4%)
Hepatocellular carcinoma, metastatic, multiple				1 (2%)
Hepatocellular adenoma	7 (14%)	6 (12%)	5 (10%)	2 (4%)
Hepatocellular adenoma, multiple	1 (2%)			1 (2%)
Histiocytic sarcoma, metastatic, metastatic		1 (2%)		
Histiocytic sarcoma, metastatic, metastatic, metastatic			1 (2%)	
Lymphoma malignant histiocytic			2 (4%)	
Lymphoma malignant lymphocytic	1 (2%)			
Lymphoma malignant mixed	5 (10%)			
Squamous cell carcinoma, metastatic				2 (4%)
Squamous cell carcinoma, metastatic, skin				1 (2%)
Mesentery	*(50)	*(50)	*(50)	*(50)
Hemangioma	1 (2%)			
Histiocytic sarcoma, metastatic, metastatic		1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)		
Lymphoma malignant mixed		1 (2%)		
Lymphoma malignant undifferentiated cell type	1 (2%)			
Osteosarcoma, metastatic, uncertain primary site	1 (2%)			
Sarcoma, metastatic			1 (2%)	
Pancreas	(50)	(49)	(50)	(50)
Histiocytic sarcoma, metastatic, metastatic			1 (2%)	
Lymphoma malignant histiocytic			1 (2%)	
Lymphoma malignant lymphocytic		1 (2%)		1 (2%)
Lymphoma malignant mixed	1 (2%)	1 (2%)		
Lymphoma malignant undifferentiated cell type	1 (2%)		1 (2%)	
Osteosarcoma, metastatic, uncertain primary site	1 (2%)			
Salivary glands	(50)	(49)	(50)	(50)
Lymphoma malignant histiocytic			1 (2%)	
Lymphoma malignant lymphocytic				1 (2%)
Stomach, forestomach	(49)	(50)	(50)	(50)
Lymphoma malignant lymphocytic				1 (2%)
Papilloma squamous	3 (6%)		1 (2%)	3 (6%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
ALIMENTARY SYSTEM (Continued)				
Stomach, glandular	(50)	(49)	(50)	(50)
Adenoma	1 (2%)			
Lymphoma malignant lymphocytic				1 (2%)
Lymphoma malignant mixed			1 (2%)	
Tooth	*(50)	*(50)	*(50)	*(50)
Peridontal tissue, histiocytic sarcoma, metastatic		1 (2%)		
CARDIOVASCULAR SYSTEM				
Heart	(50)	(50)	(50)	(50)
Histiocytic sarcoma, metastatic, metastatic			1 (2%)	
Lymphoma malignant lymphocytic				1 (2%)
Lymphoma malignant mixed	1 (2%)			
Lymphoma malignant undifferentiated cell type	1 (2%)			
Squamous cell carcinoma, metastatic				1 (2%)
Squamous cell carcinoma, metastatic, skin			1 (2%)	2 (4%)
ENDOCRINE SYSTEM				
Adrenal gland	(50)	(50)	(50)	(50)
Leukemia granulocytic			1 (2%)	
Bilateral, capsule, adenoma			1 (2%)	
Capsule, adenoma	2 (4%)	1 (2%)	6 (12%)	3 (6%)
Capsule, carcinoma				1 (2%)
Capsule, lymphoma malignant lymphocytic	1 (2%)			
Extra adrenal tissue, histiocytic sarcoma, metastatic		1 (2%)	1 (2%)	
Extra adrenal tissue, lymphoma malignant lymphocytic		1 (2%)		
Adrenal gland, cortex	(50)	(50)	(50)	(49)
Lymphoma malignant lymphocytic				1 (2%)
Squamous cell carcinoma, metastatic				1 (2%)
Adrenal gland, medulla	(50)	(49)	(50)	(48)
Pheochromocytoma malignant			1 (2%)	
Pheochromocytoma benign		1 (2%)	1 (2%)	
Islets, pancreatic	(49)	(50)	(49)	(50)
Adenoma		1 (2%)		
Pituitary gland	(49)	(48)	(47)	(45)
Pars distalis, adenoma	17 (35%)	16 (33%)	5 (11%)	
Pars distalis, carcinoma			1 (2%)	
Pars distalis, granular cell tumor malignant, metastatic				1 (2%)
Pars intermedia, adenoma	2 (4%)			1 (2%)
Thyroid gland	(49)	(49)	(50)	(50)
Lymphoma malignant lymphocytic		1 (2%)		
Follicular cell, adenoma	2 (4%)	1 (2%)	2 (4%)	
GENERAL BODY SYSTEM				
Tissue, NOS	*(50)	*(50)	*(50)	*(50)
Osteosarcoma, metastatic, metastatic	1 (2%)			
GENITAL SYSTEM				
Ovary	(50)	(49)	(49)	(50)
Cystadenoma	1 (2%)			
Granulosa cell tumor malignant			2 (4%)	2 (4%)
Granulosa cell tumor benign			5 (10%)	10 (20%)
Histiocytic sarcoma, metastatic, metastatic		1 (2%)	1 (2%)	
Luteoma	1 (2%)			

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
GENITAL SYSTEM				
Ovary (Continued)	(50)	(49)	(49)	(50)
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)		1 (2%)
Lymphoma malignant mixed	2 (4%)	1 (2%)	1 (2%)	
Mixed tumor benign			9 (18%)	6 (12%)
Bilateral, histiocytic sarcoma, metastatic		1 (2%)		
Bilateral, lymphoma malignant histiocytic			1 (2%)	
Bilateral, lymphoma malignant lymphocytic		1 (2%)		
Bilateral, lymphoma malignant mixed			1 (2%)	
Bilateral, mixed tumor benign			2 (4%)	
Uterus	(50)	(49)	(49)	(50)
Hemangioma	1 (2%)			
Histiocytic sarcoma		2 (4%)	1 (2%)	
Lymphoma malignant lymphocytic	1 (2%)			1 (2%)
Lymphoma malignant mixed	1 (2%)			
Polyp stromal	1 (2%)	1 (2%)		1 (2%)
HEMATOPOIETIC SYSTEM				
Bone marrow	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)			
Mast cell tumor, NOS	1 (2%)			
Femoral, hemangiosarcoma		1 (2%)		
Lymph node	(49)	(49)	(47)	(50)
Squamous cell carcinoma, metastatic			1 (2%)	2 (4%)
Squamous cell carcinoma, metastatic, metastatic			1 (2%)	
Axillary, adenocarcinoma, metastatic, mammary gland			1 (2%)	
Axillary, squamous cell carcinoma, metastatic, skin			1 (2%)	1 (2%)
Deep cervical, lymphoma malignant lymphocytic				1 (2%)
Lumbar, histiocytic sarcoma, metastatic		1 (2%)		
Lumbar, lymphoma malignant histiocytic			2 (4%)	
Lumbar, lymphoma malignant lymphocytic	1 (2%)			
Lumbar, lymphoma malignant mixed			1 (2%)	
Mediastinal, lymphoma malignant histiocytic			2 (4%)	
Mediastinal, lymphoma malignant lymphocytic	2 (4%)	1 (2%)		1 (2%)
Mediastinal, lymphoma malignant mixed	1 (2%)	1 (2%)	2 (4%)	
Mediastinal, lymphoma malignant undifferentiated cell type			1 (2%)	
Mediastinal, squamous cell carcinoma, metastatic, skin			1 (2%)	
Pancreatic, lymphoma malignant histiocytic			2 (4%)	
Pancreatic, lymphoma malignant lymphocytic				1 (2%)
Pancreatic, lymphoma malignant mixed		1 (2%)		
Renal, lymphoma malignant histiocytic			2 (4%)	
Renal, lymphoma malignant lymphocytic				1 (2%)
Renal, lymphoma malignant mixed			2 (4%)	
Lymph node, mandibular	(48)	(49)	(47)	(48)
Histiocytic sarcoma, metastatic			1 (2%)	
Lymphoma malignant histiocytic			2 (4%)	
Lymphoma malignant lymphocytic	2 (4%)	2 (4%)		1 (2%)
Lymphoma malignant mixed	3 (6%)	1 (2%)	2 (4%)	
Squamous cell carcinoma, metastatic, skin		1 (2%)	5 (11%)	4 (8%)
Axillary, squamous cell carcinoma, metastatic, skin				1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
HEMATOPOIETIC SYSTEM				
Lymph node, mandibular (Continued)	(48)	(49)	(47)	(48)
Deep cervical, squamous cell carcinoma, metastatic, skin				1 (2%)
Lumbar, squamous cell carcinoma, metastatic, skin				1 (2%)
Lymph node, mesenteric	(6)	(4)	(6)	(7)
Histiocytic sarcoma, metastatic		1 (25%)		
Lymphoma malignant histiocytic			1 (17%)	
Lymphoma malignant lymphocytic	1 (17%)	1 (25%)		1 (14%)
Lymphoma malignant mixed	1 (17%)		2 (33%)	
Lymphoma malignant undifferentiated cell type	1 (17%)			
Spleen	(50)	(50)	(50)	(50)
Hemangioma	2 (4%)			
Hemangiosarcoma		1 (2%)		
Hemangiosarcoma, metastatic	1 (2%)			
Histiocytic sarcoma, metastatic, metastatic		1 (2%)		
Lymphoma malignant histiocytic			2 (4%)	
Lymphoma malignant lymphocytic	3 (6%)			1 (2%)
Lymphoma malignant mixed	9 (18%)	2 (4%)	1 (2%)	
Lymphoma malignant undifferentiated cell type	3 (6%)		1 (2%)	
Osteosarcoma, metastatic, uncertain primary site	1 (2%)			
Squamous cell carcinoma, metastatic, skin			1 (2%)	
Capsule, fibrous histiocytoma			1 (2%)	
Capsule, histiocytic sarcoma, metastatic		1 (2%)		
Thymus	(42)	(45)	(33)	(33)
Lymphoma malignant lymphocytic	1 (2%)	1 (2%)		
Lymphoma malignant mixed	2 (5%)	1 (2%)		
Lymphoma malignant undifferentiated cell type	1 (2%)			
Squamous cell carcinoma, metastatic				1 (3%)
Thymoma benign			1 (3%)	
INTEGUMENTARY SYSTEM				
Mammary gland	(44)	(41)	(41)	(39)
Adenocarcinoma	1 (2%)	1 (2%)	3 (7%)	4 (10%)
Inguinal, lymphoma malignant mixed	1 (2%)			
Skin	(50)	(50)	(50)	(50)
Hemangioma	1 (2%)			
Hemangiosarcoma	1 (2%)			
Lymphoma malignant lymphocytic		1 (2%)		1 (2%)
Squamous cell carcinoma			3 (6%)	2 (4%)
Squamous cell carcinoma, multiple				1 (2%)
Back, fibrous histiocytoma			1 (2%)	
Back, lymphoma malignant lymphocytic		1 (2%)		1 (2%)
Back, osteosarcoma, metastatic			1 (2%)	
Back, squamous cell carcinoma		1 (2%)	3 (6%)	
Back, squamous cell carcinoma, multiple			1 (2%)	
Scapula, basosquamous tumor malignant			1 (2%)	1 (2%)
Scapula, fibrous histiocytoma			1 (2%)	
Scapula, lymphoma malignant lymphocytic		1 (2%)		1 (2%)
Scapula, squamous cell carcinoma		5 (10%)	14 (28%)	31 (62%)
Scapula, squamous cell carcinoma, multiple		1 (2%)	23 (46%)	10 (20%)
Scapula, squamous cell carcinoma, metastatic				2 (4%)
Scapula, squamous cell carcinoma, metastatic, multiple				2 (4%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
INTEGUMENTARY SYSTEM				
Skin (Continued)	(50)	(50)	(50)	(50)
Sebaceous gland, adenocarcinoma		1 (2%)		
Subcutaneous tissue, fibrosarcoma			1 (2%)	
Subcutaneous tissue, scapula, squamous cell carcinoma, metastatic			1 (2%)	
MUSCULOSKELETAL SYSTEM				
Bone	(50)	(50)	(49)	(50)
Osteosarcoma			1 (2%)	
Skeletal muscle	*(50)	*(50)	*(50)	*(50)
Abdominal, lymphoma malignant lymphocytic	1 (2%)			
Back, sarcoma, metastatic			1 (2%)	
Intercostal, squamous cell carcinoma, metastatic, skin			1 (2%)	1 (2%)
Neck, lymphoma malignant lymphocytic				1 (2%)
NERVOUS SYSTEM				
Brain	(50)	(50)	(50)	(50)
Lymphoma malignant lymphocytic				1 (2%)
RESPIRATORY SYSTEM				
Lung	(50)	(50)	(50)	(50)
Adenocarcinoma, metastatic, mammary gland		1 (2%)	1 (2%)	1 (2%)
Alveolar/bronchiolar adenoma	3 (6%)	5 (10%)	8 (16%)	6 (12%)
Alveolar/bronchiolar carcinoma	1 (2%)	4 (8%)	3 (6%)	1 (2%)
Basosquamous tumor malignant, metastatic, skin			1 (2%)	
Granulosa cell tumor malignant, metastatic, ovary			1 (2%)	2 (4%)
Hepatocellular carcinoma, metastatic, liver	1 (2%)	1 (2%)		
Hepatocellular carcinoma, metastatic, skin			1 (2%)	
Hepatocellular carcinoma, metastatic, metastatic		1 (2%)		
Histiocytic sarcoma, metastatic, metastatic		1 (2%)	1 (2%)	
Lymphoma malignant histiocytic			2 (4%)	
Lymphoma malignant lymphocytic	1 (2%)	2 (4%)		1 (2%)
Lymphoma malignant mixed	2 (4%)	1 (2%)	2 (4%)	
Osteosarcoma, metastatic, uncertain primary site	1 (2%)			
Sarcoma, metastatic			1 (2%)	
Squamous cell carcinoma, metastatic				2 (4%)
Squamous cell carcinoma, metastatic, skin		1 (2%)	9 (18%)	18 (36%)
Bronchiole, adenocarcinoma, metastatic				1 (2%)
Mediastinum, lymphoma malignant undifferentiated cell type	2 (4%)			
SPECIAL SENSES SYSTEM				
Harderian gland	*(50)	*(50)	*(50)	*(50)
Adenoma	5 (10%)	1 (2%)	4 (8%)	8 (16%)
Carcinoma		1 (2%)		
Lymphoma malignant lymphocytic		1 (2%)		1 (2%)

TABLE D1. SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
URINARY SYSTEM				
Kidney	(50)	(50)	(50)	(50)
Histiocytic sarcoma, metastatic, metastatic		1 (2%)		
Lymphoma malignant histiocytic			2 (4%)	
Lymphoma malignant lymphocytic	2 (4%)	1 (2%)		1 (2%)
Lymphoma malignant mixed	3 (6%)		2 (4%)	
Lymphoma malignant undifferentiated cell type	1 (2%)			
Osteosarcoma, metastatic, uncertain primary site	1 (2%)			
Squamous cell carcinoma				1 (2%)
Squamous cell carcinoma, metastatic				1 (2%)
Squamous cell carcinoma, metastatic, skin			1 (2%)	3 (6%)
Urinary bladder	(49)	(49)	(48)	(50)
Histiocytic sarcoma, metastatic		1 (2%)		
Lymphoma malignant lymphocytic	1 (2%)			1 (2%)
Lymphoma malignant mixed		1 (2%)		
Lymphoma malignant undifferentiated cell type			1 (2%)	
SYSTEMIC LESIONS				
Multiple organs	*(50)	*(50)	*(50)	*(50)
Lymphoma malignant mixed	10 (20%)	3 (6%)	2 (4%)	
Lymphoma malignant undifferentiated cell	4 (8%)		2 (4%)	
Lymphoma malignant lymphocytic	4 (8%)	2 (4%)		1 (2%)
Hemangiosarcoma	1 (2%)	1 (2%)	1 (2%)	
Hemangioma	4 (8%)		1 (2%)	1 (2%)
Lymphoma malignant histiocytic			2 (4%)	
Leukemia granulocytic			1 (2%)	
ANIMAL DISPOSITION SUMMARY				
Animals initially in study	60	60	60	60
Terminal sacrifice	30	31	14	10
Moribund	10	10	23	29
Dead	7	8	13	9
Accident	1			
Accidently killed	1			
Drowned	1	1		
Scheduled sacrifice	10	10	10	12
TUMOR SUMMARY				
Total animals with primary neoplasms **	41	36	47	46
Total primary neoplasms	74	58	123	99
Total animals with benign neoplasms	31	25	34	29
Total benign neoplasms	52	33	51	42
Total animals with malignant neoplasms	22	22	44	44
Total malignant neoplasms	23	25	72	57
Total animals with secondary neoplasms ***	3	7	20	29
Total secondary neoplasms	8	19	40	53
Total animals with malignant neoplasms--uncertain primary site	1			
Total animals with neoplasms--uncertain benign or malignant	1			
Total uncertain neoplasms	1			

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

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: VEHICLE CONTROL

WEEKS ON STUDY	010	056	063	065	065	072	077	082	085	085	095	097	097	100	100	101	102	103	103	103	105	105	105	105	105
CARCASS ID	09311	10611	10111	06211	08711	08011	09211	10811	07011	09411	06711	09711	09811	08311	10511	07611	11011	07511	08511	08811	06611	06631	06641	06651	06661
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																					X				
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic										X															
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma							X							X											X
Hepatocellular adenoma											X						X								
Hepatocellular adenoma, multiple														X											
Lymphoma malignant lymphocytic																		X							
Lymphoma malignant mixed							X											X							
Mesentery									+		+							+		+					+
Hemangioma																		X							
Lymphoma malignant lymphocytic											X														
Lymphoma malignant undifferentiated cell type																				X					
Osteosarcoma, metastatic uncertain primary site																									X
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																				X					
Osteosarcoma, metastatic, uncertain primary site																									X
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach forestomach	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous									X												X				
Stomach glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma									X																
CARDIOVASCULAR SYSTEM																									
Blood vessel																								+	
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																				X					
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule adenoma																									
Capsule lymphoma malignant lymphocytic											X														
Adrenal gland cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	M	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma											X				X						X	X			
Pars intermedia adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Follicular cell adenoma																									
GENERAL BODY SYSTEM																									
Tissue, NOS																									+
Osteosarcoma, metastatic metastatic																									X
GENITAL SYSTEM																									
Clitoral gland																		+							
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cystadenoma																									
Luteoma																									
Lymphoma malignant lymphocytic											X			X											
Lymphoma malignant mixed																				X					
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																	X								
Lymphoma malignant lymphocytic											X														
Lymphoma malignant mixed																									
Polyp stromal																									

+ Tissue examined microscopically
Not examined
– Present but not examined microscopically
I Insufficient tissue

M Missing
A. Autolysis precludes examination
X Incidence of listed morphology

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

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	TOTAL.
CARCASS ID	06811	06911	07111	07211	07311	07411	07711	07811	07911	08211	08411	08611	08811	08911	09011	09111	09511	09611	09911	10011	10211	10311	10411	10711	10911	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant mixed																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma																										2
Hepatocellular adenoma		X											X	X								X				7
Hepatocellular adenoma, multiple	X																									1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed						X	X								X											3
Mesentery																										5
Hemangioma																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant undifferentiated cell type																										1
Osteosarcoma, metastatic, uncertain primary site																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed						X																				1
Lymphoma malignant undifferentiated cell type																										1
Osteosarcoma, metastatic, uncertain primary site																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Papilloma squamous																				X						3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																										1
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed						X																				1
Lymphoma malignant undifferentiated cell type																										1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma				X											X											2
Capsule, lymphoma malignant lymphocytic																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	M	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	49
Pars distalis, adenoma			X	X	X	X			X	X	X		X		X					X		X	X	X		17
Pars intermedia, adenoma																			X				X			2
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Follicular cell, adenoma						X									X											2
GENERAL BODY SYSTEM																										
Tissue, NOS																										1
Osteosarcoma, metastatic, metastatic																										1
GENITAL SYSTEM																										
Clitoral gland																										1
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Cystadenoma															X											1
Luteoma	X																									1
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed															X											2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed						X																				1
Polyp stromal																					X					1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

WEEKS ON STUDY	010	056	063	065	065	072	077	082	085	085	095	097	097	100	100	101	102	103	103	103	105	105	105	105	105
CARCASS ID	093 1	106 1	101 1	062 1	087 1	080 1	092 1	081 1	070 1	094 1	067 1	097 1	098 1	083 1	051 1	076 1	110 1	075 1	085 1	081 1	061 1	063 1	064 1	065 1	066 1
HEMATOPOIETIC SYSTEM																									
Blood		+																							
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																		X							
Mast cell tumor, NOS																									
Lymph node	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, lymphoma malignant lymphocytic														X											
Mediastinal, lymphoma malignant lymphocytic											X			X											
Mediastinal, lymphoma malignant mixed																									
Lymph node, mandibular	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Lymphoma malignant lymphocytic														X											
Lymphoma malignant mixed																					X				
Lymph node, mesenteric											+		+		+									+	
Lymphoma malignant lymphocytic											X														
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma																		X							
Hemangiosarcoma, metastatic																								X	
Lymphoma malignant lymphocytic											X			X											
Lymphoma malignant mixed							X					X						X			X				
Lymphoma malignant undifferentiated cell type																				X		X			
Osteosarcoma, metastatic, uncertain primary site																									X
Thymus	+	+	+	M	+	M	+	+	+	M	M	+	+	+	M	+	+	+	+	M	+	+	+	+	+
Lymphoma malignant lymphocytic																							X		
Lymphoma malignant mixed																					X				
Lymphoma malignant undifferentiated cell type																						X			
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	M	+
Adenocarcinoma																									
Inguinal, lymphoma malignant mixed																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma					X																				
Hemangiosarcoma																								X	
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle											+														
Abdominal lymphoma malignant lymphocytic											X														
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Alveolar/bronchiolar adenoma																					X	X			
Alveolar/bronchiolar carcinoma																			X						
Hepatocellular carcinoma, metastatic, liver															X										
Lymphoma malignant lymphocytic														X											
Lymphoma malignant mixed																					X				
Osteosarcoma, metastatic, uncertain primary site																									X
Mediastinum, lymphoma malignant undifferentiated cell type																				X		X			
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	M	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+		+	+	+	M
Adenoma									X	X								X	X	X					
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic											X			X											
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																				X					
Osteosarcoma, metastatic, uncertain primary site																									X
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Lymphoma malignant lymphocytic											X														

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: VEHICLE CONTROL (Continued)

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	TOTAL
CARCASS ID	0681	0691	0711	0721	0731	0741	0771	0781	0791	0821	0841	0861	0881	0891	0901	0911	0951	0961	0991	1001	1021	1031	1041	1071	1091	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Blood																										1
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Mast cell tumor, NOS	X																									1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lumbar, lymphoma malig lymphocytic																										1
Mediastinal, lymphoma malignant lymphocytic																										2
Mediastinal, lymphoma malig mixed															X											1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																		X								2
Lymphoma malignant mixed						X									X											3
Lymph node, mesenteric					+										+											6
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed															X											1
Lymphoma malignant undifferentiated cell type					X																					1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma				X																						2
Hemangiosarcoma, metastatic																										1
Lymphoma malignant lymphocytic																		X								3
Lymphoma malignant mixed				X		X	X								X										X	9
Lymphoma malignant undifferentiated cell type	X																									3
Osteosarcoma, metastatic, uncertain primary site																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	42
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed															X											2
Lymphoma malignant undifferentiated cell type																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	44
Adenocarcinoma													X													1
Inguinal, lymphoma malignant mixed						X																				1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										1
Abdominal, lymphoma malignant lymphocytic																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Alveolar/bronchiolar adenoma												X														3
Alveolar/bronchiolar carcinoma																										1
Hepatocellular carcinoma, metastatic, liver																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed						X																				2
Osteosarcoma, metastatic, uncertain primary site																										1
Mediastinum, lymphoma malignant undifferentiated cell type																										2
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	I	43
Adenoma																										5
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed						X	X																		X	3
Lymphoma malignant undifferentiated cell type																										1
Osteosarcoma, metastatic, uncertain primary site																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: 2.5 mg/Mouse

WEEKS ON STUDY	005	028	031	060	062	066	069	074	079	080	083	092	101	102	102	102	102	102	104	105	105	105	105	105	105
CARCASS ID	23331	18411	18111	21801	24001	21961	22261	19611	22881	18711	20091	20551	20111	18331	19881	20221	21011	19221	21221	18221	18551	18661	18881	18991	19001
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+
Lymphoma malignant mixed																									
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sarcoma, metastatic																									
Intestine large, rectum	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hepatocellular carcinoma																								X	
Hepatocellular adenoma						X								X								X	X		
Histiocytic sarcoma, metastatic, metastatic				X																					
Mesentery									+	+			+												
Histiocytic sarcoma, metastatic, metastatic													X												
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed																									
Pancreas	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Lymphoma malignant mixed																									
Salivary glands	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	A	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Tooth				+																					
Periodontal tissue, histiocytic sarcoma, metastatic				X																					
CARDIOVASCULAR SYSTEM																									
Blood vessel															+										
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma																									
Extra adrenal tissue, histiocytic sarcoma, metastatic													X												
Extra adrenal tissue, lymphoma malignant lymphocytic									X																
Adrenal gland cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Parathyroid gland	M	M	M	+	M	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	M	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma															X		X		X	X		X	X		X
Thyroid gland	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic									X																
Follicular cell, adenoma												X													
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, metastatic													X												
Lymphoma malignant lymphocytic															X										
Lymphoma malignant mixed																									
Bilateral, histiocytic sarcoma, metastatic				X																					
Bilateral, lymphoma malignant lymphocytic									X																
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma				X									X												
Polyp stromal																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 2.5 mg/Mouse (Continued)

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	TOTAL.
CARCASS ID	19111	19331	19441	19551	19771	19991	20001	20031	20041	20061	20071	20081	21111	21131	21141	21151	21161	21171	21201	22121	22221	22231	22241	22251	22271	TISSUES TUMORS
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant mixed																								X		1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Sarcoma, metastatic																X										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hepatocellular carcinoma									X														X			3
Hepatocellular adenoma	X														X											6
Histiocytic sarcoma, metastatic, metastatic																								+		1
Mesentery																								+		4
Histiocytic sarcoma, metastatic, metastatic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																								X		1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																								X		1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Tooth																										1
Periodontal tissue, histiocytic sarcoma, metastatic																										1
CARDIOVASCULAR SYSTEM																										
Blood vessel																										1
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma		X																								1
Extra adrenal tissue, histiocytic sarcoma, metastatic																										1
Extra adrenal tissue, lymphoma malignant lymphocytic																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Pheochromocytoma benign					X																					1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenoma																								X		1
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Pars distalis, adenoma								X			X	X	X	X	X	X	X							X		16
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Follicular cell, adenoma																										1
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma, metastatic, metastatic																										1
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed																								X		1
Bilateral, histiocytic sarcoma, metastatic																										1
Bilateral, lymphoma malignant lymphocytic																										1
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	49
Histiocytic sarcoma																										2
Polyp stromal																X										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 2.5 mg/Mouse (Continued)

WEEKS ON STUDY	005	028	031	060	062	066	069	074	079	080	083	092	101	102	102	102	102	102	104	105	105	105	105	105	105
CARCASS ID	23311	18411	18111	21181	24011	21911	22611	19611	22811	18711	20911	20511	20111	18311	19811	20211	21011	19211	21211	18211	18511	18611	18811	18911	19011
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Femoral, hemangiosarcoma											X														
Lymph node	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lumbar, histiocytic sarcoma, metastatic													X												
Mediastinal, lymphoma malignant lymphocytic															X										
Mediastinal, lymphoma malignant mixed																									
Pancreatic, lymphoma malignant mixed																									
Lymph node, mandibular	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic									X						X										
Lymphoma malignant mixed																									
Squamous cell carcinoma, metastatic, skin												X													
Lymph node, mesenteric	+			+											+	+									
Histiocytic sarcoma, metastatic				X																					
Lymphoma malignant lymphocytic															X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangiosarcoma											X														
Histiocytic sarcoma, metastatic, metastatic				X																					
Lymphoma malignant mixed																						X			
Capsule, histiocytic sarcoma, metastatic													X												
Thymus	+	M	+	+	M	+	+	+	+	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic									X																
Lymphoma malignant mixed																									
INTEGUMENTARY SYSTEM																									
Mammary gland	+	M	M	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma																									
Skin	+	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+	+	+
Lymphoma malignant lymphocytic									X																
Back, lymphoma malignant lymphocytic									X																
Back, squamous cell carcinoma												X													
Scapula, lymphoma malignant lymphocytic									X																
Scapula, squamous cell carcinoma														X		X									
Scapula, squamous cell carcinoma, multiple												X													
Sebaceous gland, adenocarcinoma												X													
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland																									
Alveolar/bronchiolar adenoma																									
Alveolar/bronchiolar carcinoma																X	X			X					
Hepatocellular carcinoma, metastatic, liver																									
Hepatocellular carcinoma, metastatic, metastatic																									
Histiocytic sarcoma, metastatic, metastatic				X																					
Lymphoma malignant lymphocytic									X						X										
Lymphoma malignant mixed																									
Squamous cell carcinoma, metastatic, skin												X													
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma																									
Carcinoma																									
Lymphoma malignant lymphocytic									X																
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, metastatic				X																					
Lymphoma malignant lymphocytic									X																
Urinary bladder	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic				X																					
Lymphoma malignant mixed																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 2.5 mg/Mouse (Continued)

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	TOTAL:
CARCASS ID	19111	19931	19441	19951	19971	19991	20001	20031	20041	20061	20071	20081	21111	21131	21141	21151	21161	21171	22201	22211	22221	22231	22241	22251	22271	TISSUES TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Femoral, hemangiosarcoma																										1
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lumbar, histiocytic sarcoma, metastatic																										1
Mediastinal, lymphoma malignant lymphocytic																										1
Mediastinal, lymphoma malig mixed																								X		1
Pancreatic, lymphoma malignant mixed																								X		1
Lymph node, mandibular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed																								X		1
Squamous cell carcinoma, metastatic, skin																										1
Lymph node, mesenteric																										4
Histiocytic sarcoma, metastatic																										1
Lymphoma malignant lymphocytic																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangiosarcoma																										1
Histiocytic sarcoma, metastatic, metastatic																										1
Lymphoma malignant mixed			X																							2
Capsule, histiocytic sarcoma, metastatic																										1
Thymus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Lymphoma malignant lymphocytic																										1
Lymphoma malignant mixed			X																							1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	M	M	+	41
Adenocarcinoma																									X	1
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Back, lymphoma malignant lymphocytic																										1
Back, squamous cell carcinoma																										1
Scapula, lymphoma malignant lymphocytic																										1
Scapula, squamous cell carcinoma			X										X						X							5
Scapula, squamous cell carcinoma, multiple																										1
Sebaceous gland, adenocarcinoma																										1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, mammary gland																									X	1
Alveolar/bronchiolar adenoma			X					X	X						X	X										5
Alveolar/bronchiolar carcinoma														X												4
Hepatocellular carcinoma, metastatic, liver									X																	1
Hepatocellular carcinoma, metastatic, metastatic																								X		1
Histiocytic sarcoma, metastatic, metastatic																										1
Lymphoma malignant lymphocytic																										2
Lymphoma malignant mixed																								X		1
Squamous cell carcinoma, metastatic, skin																										1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
SPECIAL SENSES SYSTEM																										
Harderian gland	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	46
Adenoma										X																1
Carcinoma								X																		1
Lymphoma malignant lymphocytic																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, metastatic																										1
Lymphoma malignant lymphocytic																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma, metastatic																										1
Lymphoma malignant mixed																								X		1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: 5 mg/Mouse

WEEKS ON STUDY	001	001	007	058	063	065	067	071	071	081	082	082	083	083	084	085	086	087	093	096	096	097	097	098	098
CARCASS ID	31411	33411	32211	30111	33711	33611	32111	32011	34911	33811	32611	31611	31211	32411	32311	33211	30411	35011	32811	30511	34511	34711	30211	34111	30911
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic										X															X
Sarcoma, metastatic								X																	
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma															X										
Hemangiosarcoma																X									
Hepatocellular carcinoma																			X			X			
Hepatocellular adenoma																	X								
Histiocytic sarcoma, metastatic, metastatic, metastatic					X																				
Lymphoma malignant histiocytic											X														X
Mesentery								+																	+
Sarcoma, metastatic								X																	
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, metastatic					X																				
Lymphoma malignant histiocytic																									X
Lymphoma malignant undifferentiated cell type																									
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic																									X
Stomach	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Papilloma squamous																		X							
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant mixed																									
CARDIOVASCULAR SYSTEM																									
Blood vessel									+									+							
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic, metastatic					X																				
Squamous cell carcinoma, metastatic, skin																									
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Leukemia granulocytic																									
Bilateral, capsule, adenoma																									
Capsule, adenoma											X										X				
Extra adrenal tissue, histiocytic sarcoma, metastatic					X																				
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pheochromocytoma malignant																									
Pheochromocytoma benign																									
Islets, pancreatic	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	M	+	+	+	+	+	+	+	+	+
Pars distalis, adenoma										X															X
Pars distalis, carcinoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Follicular cell, adenoma																									
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant													X												
Granulosa cell tumor benign																							X		
Histiocytic sarcoma, metastatic, metastatic					X																				
Lymphoma malignant mixed																									
Mixed tumor benign									X	X						X				X			X		
Bilateral, lymphoma malignant histiocytic											X														
Bilateral, lymphoma malignant mixed																									
Bilateral, mixed tumor benign																									
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma					X																				

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 5 mg/Mouse (Continued)

WEEKS ON STUDY	099	100	101	101	103	104	104	104	104	104	105	105	105	105	105	105	105	105	105	105	105	105	105	105	TOTAL TISSUES TUMORS
CARCASS ID	31431	34661	32511	31101	31181	33311	33351	33331	34211	34311	30311	30061	30071	30081	31111	31151	31171	31191	33301	32711	32291	33391	34401	34411	34481	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant histiocytic																										2
Sarcoma, metastatic																										1
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hemangiosarcoma																										1
Hepatocellular carcinoma						X																				3
Hepatocellular adenoma			X												X				X	X						5
Histiocytic sarcoma, metastatic, metastatic, metastatic																										1
Lymphoma malignant histiocytic																										2
Mesentery																										2
Sarcoma, metastatic																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, metastatic																										1
Lymphoma malignant histiocytic																										1
Lymphoma malignant undifferentiated cell type															X											1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Papilloma squamous																										1
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant mixed															X											1
CARDIOVASCULAR SYSTEM																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Histiocytic sarcoma, metastatic, metastatic																										1
Squamous cell carcinoma metastatic skin						X																				1
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Leukemia granulocytic																			X							1
Bilateral, capsule, adenoma																							X			1
Capsule, adenoma			X				X					X								X						6
Extra adrenal tissue, histiocytic sarcoma, metastatic																										1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Pheochromocytoma malignant									X																	1
Pheochromocytoma benign									X																	1
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Parathyroid gland	+	+	+	+	+	M	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	44
Pituitary gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	47
Pars distalis, adenoma													X	X											X	5
Pars distalis, carcinoma					X																					1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Follicular cell, adenoma												X													X	2
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	49
Granulosa cell tumor malignant								X																		2
Granulosa cell tumor benign		X			X												X								X	5
Histiocytic sarcoma, metastatic, metastatic																										1
Lymphoma malignant mixed															X											1
Mixed tumor benign							X								X				X					X		9
Bilateral, lymphoma malignant histiocytic																										1
Bilateral, lymphoma malignant mixed			X																							1
Bilateral, mixed tumor benign											X									X						2
Uterus	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	49
Histiocytic sarcoma																										1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 5 mg/Mouse (Continued)

WEEKS ON STUDY	001	001	007	058	063	065	067	071	071	081	082	082	083	083	084	085	086	087	093	096	096	097	097	098	098
CARCASS ID	31441	33411	32211	30111	33711	33611	32111	32011	34911	33811	32661	31611	31221	32411	32331	33211	30411	35011	32881	30551	34551	34771	30211	34111	30991
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									
Squamous cell carcinoma, metastatic, metastatic																									
Axillary, adenocarcinoma, metastatic, mammary gland														X											
Axillary, squamous cell carcinoma, metastatic, skin																									
Lumbar, lymphoma malignant histiocytic											X														X
Lumbar, lymphoma malignant mixed																									
Mediastinal, lymphoma malignant histiocytic											X														X
Mediastinal, lymphoma malignant mixed																									
Mediastinal, lymphoma malignant undifferentiated cell type																									
Mediastinal, squamous cell carcinoma, metastatic, skin						X																			
Pancreatic, lymphoma malignant histiocytic											X														X
Renal, lymphoma malignant histiocytic											X														X
Renal, lymphoma malignant mixed																									
Lymph node, mandibular	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Histiocytic sarcoma, metastatic					X																				
Lymphoma malignant histiocytic											X														X
Lymphoma malignant mixed																									
Squamous cell carcinoma, metastatic, skin													X												
Lymph node, mesenteric																		+					+		+
Lymphoma malignant histiocytic																									X
Lymphoma malignant mixed																									
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic											X														X
Lymphoma malignant mixed																									
Lymphoma malignant undifferentiated cell type																									
Squamous cell carcinoma, metastatic, skin						X																			
Capsule, fibrous histiocytoma								X																	
Thymus	+	+	+	M	+	+	+	M	+	+	M	+	+	M	+	M	M	+	+	M	M	+	M	+	M
Thymoma benign																									
INTEGUMENTARY SYSTEM																									
Mammary gland	M	+	M	+	+	+	M	+	+	M	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+
Adenocarcinoma														X							X				
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma																									
Back, fibrous histiocytoma								X																	
Back, osteosarcoma, metastatic																									
Back, squamous cell carcinoma																									
Back, squamous cell carcinoma multiple																						X			
Scapula, basosquamous tumor malignant																									
Scapula, fibrous histiocytoma								X																	
Scapula, squamous cell carcinoma				X		X							X		X	X	X	X							
Scapula, squamous cell carcinoma, multiple																			X	X	X	X	X	X	
Subcutaneous tissue, fibrosarcoma																									
Subcutaneous tissue, scapula, squamous cell carcinoma, metastatic																									
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+
Osteosarcoma																									
Skeletal muscle								+																	
Back, sarcoma, metastatic								X																	
Intercostal, squamous cell carcinoma, metastatic, skin																									
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 5 mg/Mouse (Continued)

WEEKS ON STUDY	0 9 9	1 0 0	1 0 1	1 0 1	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TOTAL:
CARCASS ID	3 1 3 1	3 4 6 1	3 2 5 1	3 1 0 1	3 1 8 1	3 3 1 1	3 3 5 1	3 3 3 1	3 4 2 1	3 4 3 1	3 0 3 1	3 0 6 1	3 0 7 1	3 0 8 1	3 1 1 1	3 1 5 1	3 1 7 1	3 1 9 1	3 3 0 1	3 2 7 1	3 2 9 1	3 3 9 1	3 4 0 1	3 4 4 1	3 4 8 1	TISSUES / TUMORS
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Squamous cell carcinoma, metastatic																									X	1
Squamous cell carcinoma, metastatic, metastatic				X																						1
Axillary, adenocarcinoma, metastatic, mammary gland																										1
Axillary, squamous cell carcinoma, metastatic, skin																					X					1
Lumbar, lymphoma malig histiocytic																										2
Lumbar, lymphoma malignant mixed			X																							1
Mediastinal, lymphoma malignant histiocytic																										2
Mediastinal, lymphoma malig mixed			X												X											2
Mediastinal, lymphoma malignant undifferentiated cell type										X																1
Mediastinal, squamous cell carcinoma, metastatic, skin																										1
Pancreatic, lymphoma malignant histiocytic																										2
Renal, lymphoma malignant histiocytic																										2
Renal, lymphoma malignant mixed			X												X											2
Lymph node, mandibular	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	47
Histiocytic sarcoma, metastatic																										1
Lymphoma malignant histiocytic																										2
Lymphoma malignant mixed			X												X											2
Squamous cell carcinoma, metastatic, skin	X							X			X	X														5
Lymph node, mesenteric			+	+											+											6
Lymphoma malignant histiocytic																										1
Lymphoma malignant mixed			X												X											2
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										2
Lymphoma malignant mixed															X											1
Lymphoma malignant undifferentiated cell type										X																1
Squamous cell carcinoma, metastatic, skin																										1
Capsule, fibrous histiocytoma																										1
Thymus	M	+	M	+	+	+	M	+	+	+	M	+	+	+	+	+	M	M	+	+	+	+	+	+	M	33
Thymoma benign																								X		1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	41
Adenocarcinoma											X															3
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma	X			X								X														3
Back, fibrous histiocytoma																										1
Back, osteosarcoma, metastatic																		X								1
Back, squamous cell carcinoma	X			X														X								3
Back, squamous cell carcinoma, multiple																										1
Scapula, basosquamous tumor malignant										X																1
Scapula, fibrous histiocytoma																										1
Scapula, squamous cell carcinoma	X				X		X		X		X								X					X		14
Scapula, squamous cell carcinoma, multiple		X	X	X		X		X				X	X	X	X	X	X	X		X	X	X	X		X	23
Subcutaneous tissue, fibrosarcoma							X																			1
Subcutaneous tissue, scapula, squamous cell carcinoma, metastatic															X											1
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	49
Osteosarcoma																		X								1
Skeletal muscle				+																						2
Back, sarcoma, metastatic																										1
Intercostal, squamous cell carcinoma, metastatic, skin				X																						1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 5 mg/Mouse (Continued)

WEEKS ON STUDY	001	001	007	058	063	065	067	071	071	081	082	082	083	083	084	085	086	087	093	096	096	097	097	098	098
CARCASS ID	31441	33411	32211	30111	33711	33611	32111	32201	34911	33811	32611	31611	31221	32241	32311	33211	30411	35011	32811	30551	34511	34471	30211	34111	30911
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland														X											
Alveolar/bronchiolar adenoma								X						X				X			X				
Alveolar/bronchiolar carcinoma									X																
Basosquamous tumor malignant, metastatic, skin																				X					
Granulosa cell tumor malignant, metastatic, ovary													X												
Hepatocellular carcinoma, metastatic, skin																						X			
Histiocytic sarcoma, metastatic, metastatic					X																				
Lymphoma malignant histiocytic											X														X
Lymphoma malignant mixed																									
Sarcoma, metastatic								X																	
Squamous cell carcinoma, metastatic, skin						X									X										
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+		+	+	+	+		+	+	+	+	+	+	+		+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	+	+	+	+	+	+	+	+	M	I	+	+	+	+	+	+	+	+	+	+	I	+	+	+	+
Adenoma							X						X												
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant histiocytic											X														X
Lymphoma malignant mixed																									
Squamous cell carcinoma, metastatic, skin						X																			
Urinary bladder	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	M	+	+	+	+	+	+	+	+
Lymphoma malignant undifferentiated cell type																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 5 mg/Mouse (Continued)

WEEKS ON STUDY	0 9 9	1 0 0	1 0 1	1 0 1	1 0 3	1 0 4	1 0 4	1 0 4	1 0 4	1 0 4	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	1 0 5	TOTAL TISSUES TUMORS
CARCASS ID	3 1 3 1	3 4 6 1	3 2 5 1	3 1 0 1	3 1 8 1	3 3 1 1	3 3 5 1	3 3 3 1	3 4 2 1	3 4 3 1	3 0 3 1	3 0 6 1	3 0 7 1	3 0 8 1	3 1 1 1	3 1 5 1	3 1 7 1	3 1 9 1	3 3 0 1	3 2 7 1	3 2 9 1	3 3 9 1	3 4 0 1	3 4 4 1	3 4 8 1	
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, mammary gland																										1
Alveolar/bronchiolar adenoma		X								X						X				X						8
Alveolar/bronchiolar carcinoma																			X				X			3
Basosquamous tumor malignant, metastatic, skin																										1
Granulosa cell tumor malignant, metastatic, ovary																										1
Hepatocellular carcinoma, metastatic, skin																										1
Histiocytic sarcoma, metastatic, *metastatic*																										1
Lymphoma malignant histiocytic																										2
Lymphoma malignant mixed			X												X											2
Sarcoma, metastatic																										1
Squamous cell carcinoma, metastatic, skin	X	X		X	X	X		X			X															9
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	47
SPECIAL SENSES SYSTEM																										
Harderian gland	+	+	+	+	+	+	I	+	+	+	I	+	M	+	+	+	+	M	+	+	+	+	+	+	I	42
Adenoma								X												X						4
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant histiocytic																										2
Lymphoma malignant mixed			X												X											2
Squamous cell carcinoma, metastatic, skin																										1
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant undifferentiated cell type										X																1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE: 10 mg/Mouse

WEEKS ON STUDY	0 0 1	0 2 4	0 2 7	0 5 4	0 5 6	0 5 9	0 6 2	0 6 4	0 6 5	0 6 7	0 6 8	0 6 8	0 7 0	0 7 1	0 7 2	0 7 2	0 7 2	0 7 5	0 7 5	0 7 5	0 7 6	0 7 7	0 7 7	0 7 8	0 7 8
CARCASS ID	4 6 3 1	4 3 5 1	4 3 8 1	4 2 5 1	4 4 3 1	4 5 6 1	4 6 7 1	4 5 5 1	4 2 4 1	4 3 6 1	4 2 3 1	4 4 2 1	4 4 6 1	4 6 9 1	4 5 4 1	4 6 1 1	4 2 2 1	4 5 3 1	4 5 8 1	4 6 2 1	4 2 1 1	4 2 6 1	4 3 2 1	4 2 8 1	4 3 7 1
ALIMENTARY SYSTEM																									
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Hemangioma												X													
Hepatocellular carcinoma																									
Hepatocellular carcinoma, metastatic, multiple																									
Hepatocellular adenoma														X											
Hepatocellular adenoma, multiple																									
Squamous cell carcinoma, metastatic																			X						
Squamous cell carcinoma, metastatic, skin									X																
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Papilloma squamous																									
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Tooth																									
CARDIOVASCULAR SYSTEM																									
Blood vessel		+	+																						
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Squamous cell carcinoma metastatic																			X						
Squamous cell carcinoma, metastatic, skin				X					X																
ENDOCRINE SYSTEM																									
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Capsule, adenoma													X	X								X			
Capsule, carcinoma																									
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Squamous cell carcinoma, metastatic																									
Adrenal gland, medulla	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Parathyroid gland	M	M	+	+	+	+		M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pituitary gland	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Pars distalis, granular cell tumor malignant, metastatic																									
Pars intermedia, adenoma																									
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
GENERAL BODY SYSTEM																									
None																									
GENITAL SYSTEM																									
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Granulosa cell tumor malignant																									
Granulosa cell tumor benign					X			X		X		X					X	X	X						
Lymphoma malignant lymphocytic															X										
Mixed tumor benign											X			X											
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Polyp stromal																									

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 10 mg/Mouse (Continued)

WEEKS ON STUDY	078	079	079	079	080	080	081	083	083	083	083	083	083	085	085	085	085	085	085	085	085	085	085	085	TOTAL TISSUES TUMORS
CARCASS ID	44481	43311	44511	45711	42701	45011	42911	43411	46511	44711	45111	45211	46611	43011	43111	43911	44011	44111	44411	44911	45911	46011	46411	46811	47011	
ALIMENTARY SYSTEM																										
Esophagus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Gallbladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	+	49
Intestine large	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine large, cecum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Intestine large, colon	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Intestine large, rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Intestine small	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, duodenum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Intestine small, ileum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Intestine small, jejunum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Liver	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Hemangioma																										1
Hepatocellular carcinoma							X		X																	2
Hepatocellular carcinoma, metastatic, multiple																							X			1
Hepatocellular adenoma				X																						2
Hepatocellular adenoma, multiple																							X			1
Squamous cell carcinoma, metastatic				X																						2
Squamous cell carcinoma, metastatic, skin																										1
Pancreas	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Salivary glands	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Stomach, forestomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Papilloma squamous									X										X				X			3
Stomach, glandular	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Tooth													+													1
CARDIOVASCULAR SYSTEM																										
Blood vessel																										2
Heart	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Squamous cell carcinoma metastatic																										1
Squamous cell carcinoma, metastatic skin																										2
ENDOCRINE SYSTEM																										
Adrenal gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Capsule, adenoma																										3
Capsule, carcinoma								X																		1
Adrenal gland, cortex	+	+	+	+	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	49
Lymphoma malignant lymphocytic																										1
Squamous cell carcinoma, metastatic																	X									1
Adrenal gland, medulla	+	+	+	+	+	+	M	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Islets, pancreatic	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Parathyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	45
Pituitary gland	+	+	+	I	I	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	M	+	45
Pars distalis, granular cell tumor malignant, metastatic														X												1
Pars intermedia, adenoma																						X				1
Thyroid gland	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
GENERAL BODY SYSTEM																										
None																										
GENITAL SYSTEM																										
Ovary	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Granulosa cell tumor malignant														X			X									2
Granulosa cell tumor benign												X											X	X		10
Lymphoma malignant lymphocytic																										1
Mixed tumor benign				X			X													X		X				6
Uterus	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Polyp stromal						X																				1

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 10 mg/Mouse (Continued)

WEEKS ON STUDY	001	024	027	054	056	059	062	064	065	067	068	068	070	071	072	072	072	075	075	075	076	077	077	078	078
CARCASS ID	46311	43511	43811	42511	44311	45611	46711	45511	42411	43611	42311	44211	44611	46911	45411	46111	42211	45311	45811	46211	42111	42611	43211	42811	43711
HEMATOPOIETIC SYSTEM																									
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																									
Axillary, squamous cell carcinoma, metastatic, skin																									
Deep cervical, lymphoma malignant lymphocytic															X										
Mediastinal, lymphoma malignant lymphocytic															X										
Pancreatic, lymphoma malignant lymphocytic															X										
Renal, lymphoma malignant lymphocytic															X										
Lymph node, mandibular	+	+	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Squamous cell carcinoma, metastatic, skin													X				X								
Axillary, squamous cell carcinoma, metastatic, skin																									
Deep cervical, squamous cell carcinoma, metastatic, skin				X																					
Lumbar, squamous cell carcinoma, metastatic, skin																									
Lymph node, mesenteric															+				+						
Lymphoma malignant lymphocytic															X										
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Thymus	+	+	+	M	+	+	+	M	+	+	+	+	M	M	+	M	M	M	+	+	+	+	+	+	+
Squamous cell carcinoma, metastatic																			X						
INTEGUMENTARY SYSTEM																									
Mammary gland	+	+	M	+	+	M	+	+	+	M	+	+	+	+	+	M	+	+	+	+	M	+	+	+	M
Adenocarcinoma																									
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Squamous cell carcinoma														X											
Squamous cell carcinoma, multiple																									
Back, lymphoma malignant lymphocytic															X										
Scapula, basosquamous tumor malignant																									X
Scapula, lymphoma malignant lymphocytic															X										
Scapula, squamous cell carcinoma				X			X	X	X			X	X	X	X	X		X	X	X	X	X	X	X	
Scapula, squamous cell carcinoma, multiple										X	X						X								
Scapula, squamous cell carcinoma, metastatic																									
Scapula, squamous cell carcinoma, metastatic, multiple																								X	
MUSCULOSKELETAL SYSTEM																									
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Skeletal muscle									+						+										
Intercostal, squamous cell carcinoma, metastatic, skin									X																
Neck, lymphoma malignant lymphocytic															X										
NERVOUS SYSTEM																									
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
RESPIRATORY SYSTEM																									
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma, metastatic, mammary gland																									
Alveolar/bronchiolar adenoma								X						X											
Alveolar/bronchiolar carcinoma																									
Granulosa cell tumor malignant, metastatic, ovary																									
Lymphoma malignant lymphocytic															X										
Squamous cell carcinoma, metastatic																									
Squamous cell carcinoma, metastatic, skin				X			X	X	X	X	X		X				X		X	X		X			
Bronchiole, adenocarcinoma, metastatic																									
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
SPECIAL SENSES SYSTEM																									
Harderian gland	+	M	+	+	+	I	+	+	M	+	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+
Adenoma										X					X				X						
Lymphoma malignant lymphocytic															X										
URINARY SYSTEM																									
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										
Squamous cell carcinoma									X																
Squamous cell carcinoma, metastatic									X																
Squamous cell carcinoma, metastatic, skin				X				X											X						
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lymphoma malignant lymphocytic															X										

TABLE D2. INDIVIDUAL ANIMAL TUMOR PATHOLOGY OF FEMALE MICE: 10 mg/Mouse (Continued)

WEEKS ON STUDY	078	079	079	079	080	080	081	083	083	083	083	083	083	085	085	085	085	085	085	085	085	085	085	TOTAL TISSUES TUMORS
CARCASS ID	44881	43311	44511	45711	42701	45001	42991	43411	46511	44711	45111	45211	46611	43011	43111	43911	44011	44111	44411	44991	45991	46001	46411	46811	47011	
HEMATOPOIETIC SYSTEM																										
Bone marrow	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymph node	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Squamous cell carcinoma, metastatic					X	X																				2
Axillary, squamous cell carcinoma, *metastatic, skin*										X																1
Deep cervical, lymphoma malignant lymphocytic																										1
Mediastinal, lymphoma malignant *lymphocytic*																										1
Pancreatic, lymphoma malignant lymphocytic																										1
Renal, lymphoma malig lymphocytic																										1
Lymph node, mandibular	M	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	48
Lymphoma malignant lymphocytic																										1
Squamous cell carcinoma, metastatic, skin																X		X								4
Axillary, *squamous cell carcinoma*, metastatic, skin													X													1
Deep cervical, squamous cell carcinoma, metastatic, skin																										1
Lumbar, squamous cell carcinoma, metastatic, skin				X																						1
Lymph node, mesenteric	+	+	+							+											+					7
Lymphoma malignant lymphocytic																										1
Spleen	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	-	+	+	50
Lymphoma malignant lymphocytic																										1
Thymus	+	M	M	M	M	+	M	+	M	+	M	+	+	M	+	M	+	+	+	+	+	+	+	M	+	33
Squamous cell carcinoma, metastatic																										1
INTEGUMENTARY SYSTEM																										
Mammary gland	+	M	M	I	+	+	M	+	+	+	+	+	+	+	+	+	+	+	+	+	M	+	+	+	+	39
Adenocarcinoma								X	X		X									X						4
Skin	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Squamous cell carcinoma								X																		2
Squamous cell carcinoma, multiple														X												1
Back, lymphoma malignant lymphocytic																										1
Scapula, basosquamous tumor malig																										1
Scapula, lymphoma malignant lymphocytic																										1
Scapula, squamous cell carcinoma	X	X	X	X		X	X			X	X	X	X		X	X	X	X		X						31
Scapula, squamous cell carcinoma, multiple									X										X		X	X	X	X	X	10
Scapula, squamous cell carcinoma, metastatic								X									X									2
Scapula, squamous cell carcinoma, metastatic, multiple																		X								2
MUSCULOSKELETAL SYSTEM																										
Bone	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Skeletal muscle																										2
Intercostal, squamous cell carcinoma, metastatic, skin																										1
Neck, lymphoma malignant lymphocytic																										1
NERVOUS SYSTEM																										
Brain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
RESPIRATORY SYSTEM																										
Lung	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Adenocarcinoma, metastatic, mammary gland								X																		1
Alveolar/bronchiolar adenoma																	X	X					X	X		6
Alveolar/bronchiolar carcinoma											X															1
Granulosa cell tumor malignant, metastatic, ovary														X			X									2
Lymphoma malignant lymphocytic																										1
Squamous cell carcinoma, metastatic							X					X														2
Squamous cell carcinoma, metastatic, skin		X		X		X			X	X			X											X		18
Bronchiole, adenocarcinoma, metastatic																				X						1
Nose	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Trachea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
SPECIAL SENSES SYSTEM																										
Harderian gland	+	+	+	+	+	+	+	+	I	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	45
Adenoma					X			X			X			X	X											8
Lymphoma malignant lymphocytic																										1
URINARY SYSTEM																										
Kidney	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1
Squamous cell carcinoma																										1
Squamous cell carcinoma, metastatic																										1
Squamous cell carcinoma, metastatic, skin																										3
Urinary bladder	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	50
Lymphoma malignant lymphocytic																										1

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Adrenal Gland Capsule: Adenoma				
Overall Rates (a)	2/50 (4%)	1/50 (2%)	7/50 (14%)	3/50 (6%)
Adjusted Rates (b)	6.7%	3.2%	31.6%	8.5%
Terminal Rates (c)	2/30 (7%)	1/31 (3%)	3/15 (20%)	0/0
Day of First Observation	729	729	572	487
Life Table Tests (d)	P<0.001	P=0.488N	P=0.013	P=0.083
Logistic Regression Tests (d)	P=0.071	P=0.488N	P=0.043	P=0.473
Cochran-Armitage Trend Test (d)	P=0.264			
Fisher Exact Test (d)		P=0.500N	P=0.080	P=0.500
Adrenal Gland Capsule: Adenoma or Carcinoma				
Overall Rates (a)	2/50 (4%)	1/50 (2%)	7/50 (14%)	4/50 (8%)
Adjusted Rates (b)	6.7%	3.2%	31.6%	13.6%
Terminal Rates (c)	2/30 (7%)	1/31 (3%)	3/15 (20%)	0/0
Day of First Observation	729	729	572	487
Life Table Tests (d)	P<0.001	P=0.488N	P=0.013	P=0.026
Logistic Regression Tests (d)	P=0.033	P=0.488N	P=0.043	P=0.292
Cochran-Armitage Trend Test (d)	P=0.151			
Fisher Exact Test (d)		P=0.500N	P=0.080	P=0.339
Harderian Gland: Adenoma				
Overall Rates (e)	5/50 (10%)	1/50 (2%)	4/50 (8%)	8/50 (16%)
Adjusted Rates (b)	13.4%	3.2%	16.1%	35.4%
Terminal Rates (c)	0/30 (0%)	1/31 (3%)	1/15 (7%)	0/0
Day of First Observation	593	729	464	464
Life Table Tests (d)	P<0.001	P=0.115N	P=0.569	P=0.001
Logistic Regression Tests (d)	P=0.067	P=0.106N	P=0.509N	P=0.203
Cochran-Armitage Trend Test (d)	P=0.078			
Fisher Exact Test (d)		P=0.102N	P=0.500N	P=0.277
Harderian Gland: Adenoma or Carcinoma				
Overall Rates (e)	5/50 (10%)	2/50 (4%)	4/50 (8%)	8/50 (16%)
Adjusted Rates (b)	13.4%	6.5%	16.1%	35.4%
Terminal Rates (c)	0/30 (0%)	2/31 (6%)	1/15 (7%)	0/0
Day of First Observation	593	729	464	464
Life Table Tests (d)	P<0.001	P=0.230N	P=0.569	P=0.001
Logistic Regression Tests (d)	P=0.078	P=0.223N	P=0.509N	P=0.203
Cochran-Armitage Trend Test (d)	P=0.103			
Fisher Exact Test (d)		P=0.218N	P=0.500N	P=0.277
Liver: Hepatocellular Adenoma				
Overall Rates (a)	8/50 (16%)	6/50 (12%)	5/50 (10%)	3/50 (6%)
Adjusted Rates (b)	24.3%	17.1%	25.7%	14.5%
Terminal Rates (c)	6/30 (20%)	4/31 (13%)	3/15 (20%)	0/0
Day of First Observation	675	457	600	495
Life Table Tests (d)	P=0.067	P=0.365N	P=0.541	P=0.034
Logistic Regression Tests (d)	P=0.413N	P=0.404N	P=0.443N	P=0.635
Cochran-Armitage Trend Test (d)	P=0.073N			
Fisher Exact Test (d)		P=0.387N	P=0.277N	P=0.100N
Liver: Hepatocellular Carcinoma				
Overall Rates (a)	2/50 (4%)	3/50 (6%)	3/50 (6%)	2/50 (4%)
Adjusted Rates (b)	5.0%	9.7%	11.1%	10.5%
Terminal Rates (c)	0/30 (0%)	3/31 (10%)	0/15 (0%)	0/0
Day of First Observation	569	729	648	562
Life Table Tests (d)	P=0.025	P=0.507	P=0.381	P=0.226
Logistic Regression Tests (d)	P=0.376	P=0.491	P=0.478	P=0.692
Cochran-Armitage Trend Test (d)	P=0.544N			
Fisher Exact Test (d)		P=0.500	P=0.500	P=0.691N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Liver: Hepatocellular Adenoma or Carcinoma				
Overall Rates (a)	10/50 (20%)	9/50 (18%)	8/50 (16%)	5/50 (10%)
Adjusted Rates (b)	28.2%	26.3%	34.0%	23.5%
Terminal Rates (c)	6/30 (20%)	7/31 (23%)	3/15 (20%)	0/0
Day of First Observation	569	457	600	495
Life Table Tests (d)	P=0.005	P=0.474N	P=0.366	P=0.012
Logistic Regression Tests (d)	P=0.563N	P=0.523N	P=0.544N	P=0.642
Cochran-Armitage Trend Test (d)	P=0.096N			
Fisher Exact Test (d)		P=0.500N	P=0.398N	P=0.131N
Lung: Alveolar/Bronchiolar Adenoma				
Overall Rates (a)	3/50 (6%)	5/50 (10%)	8/50 (16%)	6/50 (12%)
Adjusted Rates (b)	10.0%	16.1%	30.0%	36.6%
Terminal Rates (c)	3/30 (10%)	5/31 (16%)	2/15 (13%)	0/0
Day of First Observation	729	729	495	444
Life Table Tests (d)	P<0.001	P=0.372	P=0.021	P<0.001
Logistic Regression Tests (d)	P=0.037	P=0.372	P=0.076	P=0.101
Cochran-Armitage Trend Test (d)	P=0.200			
Fisher Exact Test (d)		P=0.357	P=0.100	P=0.243
Lung: Alveolar/Bronchiolar Carcinoma				
Overall Rates (a)	1/50 (2%)	4/50 (8%)	3/50 (6%)	1/50 (2%)
Adjusted Rates (b)	3.0%	11.8%	15.4%	6.3%
Terminal Rates (c)	0/30 (0%)	2/31 (6%)	2/15 (13%)	0/0
Day of First Observation	719	709	497	579
Life Table Tests (d)	P=0.061	P=0.190	P=0.158	P=0.308
Logistic Regression Tests (d)	P=0.399	P=0.174	P=0.281	P=0.660
Cochran-Armitage Trend Test (d)	P=0.431N			
Fisher Exact Test (d)		P=0.181	P=0.309	P=0.753N
Lung: Alveolar/Bronchiolar Adenoma or Carcinoma				
Overall Rates (a)	4/50 (8%)	9/50 (18%)	11/50 (22%)	7/50 (14%)
Adjusted Rates (b)	12.7%	27.0%	42.2%	40.6%
Terminal Rates (c)	3/30 (10%)	7/31 (23%)	4/15 (27%)	0/0
Day of First Observation	719	709	495	444
Life Table Tests (d)	P<0.001	P=0.130	P=0.005	P<0.001
Logistic Regression Tests (d)	P=0.033	P=0.114	P=0.032	P=0.075
Cochran-Armitage Trend Test (d)	P=0.310			
Fisher Exact Test (d)		P=0.117	P=0.045	P=0.262
Mammary Gland: Adenocarcinoma				
Overall Rates (e)	1/50 (2%)	1/50 (2%)	3/50 (6%)	4/50 (8%)
Adjusted Rates (b)	3.3%	3.2%	12.1%	23.6%
Terminal Rates (c)	1/30 (3%)	1/31 (3%)	1/15 (7%)	0/0
Day of First Observation	729	729	579	578
Life Table Tests (d)	P<0.001	P=0.755N	P=0.171	P=0.003
Logistic Regression Tests (d)	P=0.025	P=0.755N	P=0.274	P=0.071
Cochran-Armitage Trend Test (d)	P=0.075			
Fisher Exact Test (d)		P=0.753N	P=0.309	P=0.181
Ovary: Granulosa Cell Tumor				
Overall Rates (a)	0/50 (0%)	0/49 (0%)	5/49 (10%)	10/50 (20%)
Adjusted Rates (b)	0.0%	0.0%	24.6%	35.3%
Terminal Rates (c)	0/30 (0%)	0/31 (0%)	2/14 (14%)	0/0
Day of First Observation			679	388
Life Table Tests (d)	P<0.001	(f)	P=0.007	P<0.001
Logistic Regression Tests (d)	P<0.001	(f)	P=0.013	P=0.006
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		(f)	P=0.027	P<0.001

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Ovary: Granulosa Cell Tumor or Malignant Granulosa Cell Tumor				
Overall Rates (a)	0/50 (0%)	0/49 (0%)	7/49 (14%)	12/50 (24%)
Adjusted Rates (b)	0.0%	0.0%	30.6%	48.2%
Terminal Rates (c)	0/30 (0%)	0/31 (0%)	2/14 (14%)	0/0
Day of First Observation			579	388
Life Table Tests (d)	P<0.001	(f)	P=0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	(f)	P=0.004	P=0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		(f)	P=0.006	P<0.001
Ovary: Benign Mixed Tumor				
Overall Rates (a)	0/50 (0%)	0/49 (0%)	11/49 (22%)	6/50 (12%)
Adjusted Rates (b)	0.0%	0.0%	47.4%	28.2%
Terminal Rates (c)	0/30 (0%)	0/31 (0%)	5/14 (36%)	0/0
Day of First Observation			497	474
Life Table Tests (d)	P<0.001	(f)	P<0.001	P=0.001
Logistic Regression Tests (d)	P<0.001	(f)	P<0.001	P=0.024
Cochran-Armitage Trend Test (d)	P=0.005			
Fisher Exact Test (d)		(f)	P<0.001	P=0.013
Ovary: Luteoma, Granulosa Cell Tumor, or Benign Mixed Tumor				
Overall Rates (a)	1/50 (2%)	0/49 (0%)	15/49 (31%)	16/50 (32%)
Adjusted Rates (b)	3.3%	0.0%	62.7%	55.4%
Terminal Rates (c)	1/30 (3%)	0/31 (0%)	7/14 (50%)	0/0
Day of First Observation	729		497	388
Life Table Tests (d)	P<0.001	P=0.493N	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.493N	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.505N	P<0.001	P<0.001
Ovary: Luteoma, Granulosa Cell Tumor, Benign Mixed Tumor, or Malignant Granulosa Cell Tumor				
Overall Rates (a)	1/50 (2%)	0/49 (0%)	17/49 (35%)	18/50 (36%)
Adjusted Rates (b)	3.3%	0.0%	65.7%	66.6%
Terminal Rates (c)	1/30 (3%)	0/31 (0%)	7/14 (50%)	0/0
Day of First Observation	729		497	388
Life Table Tests (d)	P<0.001	P=0.493N	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.493N	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.505N	P<0.001	P<0.001
Pituitary Gland/Pars Distalis: Adenoma				
Overall Rates (a)	17/49 (35%)	16/48 (33%)	5/47 (11%)	0/45 (0%)
Adjusted Rates (b)	54.3%	46.9%	26.3%	0.0%
Terminal Rates (c)	15/29 (52%)	13/31 (42%)	3/14 (21%)	0/0
Day of First Observation	675	709	566	
Life Table Tests (d)	P=0.131N	P=0.407N	P=0.127N	(g)
Logistic Regression Tests (d)	P=0.015N	P=0.450N	P=0.020N	P=0.953N
Cochran-Armitage Trend Test (d)	P<0.001N			
Fisher Exact Test (d)		P=0.529N	P=0.005N	P<0.001N
Pituitary Gland/Pars Distalis: Adenoma or Carcinoma				
Overall Rates (a)	17/49 (35%)	16/48 (33%)	6/47 (13%)	0/45 (0%)
Adjusted Rates (b)	54.3%	46.9%	29.8%	0.0%
Terminal Rates (c)	15/29 (52%)	13/31 (42%)	3/14 (21%)	0/0
Day of First Observation	675	709	566	
Life Table Tests (d)	P=0.209N	P=0.407N	P=0.218N	(g)
Logistic Regression Tests (d)	P=0.029N	P=0.450N	P=0.042N	P=0.953N
Cochran-Armitage Trend Test (d)	P<0.001N			
Fisher Exact Test (d)		P=0.529N	P=0.011N	P<0.001N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Skin (Aplication Site): Squamous Cell Carcinoma				
Overall Rates (e)	0/50 (0%)	6/50 (12%)	37/50 (74%)	41/50 (82%)
Adjusted Rates (b)	0.0%	16.8%	100.0%	100.0%
Terminal Rates (c)	0/30 (0%)	3/31 (10%)	15/15 (100%)	0/0
Day of First Observation		642	402	376
Life Table Tests (d)	P<0.001	P=0.022	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.016	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.013	P<0.001	P<0.001
Skin (All Sites): Squamous Cell Carcinoma				
Overall Rates (e)	0/50 (0%)	6/50 (12%)	37/50 (74%)	43/50 (86%)
Adjusted Rates (b)	0.0%	16.8%	100.0%	100.0%
Terminal Rates (c)	0/30 (0%)	3/31 (10%)	15/15 (100%)	0/0
Day of First Observation		642	402	376
Life Table Tests (d)	P<0.001	P=0.022	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.016	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.013	P<0.001	P<0.001
Forestomach: Squamous Papilloma				
Overall Rates (e)	3/49 (6%)	0/50 (0%)	1/50 (2%)	3/50 (6%)
Adjusted Rates (b)	8.9%	0.0%	3.0%	21.9%
Terminal Rates (c)	2/30 (7%)	0/31 (0%)	0/15 (0%)	0/0
Day of First Observation	593		604	579
Life Table Tests (d)	P=0.023	P=0.123N	P=0.470N	P=0.031
Logistic Regression Tests (d)	P=0.358	P=0.120N	P=0.312N	P=0.420
Cochran-Armitage Trend Test (d)	P=0.429			
Fisher Exact Test (d)		P=0.117N	P=0.301N	P=0.651N
Circulatory System: Hemangioma				
Overall Rates (e)	4/50 (8%)	0/50 (0%)	1/50 (2%)	1/50 (2%)
Adjusted Rates (b)	11.0%	0.0%	2.8%	2.5%
Terminal Rates (c)	1/30 (3%)	0/31 (0%)	0/15 (0%)	0/0
Day of First Observation	451		584	474
Life Table Tests (d)	P=0.483N	P=0.066N	P=0.306N	P=0.732
Logistic Regression Tests (d)	P=0.143N	P=0.062N	P=0.173N	P=0.201N
Cochran-Armitage Trend Test (d)	P=0.163N			
Fisher Exact Test (d)		P=0.059N	P=0.181N	P=0.181N
Circulatory System: Hemangioma or Hemangiosarcoma				
Overall Rates (e)	5/50 (10%)	1/50 (2%)	2/50 (4%)	1/50 (2%)
Adjusted Rates (b)	14.0%	2.5%	5.6%	2.5%
Terminal Rates (c)	2/30 (7%)	0/31 (0%)	0/15 (0%)	0/0
Day of First Observation	451	576	584	474
Life Table Tests (d)	P=0.470N	P=0.110N	P=0.391N	P=0.732
Logistic Regression Tests (d)	P=0.081N	P=0.101N	P=0.215N	P=0.159N
Cochran-Armitage Trend Test (d)	P=0.092N			
Fisher Exact Test (d)		P=0.102N	P=0.218N	P=0.102N
Hematopoietic System: Lymphoma, All Malignant				
Overall Rates (e)	17/50 (34%)	5/50 (10%)	5/50 (10%)	1/50 (2%)
Adjusted Rates (b)	46.3%	14.3%	21.0%	2.8%
Terminal Rates (c)	11/30 (37%)	3/31 (10%)	1/15 (7%)	0/0
Day of First Observation	534	553	569	499
Life Table Tests (d)	P=0.092N	P=0.005N	P=0.101N	P=0.688
Logistic Regression Tests (d)	P<0.001N	P=0.004N	P=0.011N	P=0.054N
Cochran-Armitage Trend Test (d)	P<0.001N			
Fisher Exact Test (d)		P=0.004N	P=0.004N	P<0.001N

TABLE D3. ANALYSIS OF PRIMARY TUMORS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
All Sites: Benign Tumors				
Overall Rates (e)	31/50 (62%)	25/50 (50%)	34/50 (68%)	29/50 (58%)
Adjusted Rates (b)	79.2%	67.2%	91.1%	88.7%
Terminal Rates (c)	22/30 (73%)	19/31 (61%)	12/15 (80%)	0/0
Day of First Observation	451	457	464	388
Life Table Tests (d)	P<0.001	P=0.141N	P=0.002	P<0.001
Logistic Regression Tests (d)	P=0.010	P=0.176N	P=0.126	P=0.052
Cochran-Armitage Trend Test (d)	P=0.510			
Fisher Exact Test (d)		P=0.157N	P=0.338	P=0.419N
All Sites: Malignant Tumors				
Overall Rates (e)	23/50 (46%)	23/50 (46%)	44/50 (88%)	45/50 (90%)
Adjusted Rates (b)	58.4%	55.6%	100.0%	100.0%
Terminal Rates (c)	14/30 (47%)	13/31 (42%)	15/15 (100%)	0/0
Day of First Observation	534	415	402	376
Life Table Tests (d)	P<0.001	P=0.535N	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.534	P<0.001	P<0.001
Cochran-Armitage Trend Test (d)	P<0.001			
Fisher Exact Test (d)		P=0.579N	P<0.001	P<0.001
All Sites: All Tumors				
Overall Rates (e)	41/50 (82%)	36/50 (72%)	47/50 (94%)	46/50 (92%)
Adjusted Rates (b)	93.1%	83.7%	100.0%	100.0%
Terminal Rates (c)	27/30 (90%)	24/31 (77%)	15/15 (100%)	0/0
Day of First Observation	451	415	402	376
Life Table Tests (d)	P<0.001	P=0.202N	P<0.001	P<0.001
Logistic Regression Tests (d)	P<0.001	P=0.222N	P=0.002	P<0.001
Cochran-Armitage Trend Test (d)	P=0.019			
Fisher Exact Test (d)		P=0.171N	P=0.061	P=0.117

(a) Number of tumor-bearing animals/number of animals examined microscopically at the site
(b) Kaplan-Meier estimated tumor incidences at the end of the study after adjusting for intercurrent mortality
(c) Observed tumor incidence in animals killed at the end of the study
(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 a lower incidence in a dosed group than in vehicle controls is indicated by (N).
(e) Number of tumor-bearing animals/number of animals examined grossly at the site
(f) No P value is reported because no tumors were observed in the 2.5 mg/mouse and vehicle control groups.
(g) No P value is reported because all high dose animals died before the first tumor was observed in the vehicle control group.

TABLE D4a. HISTORICAL INCIDENCE OF INTEGUMENTARY SYSTEM SQUAMOUS CELL TUMORS IN FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Papilloma	Carcinoma	Papilloma or Carcinoma
Historical Incidence in Dermal Studies Using Acetone as a Vehicle (b)			
JP-5 navy fuel	0/48	0/48	0/48
Marine diesel fuel	0/50	0/50	0/50
TOTAL	0/98 (0.0%)	0/98 (0.0%)	0/98 (0.0%)
Overall Historical Incidence for Untreated Controls			
TOTAL	2/1,689 (0.1%)	2/1,689 (0.1%)	4/1,689 (0.2%)
SD (c)	0.49%	0.49%	0.84%
Range (d)			
High	1/48	1/48	2/48
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Studies conducted at Litton Bionetics, Inc.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE D4b. HISTORICAL INCIDENCE OF OVARIAN TUMORS IN FEMALE B6C3F$_1$ MICE (a)

Study	Incidence of Granulosa Cell Tumors in Controls
Historical Incidence in Dermal Studies Using Acetone as a Vehicle (b)	
JP-5 navy fuel	(c) 1/47
Marine diesel fuel	0/50
TOTAL	1/97 (1.0%)
Overall Historical Incidence for Untreated Controls	
TOTAL	(d) 16/1,577 (1.0%)
SD (e)	1.71%
Range (f)	
High	3/47
Low	0/49

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Studies conducted at Litton Bionetics, Inc.
(c) Luteoma
(d) Includes four luteomas, two benign mixed tumors, and one granulosa cell carcinoma
(e) Standard deviation
(f) Range and SD are presented for groups of 35 or more animals.

TABLE D4c. HISTORICAL INCIDENCE OF ALVEOLAR/BRONCHIOLAR TUMORS IN FEMALE B6C3F$_1$ MICE (a)

Study	Incidence in Controls		
	Adenoma	Carcinoma	Adenoma or Carcinoma
Historical Incidence in Dermal Studies Using Acetone as a Vehicle (b)			
JP-5 navy fuel	0/48	3/48	3/48
Marine diesel fuel	0/50	0/50	0/50
TOTAL	0/98	3/98 (3.1%)	3/98 (3.1%)
Overall Historical Incidence for Untreated Controls			
TOTAL	73/1,676 (4.4%)	35/1,676 (2.1%)	107/1,676 (6.4%)
SD (c)	3.35%	1.68%	3.76%
Range (d)			
High	6/49	3/50	8/50
Low	0/50	0/50	0/50

(a) Data as of May 12, 1988, for studies of at least 104 weeks
(b) Studies conducted at Litton Bionetics, Inc.
(c) Standard deviation
(d) Range and SD are presented for groups of 35 or more animals.

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Animals initially in study	60	60	60	60
Animals removed	60	60	60	60
Animals examined histopathologically	50	50	50	50
ALIMENTARY SYSTEM				
Gallbladder	(48)	(49)	(48)	(49)
Inflammation, chronic active	1 (2%)			
Intestine large, colon	(50)	(50)	(50)	(50)
Amyloid deposition	1 (2%)			
Inflammation, necrotizing				1 (2%)
Intestine small, duodenum	(49)	(50)	(50)	(50)
Inflammation, necrotizing				1 (2%)
Intestine small, jejunum	(50)	(50)	(50)	(50)
Amyloid deposition	1 (2%)			
Necrosis, coagulative	1 (2%)			
Liver	(50)	(50)	(50)	(50)
Amyloid deposition			1 (2%)	1 (2%)
Angiectasis	1 (2%)		1 (2%)	
Basophilic focus		1 (2%)		1 (2%)
Cyst	1 (2%)		2 (4%)	
Degeneration, cystic	2 (4%)			
Erythrophagocytosis	1 (2%)			
Hematopoietic cell proliferation	1 (2%)		3 (6%)	2 (4%)
Hepatodiaphragmatic nodule	1 (2%)			
Inclusion body intracytoplasmic	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Inflammation, chronic active, multifocal			6 (12%)	5 (10%)
Necrosis, coagulative, multifocal	2 (4%)	1 (2%)	4 (8%)	8 (16%)
Necrosis, caseous, multifocal			1 (2%)	
Thrombus		1 (2%)	5 (10%)	1 (2%)
Centrilobular, degeneration, hydropic		1 (2%)		
Serosa, fibrosis, focal	1 (2%)			
Sinusoid, centrilobular, dilatation			1 (2%)	
Mesentery	(5)	(4)	(2)	
Inflammation, chronic	1 (20%)		1 (50%)	
Inflammation, subacute	1 (20%)			
Necrosis	1 (20%)	1 (25%)		
Pancreas	(50)	(49)	(50)	(50)
Ectopic tissue			1 (2%)	
Hypoplasia				1 (2%)
Inflammation, chronic	1 (2%)		1 (2%)	
Inflammation, granulomatous			1 (2%)	
Acinus, atrophy	4 (8%)	5 (10%)	3 (6%)	1 (2%)
Duct, ectasia	1 (2%)	4 (8%)		
Duct, mineralization, multifocal		1 (2%)		
Salivary glands	(50)	(49)	(50)	(50)
Inflammation, subacute, multifocal			2 (4%)	
Necrosis, coagulative				1 (2%)
Stomach, forestomach	(49)	(50)	(50)	(50)
Acanthosis	6 (12%)			2 (4%)
Erosion	1 (2%)			
Hyperkeratosis	2 (4%)			
Inflammation, chronic active	1 (2%)			1 (2%)
Ulcer	6 (12%)		1 (2%)	3 (6%)
Stomach, glandular	(50)	(49)	(50)	(50)
Hyperplasia				1 (2%)
Inflammation, acute				4 (8%)
Ulcer	2 (4%)			
Tooth		(1)		(1)
Gingiva, abscess				1 (100%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
CARDIOVASCULAR SYSTEM				
Blood vessel	(1)	(1)	(2)	(2)
Aorta, bacterium			1 (50%)	2 (100%)
Aorta, inflammation, chronic active	1 (100%)		1 (50%)	2 (100%)
Aorta, mineralization		1 (100%)		
Aorta, thrombus			1 (50%)	2 (100%)
Heart	(50)	(50)	(50)	(50)
Cardiomyopathy		1 (2%)		
Atrium left, thrombus		1 (2%)		
Coronary artery, inflammation, chronic		1 (2%)	1 (2%)	
Myocardium, inflammation, chronic, multifocal			3 (6%)	
Myocardium, inflammation, subacute, focal			1 (2%)	1 (2%)
Valve, bacterium	1 (2%)	3 (6%)	1 (2%)	
Valve, inflammation, subacute	1 (2%)	2 (4%)		
Valve, thrombus	1 (2%)	3 (6%)	2 (4%)	
Vein, thrombus			1 (2%)	
ENDOCRINE SYSTEM				
Adrenal gland	(50)	(50)	(50)	(50)
Bilateral, hyperplasia				1 (2%)
Bilateral, capsule, hyperplasia			1 (2%)	
Capsule, hyperplasia	49 (98%)	50 (100%)	47 (94%)	47 (94%)
Adrenal gland, cortex	(50)	(50)	(50)	(49)
Ectopic tissue				1 (2%)
Hematopoietic cell proliferation			1 (2%)	1 (2%)
Hyperplasia, nodular	5 (10%)	3 (6%)	1 (2%)	2 (4%)
Inflammation, chronic				1 (2%)
Inflammation, subacute			2 (4%)	
Adrenal gland, medulla	(50)	(49)	(50)	(48)
Hyperplasia, nodular	3 (6%)			
Islets, pancreatic	(49)	(50)	(49)	(50)
Hyperplasia	2 (4%)	2 (4%)	2 (4%)	1 (2%)
Pituitary gland	(49)	(48)	(47)	(45)
Pars distalis, hyperplasia, nodular	4 (8%)	1 (2%)	4 (9%)	3 (7%)
Thyroid gland	(49)	(49)	(50)	(50)
Cyst			1 (2%)	
Follicle, cyst	1 (2%)			
Follicle, hyperplasia, nodular	14 (29%)	13 (27%)	5 (10%)	
GENERAL BODY SYSTEM				
None				
GENITAL SYSTEM				
Clitoral gland	(1)			
Duct, dilatation	1 (100%)			
Ovary	(50)	(49)	(49)	(50)
Atrophy	9 (18%)	11 (22%)	13 (27%)	8 (16%)
Congestion			1 (2%)	
Cyst	20 (40%)	22 (45%)	16 (33%)	16 (32%)
Hemorrhage				2 (4%)
Hyperplasia, tubular	1 (2%)	15 (31%)	17 (35%)	13 (26%)
Infiltration cellular, lymphocytic			1 (2%)	
Necrosis, acute		2 (4%)		
Thrombus		2 (4%)	1 (2%)	
Bilateral, atrophy	3 (6%)	32 (65%)	29 (59%)	39 (78%)
Bilateral, cyst	4 (8%)	5 (10%)	10 (20%)	10 (20%)
Bilateral, hyperplasia, tubular	4 (8%)	20 (41%)	21 (43%)	21 (42%)
Periovarian tissue, inflammation, subacute				1 (2%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
GENITAL SYSTEM (Continued)				
Uterus	(50)	(49)	(49)	(50)
Inflammation, chronic active	1 (2%)			
Inflammation, suppurative				1 (2%)
Endometrium, fibrosis				1 (2%)
Endometrium, hyperplasia, cystic	44 (88%)	36 (73%)	38 (78%)	21 (42%)
HEMATOPOIETIC SYSTEM				
Bone marrow	(50)	(50)	(50)	(50)
Femoral, myelofibrosis, multifocal	1 (2%)	2 (4%)		2 (4%)
Femoral, necrosis, caseous				1 (2%)
Femoral, thrombus		1 (2%)		
Sternal, myelofibrosis, multifocal	1 (2%)	12 (24%)		1 (2%)
Lymph node	(49)	(49)	(47)	(50)
Mediastinal, hyperplasia, lymphoid			1 (2%)	
Mediastinal, infiltration cellular, mononuclear cell			1 (2%)	
Mediastinal, infiltration cellular, polymorphonuclear			1 (2%)	
Pancreatic, infiltration cellular, polymorphonuclear			1 (2%)	
Renal, infiltration cellular, polymorphonuclear				1 (2%)
Lymph node, mandibular	(48)	(49)	(47)	(48)
Infiltration cellular, polymorphonuclear				1 (2%)
Infiltration cellular, histiocytic	1 (2%)		1 (2%)	
Lymph node, mesenteric	(6)	(4)	(6)	(7)
Amyloid deposition	1 (17%)			
Hematopoietic cell proliferation			1 (17%)	1 (14%)
Infiltration cellular, polymorphonuclear		1 (25%)	2 (33%)	3 (43%)
Sinus, ectasia	1 (17%)			2 (29%)
Spleen	(50)	(50)	(50)	(50)
Amyloid deposition			2 (4%)	2 (4%)
Depletion lymphoid	2 (4%)	4 (8%)	4 (8%)	1 (2%)
Hematopoietic cell proliferation	3 (6%)	7 (14%)	28 (56%)	30 (60%)
Hyperplasia, lymphoid		1 (2%)		
Thrombus		1 (2%)		
Thymus	(42)	(45)	(33)	(33)
Ectopic thyroid			1 (3%)	
INTEGUMENTARY SYSTEM				
Mammary gland	(44)	(41)	(41)	(39)
Cervical, atypia cytologic				1 (3%)
Inguinal, hyperplasia, cystic	4 (9%)	4 (10%)	3 (7%)	9 (23%)
Inguinal, inflammation, acute				1 (3%)
Inguinal, inflammation, chronic	1 (2%)		1 (2%)	
Skin	(50)	(50)	(50)	(50)
Abscess				1 (2%)
Acanthosis	4 (8%)		5 (10%)	4 (8%)
Edema	2 (4%)			
Hyperkeratosis	1 (2%)		5 (10%)	2 (4%)
Inflammation, chronic			3 (6%)	1 (2%)
Inflammation, necrotizing	1 (2%)		6 (12%)	6 (12%)
Parasite metazoan	1 (2%)			
Back, acanthosis	1 (2%)		5 (10%)	4 (8%)
Back, hyperkeratosis		1 (2%)	4 (8%)	2 (4%)
Back, inflammation, necrotizing			5 (10%)	1 (2%)
Back, parasite metazoan	1 (2%)			
Scapula, abscess				2 (4%)
Scapula, acanthosis	4 (8%)	31 (62%)	41 (82%)	36 (72%)
Scapula, hyperkeratosis	1 (2%)	27 (54%)	29 (58%)	20 (40%)

TABLE D5. SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE IN THE TWO-YEAR DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
INTEGUMENTARY SYSTEM				
Skin (Continued)	(50)	(50)	(50)	(50)
Scapula, inflammation, chronic	2 (4%)	2 (4%)		
Scapula, inflammation, necrotizing	2 (4%)	5 (10%)	15 (30%)	16 (32%)
Scapula, parasite metazoan	2 (4%)			
Sebaceous gland, scapula, hyperplasia		1 (2%)		
Subcutaneous tissue, fibrosis	1 (2%)			1 (2%)
Subcutaneous tissue, inflammation, chronic active			1 (2%)	
Subcutaneous tissue, necrosis, multifocal	1 (2%)	1 (2%)		
Subcutaneous tissue, scapula, necrosis, multifocal	1 (2%)			
MUSCULOSKELETAL SYSTEM				
Bone	(50)	(50)	(49)	(50)
Humerus, proliferation			1 (2%)	
Skeletal muscle	(1)		(2)	(2)
Abdominal, inflammation, acute	1 (100%)			
NERVOUS SYSTEM				
Brain	(50)	(50)	(50)	(50)
Hemorrhage, multifocal	1 (2%)			
Mineralization, multifocal	28 (56%)	36 (72%)	24 (48%)	24 (48%)
Hypothalamus, compression	3 (6%)	2 (4%)	2 (4%)	
RESPIRATORY SYSTEM				
Lung	(50)	(50)	(50)	(50)
Congestion, diffuse	2 (4%)	1 (2%)	1 (2%)	
Hemorrhage, focal			1 (2%)	
Hemorrhage, multifocal	3 (6%)	1 (2%)	2 (4%)	2 (4%)
Inflammation, suppurative, focal				2 (4%)
Alveolar epithelium, hyperplasia	1 (2%)	1 (2%)		1 (2%)
Alveolus, infiltration cellular, histiocytic	1 (2%)			1 (2%)
Artery, inflammation, subacute		1 (2%)		1 (2%)
Interstitium, inflammation, chronic	1 (2%)			
Nose	(50)	(50)	(50)	(50)
Glands, inflammation, acute				1 (2%)
Nerve, nares, inflammation, subacute				1 (2%)
SPECIAL SENSES SYSTEM				
Harderian gland	(43)	(46)	(42)	(45)
Hyperplasia	1 (2%)			
Hyperplasia, nodular				1 (2%)
Inflammation, necrotizing				1 (2%)
Inflammation, subacute			2 (5%)	3 (7%)
URINARY SYSTEM				
Kidney	(50)	(50)	(50)	(50)
Amyloid deposition			1 (2%)	
Inflammation, necrotizing	1 (2%)		1 (2%)	1 (2%)
Inflammation, subacute, multifocal			1 (2%)	2 (4%)
Thrombus	1 (2%)			
Renal tubule, bacterium			1 (2%)	1 (2%)
Renal tubule, casts protein, multifocal			1 (2%)	1 (2%)
Renal tubule, mineralization, multifocal				1 (2%)
Renal tubule, necrosis, coagulative, multifocal				1 (2%)
Urinary bladder	(49)	(49)	(48)	(50)
Inflammation, acute				2 (4%)
Wall, inflammation, chronic			1 (2%)	

APPENDIX E

SENTINEL ANIMAL PROGRAM

APPENDIX E. SENTINEL ANIMAL PROGRAM

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

	Hemagglutination Inhibition	Complement Fixation	ELISA
Mice	PVM (pneumonia virus of mice) Reo 3 (reovirus type 3) GDVII (Theiler's encephalomyelitis virus) (6,18 mo) Poly (polyoma virus) MVM (minute virus of mice) Ectro (infectious ectromelia) Sendai	M. Ad. (mouse adenovirus) LCM (lymphocytic choriomeningitis virus)	MHV (mouse hepatitis virus) GDVII (24 mo)
Rats	PVM (6,12,18 mo) KRV (Kilham rat virus) H-1 (Toolan's H-1 virus) Sendai (6,12,18 mo)	RCV (rat coronavirus) (6 mo)	RCV/SDA (sialodacryoadenitis virus) (12,18,24 mo) *M. pul. (Mycoplasma pulmonis)* (24 mo) PVM (24 mo) Sendai (24 mo) *M. arth. (Mycoplasma arthritidis)* (24 mo)

Results

Results are presented in Table E1.

TABLE E1. MURINE ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Interval (months)	Number of Animals	Positive Serologic Reaction for
RATS		
6	(b)	None positive
12	4/10	PVM
18	(b)	None positive
24	7/10	PVM
	5/8	*M. arth.*
MICE		
6	9/10	MHV
12	(c)	--
(d) 18	3/10	PVM
	10/10	MHV
24	2/10	PVM
	10/10	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 (Bethesda, MD) for determination of antibody titers.
(b) No positive viral antibody titers were observed for any of the 10 rats tested.
(c) Sentinel animals died of exposure after a cage flooding incident.
(d) Vehicle control animals were bled for these tests.

APPENDIX F

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

Pelleted Diet: August 1982 to September 1984

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

TABLE F1. 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
Dried brewer's 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) NCI, 1976; NIH, 1978
(b) Ingredients ground to pass through a U.S. Standard Screen No. 16 before being mixed

TABLE F2. 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
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 F3. NUTRIENT COMPOSITION OF NIH 07 RAT AND MOUSE RATION

Nutrients	Mean ± Standard Deviation	Range	Number of Samples
Protein (percent by weight)	23.07 ± 1.06	21.3-26.3	26
Crude fat (percent by weight)	5.20 ± 0.66	3.3-6.5	26
Crude fiber (percent by weight)	3.49 ± 0.52	2.8-5.6	26
Ash (percent by weight)	6.63 ± 0.34	6.1-7.3	26
Amino Acids (percent of total diet)			
Arginine	1.32 ± 0.072	1.310-1.390	5
Cystine	0.319 ± 0.088	0.218-0.400	5
Glycine	1.146 ± 0.063	1.060-1.210	5
Histidine	0.571 ± 0.026	0.531-0.603	5
Isoleucine	0.914 ± 0.030	0.881-0.944	5
Leucine	1.946 ± 0.056	1.850-1.990	5
Lysine	1.280 ± 0.067	1.200-1.370	5
Methionine	0.436 ± 0.165	0.306-0.699	5
Phenylalanine	0.938 ± 0.158	0.665-1.05	5
Threonine	0.855 ± 0.035	0.824-0.898	5
Tryptophan	0.277 ± 0.221	0.156-0.671	5
Tyrosine	0.618 ± 0.086	0.564-0.769	5
Valine	1.108 ± 0.043	1.050-1.170	5
Essential Fatty Acids (percent of total diet)			
Linoleic	2.290 ± 0.313	1.83-2.52	5
Linolenic	0.258 ± 0.040	0.210-0.308	5
Vitamins			
Vitamin A (IU/kg)	12,269 ± 4,639	4,100-24,000	26
Vitamin D (IU/kg)	4,450 ± 1,382	3,000-6,300	4
α-Tocopherol (ppm)	43.58 ± 6.92	31.1-48.0	5
Thiamine (ppm)	17.89 ± 3.9	12.0-27.0	26
Riboflavin (ppm)	7.6 ± 0.85	6.10-8.2	5
Niacin (ppm)	97.8 ± 31.68	65.0-150.0	5
Pantothenic acid (ppm)	30.06 ± 4.31	23.0-34.0	5
Pyridoxine (ppm)	7.68 ± 1.31	5.60-8.8	5
Folic acid (ppm)	2.62 ± 0.89	1.80-3.7	5
Biotin (ppm)	0.254 ± 0.053	0.19-0.32	5
Vitamin B_{12} (ppb)	24.21 ± 12.66	10.6-38.0	5
Choline (ppm)	3,122 ± 416.8	2,400-3,430	5
Minerals			
Calcium (percent) (a)	1.30 ± 0.15	0.95-1.63	25
Phosphorus (percent)	0.96 ± 0.06	0.87-1.10	26
Potassium (percent)	0.900 ± 0.098	0.772-0.971	3
Chloride (percent)	0.513 ± 0.114	0.380-0.635	5
Sodium (percent)	0.323 ± 0.043	0.258-0.371	5
Magnesium (percent)	0.167 ± 0.012	0.151-0.181	5
Sulfur (percent)	0.304 ± 0.064	0.268-0.420	5
Iron (ppm)	410.3 ± 94.04	262.0-523.0	5
Manganese (ppm)	90.29 ± 7.15	81.7-99.4	5
Zinc (ppm)	52.78 ± 4.94	46.1-58.2	5
Copper (ppm)	10.72 ± 2.76	8.09-15.39	5
Iodine (ppm)	2.95 ± 1.05	1.52-3.82	4
Chromium (ppm)	1.85 ± 0.25	1.44-2.09	5
Cobalt (ppm)	0.681 ± 0.14	0.490-0.780	4

(a) No value was reported on August 14, 1984.

TABLE F4. CONTAMINANT LEVELS IN NIH 07 RAT AND MOUSE RATION

Contaminants	Mean ± Standard Deviation	Range	Number of Samples
Arsenic (ppm)	0.53 ± 0.16	0.17-0.77	26
Cadmium (ppm)	<0.10		26
Lead (ppm)	0.62 ± 0.29	0.33-1.63	26
Mercury (ppm) (a)	<0.05		26
Selenium (ppm)	0.32 ± 0.07	0.13-0.42	26
Aflatoxins (ppb) (a)	<5.0		26
Nitrate nitrogen (ppm) (b)	9.32 ± 4.64	0.10-22.0	26
Nitrite nitrogen (ppm) (b)	1.18 ± 1.60	0.10-7.20	26
BHA (ppm) (c)	3.96 ± 4.70	2.0-17.0	26
BHT (ppm) (c)	2.85 ± 2.53	1.0-12.0	26
Aerobic plate count (CFU/g) (d)	46,804 ± 34,612	6,600-130,000	26
Coliform (MPN/g) (e)	56.5 ± 128	3.0-460	26
E. coli (MPN/g)	3.0		26
Total nitrosamines (ppb) (f)	5.65 ± 5.66	1.8-30.9	26
N-Nitrosodimethylamine (ppb) (f)	4.61 ± 5.68	0.8-30.0	26
N-Nitrosopyrrolidine (ppb) (f)	1.04 ± 0.24	0.81-1.7	26
Pesticides (ppm)			
α-BHC (a,g)	<0.01		26
β-BHC (a)	<0.02		26
γ-BHC (a)	<0.01		26
δ-BHC (a)	<0.01		26
Heptachlor (a)	<0.01		26
Aldrin (a)	<0.01		26
Heptachlor epoxide (a)	<0.01		26
DDE (a)	<0.01		26
DDD (a)	<0.01		26
DDT (a)	<0.01		26
HCB (a)	<0.01		26
Mirex (a)	<0.01		26
Methoxychlor (a)	<0.05		26
Dieldrin (a)	<0.01		26
Endrin (a)	<0.01		26
Telodrin (a)	<0.01		26
Chlordane (a)	<0.05		26
Toxaphene (a)	<0.1		26
Estimated PCBs (a)	<0.2		26
Ronnel (a)	<0.01		26
Ethion (a)	<0.02		26
Trithion (a)	<0.05		26
Diazinon (a)	<0.1		26
Methyl parathion (a)	<0.02		26
Ethyl parathion (a)	<0.02		26
Malathion (h)	0.11 ± 0.09	0.05-0.45	26
Endosulfan I (a)	<0.01		26
Endosulfan II (a)	<0.01		26
Endosulfan sulfate (a)	<0.03		26

(a) All values were less than the detection limit, given in the table as the mean.
(b) Source of contamination: alfalfa, grains, and fish meal
(c) Source of contamination: soy oil and fish meal
(d) CFU = colony-forming unit
(e) MPN = most probable number
(f) All values were corrected for percent recovery.
(g) BHC = hexachlorocyclohexane or benzene hexachloride
(h) Fifteen lots contained more than 0.05 ppm.

APPENDIX G

FIVE-DAY DERMAL STUDY OF

4-VINYL-1-CYCLOHEXENE DIEPOXIDE

APPENDIX G. FIVE-DAY DERMAL STUDY

Materials and Methods

A 5-day dermal study was conducted to evaluate the immunotoxic and/or immunomodulatory effects of 4-vinyl-1-cyclohexene diepoxide. This study took place concurrently with the 2-year studies.

Male B6C3F$_1$ mice were obtained from Simonsen Laboratories, Inc., and were held for 6 weeks before the study began. The mice were 10 weeks old when placed on study. Further details are presented in Table G1. Blood samples were collected from the retro-orbital plexus of all mice on day 1 of the study before dermal application of the chemical. Leukocyte and differential cell counts were determined.

Groups of 16 males were administered 0, 2.5, 5.0, or 10 mg/mouse 4-vinyl-1-cyclohexene diepoxide in acetone by dermal application to the clipped dorsal interscapular region for 5 consecutive days. On day 3 of the study, blood samples were collected from the retro-orbital plexus of all mice, and eight randomly selected mice in each group were injected intravenously with 0.1 ml 10% (v/v) sheep erythrocytes in normal saline. On day 7 of the study, blood samples were collected from the retro-orbital plexus of all mice that had received sheep erythrocytes. Leukocyte and differential cell counts were determined. Animals were killed, and body weights and weights of thymus, spleen, mesenteric lymph nodes, and brain were determined. A Cunningham plaque-forming-cell assay was performed on spleen cell suspensions from individual mice.

On day 8 of the study, blood samples were collected from the retro-orbital plexus of all remaining mice. Leukocyte and differential cell counts were determined. Animals were killed, and body weights and weights of thymus, spleen, mesenteric lymph nodes, and brain were determined. A lymphocyte blastogenesis assay was performed with spleen cells cultured in the presence of optimal, suboptimal, and supraoptimal concentrations of phytohemagglutinin and concanavalin A.

Results

The relative organ weights for dosed and vehicle control mice were similar (Tables G2 and G4). In the Cunningham assay, the mean plaque-forming-cell response of the spleen cell suspensions from mice given an intravenous injection of sheep erythrocytes as well as dermal application of 0, 2.5, 5, or 10 mg 4-vinyl-1-cyclohexene diepoxide/mouse was 1,394, 1,502, 1,090, or 723 plaque-forming cells per 10^6 viable nucleated spleen cells. The leukocyte and lymphocyte counts of mice in the 10 mg/mouse group were significantly lower than those of vehicle controls (Tables G3 and G5).

TABLE G1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FIVE-DAY DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

EXPERIMENTAL DESIGN

Size of Study Groups
16 male mice

Doses
0, 2.5, 5, or 10 mg/animal 4-vinyl-1-cyclohexene diepoxide in acetone by dermal application to the dorsal interscapular region; dose vol--0.1 ml

Date of First Dose
6/12/83

Date of Last Dose
6/16/83

Duration of Dosing
5 d

Type and Frequency of Observation
Observed 2 × d

Necropsy, Histologic Examinations, and Supplemental Analyses
Cunningham plaque-forming-cell assay performed on 8 mice per group; peripheral blood samples taken for hematologic analyses; blastogenic response of splenic lymphocytes to phytohemagglutinin and concanavalin A determined; organ weights recorded at necropsy

ANIMALS AND ANIMAL MAINTENANCE

Strain and Species
$B6C3F_1$ mice

Animal Source
Simonsen Laboratories, Inc. (Gilroy, CA)

Study Laboratory
Battelle Columbus Laboratories

Method of Animal Identification
Ear tag

Time Held Before Study
6 wk

Age When Placed on Study
10 wk

Age When Killed
11 wk

Method of Animal Distribution
Animals distributed to weight classes and then assigned to cages by one table of random numbers and to groups by another table of random numbers

Diet
NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum

Bedding
Absorb-Dri® hardwood chips (Absorb-Dri, Inc., Garfield, NJ)

Water
Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum

Cages
Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)

TABLE G1. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE FIVE-DAY DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

ANIMALS AND ANIMAL MAINTENANCE (Continued)

Cage Filters
Spun-bonded polyester, Dupont 2024® (Snow Filtration, Cincinnati, OH)

Animals per Cage
4

Animal Room Environment
Temp--72°-76° F; hum--54%-60%; fluorescent light 12 h/d; 15 room air changes/h

TABLE G2. ORGAN WEIGHT TO BODY WEIGHT RATIOS AND NUMBER OF PLAQUE-FORMING CELLS FOR MALE MICE IN THE FIVE-DAY DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Analysis	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Body weight (grams)	30.6 ± 0.74	28.2 ± 0.71	28.7 ± 0.96	29.6 ± 0.45
Brain (mg/g)	13.9 ± 0.31	14.7 ± 0.45	15.2 ± 0.49	14.1 ± 0.23
Lymph nodes (mg/g)	1.1 ± 0.17	1.0 ± 0.14	1.0 ± 0.11	1.1 ± 0.09
Spleen (mg/g)	7.2 ± 0.65	*5.4 ± 0.11	6.2 ± 0.44	5.8 ± 0.25
Thymus (mg/g)	1.6 ± 0.16	1.9 ± 0.17	1.8 ± 0.11	1.2 ± 0.14
Plaque-forming cells (per 10^6 viable nucleated spleen cells)	1,394 ± 79.4	1,502 ± 166.3	1,090 ± 101.7	**723 ± 98.5
Plaque-forming cells ($\times 10^{-3}$ per spleen)	229 ± 25.8	190 ± 15.4	*157 ± 20.4	**106 ± 14.6

(a) Mean ± standard error for groups of eight animals; P values are vs. the vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
*$P < 0.05$
**$P < 0.01$

TABLE G3. HEMATOLOGIC DATA FOR MALE MICE IN THE FIVE-DAY DERMAL (PLAQUE-FORMING-CELL) STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Analysis	Day of Determination	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Leukocytes	1	9.53 ± 0.930	6.21 ± 0.927	8.78 ± 1.024	**4.89 ± 1.096
	3	11.35 ± 0.640	12.06 ± 1.260	11.64 ± 1.190	12.34 ± 1.620
	7	12.76 ± 1.710	10.32 ± 1.130	*8.59 ± 0.460	*8.34 ± 0.930
Lymphocytes	1	6.03 ± 0.437	4.66 ± 0.648	5.85 ± 0.899	**2.32 ± 0.587
	3	6.96 ± 0.614	8.94 ± 1.142	7.35 ± 1.076	8.05 ± 0.738
	7	7.01 ± 0.534	6.36 ± 0.438	(b) 6.07 ± 0.408	*5.21 ± 0.501
Segmented neutrophils	1	3.47 ± 0.954	1.52 ± 0.383	2.88 ± 0.607	2.57 ± 0.605
	3	4.29 ± 0.587	2.99 ± 0.387	4.23 ± 0.991	4.22 ± 1.322
	7	5.55 ± 1.814	3.70 ± 0.985	(b) 2.41 ± 0.257	2.99 ± 0.638
Monocytes	1	0.01 ± 0.011	0.00 ± 0.000	0.05 ± 0.034	0.00 ± 0.000
	3	0.05 ± 0.029	0.12 ± 0.062	0.05 ± 0.051	0.07 ± 0.035
	7	0.02 ± 0.016	0.04 ± 0.028	(b) 0.01 ± 0.012	0.02 ± 0.016
Eosinophils	1	0.01 ± 0.011	0.04 ± 0.031	0.00 ± 0.000	0.00 ± 0.000
	3	0.04 ± 0.030	0.02 ± 0.021	0.00 ± 0.000	0.00 ± 0.000
	7	0.08 ± 0.035	*0.19 ± 0.015	0.08 ± 0.024	0.08 ± 0.042
Nucleated erythrocytes	1	(c)	(c)	(c)	(c)
	3	0.17 ± 0.065	0.05 ± 0.035	0.10 ± 0.052	0.02 ± 0.015
	7	0.04 ± 0.026	0.06 ± 0.031	(b) 0.00 ± 0.000	0.02 ± 0.015

(a) Mean ± standard error in $10^3/mm^3$, for groups of eight animals unless otherwise specified; P values are vs. the vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
(b) Seven animals were examined.
(c) Fewer than two animals were examined.
*$P<0.05$
**$P<0.01$

TABLE G4. ORGAN WEIGHT TO BODY WEIGHT RATIOS AND LYMPHOCYTE BLASTOGENESIS VALUES FOR MALE MICE IN THE FIVE-DAY DERMAL STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Analysis		Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Body weight (grams)		29.3 ± 0.87	29.5 ± 0.49	29.9 ± 0.65	30.0 ± 0.74
Brain (mg/g)		14.7 ± 0.49	14.7 ± 0.39	14.5 ± 0.34	14.7 ± 0.39
Lymph nodes (mg/g)		1.1 ± 0.08	1.1 ± 0.12	0.8 ± 0.09	1.1 ± 0.08
Spleen (mg/g)		4.4 ± 0.38	5.0 ± 0.30	4.3 ± 0.27	5.0 ± 0.37
Thymus (mg/g)		1.8 ± 0.17	1.4 ± 0.12	1.4 ± 0.10	1.7 ± 0.13
Cell control (b)		4,982 ± 950	7,466 ± 1,710	6,053 ± 851	7,525 ± 2,181
PHA (b)	5 µg/well	24.4 ± 24.35	0.0 ± 0.00	0.0 ± 0.00	31.4 ± 28.15
	0.5 µg/well	45,245 ± 7,843	33,488 ± 3,015	43,868 ± 8,153	*19,989 ± 3,989
	0.05 µg/well	3,773 ± 828	3,911 ± 1,665	2,380 ± 733	2,010 ± 584
ConA (c)	5 µg/well	2,531 ± 836	1,263 ± 858	1,305 ± 492	256 ± 207
	1 µg/well	96,368 ± 16,715	71,167 ± 5,667	105,406 ± 21,737	69,890 ± 23,737
	0.1 µg/well	27,782 ± 6,787	11,555 ± 1,546	24,078 ± 6,885	*8,419 ± 3,800

(a) Mean ± standard error for groups of eight animals; P values are vs. the vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
(b) Counts/min; PHA = phytohemagglutinin.
(c) Counts/min; ConA = concanavalin A.
*P<0.05

TABLE G5. HEMATOLOGIC DATA FOR MALE MICE IN THE FIVE-DAY DERMAL (LYMPHOCYTE BLASTOGENESIS) STUDY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Analysis	Day of Determination	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
Leukocytes	1	8.25 ± 0.711	9.89 ± 0.733	9.55 ± 1.344	**3.73 ± 0.720
	3	9.01 ± 0.835	**13.46 ± 1.299	10.68 ± 0.668	9.56 ± 1.022
	8	11.11 ± 1.050	*8.06 ± 0.750	9.64 ± 0.320	8.71 ± 0.600
Lymphocytes	1	6.24 ± 0.638	6.31 ± 0.319	5.33 ± 0.871	**2.13 ± 0.480
	3	6.20 ± 0.582	7.23 ± 0.938	7.98 ± 0.341	5.93 ± 0.707
	8	6.53 ± 0.402	5.05 ± 0.444	6.90 ± 0.302	**4.31 ± 0.545
Segmented neutrophils	1	1.93 ± 0.215	3.47 ± 0.740	4.17 ± 1.003	1.58 ± 0.372
	3	2.73 ± 0.585	5.97 ± 1.357	2.67 ± 0.556	3.60 ± 1.361
	8	4.29 ± 1.076	2.89 ± 0.659	2.56 ± 0.216	3.94 ± 0.787
Monocytes	1	0.05 ± 0.036	0.06 ± 0.032	0.03 ± 0.023	0.00 ± 0.000
	3	0.05 ± 0.034	0.13 ± 0.062	0.02 ± 0.015	0.04 ± 0.025
Eosinophils	1	0.02 ± 0.021	0.05 ± 0.038	0.02 ± 0.022	0.02 ± 0.019
	3	0.04 ± 0.026	0.13 ± 0.047	0.00 ± 0.000	0.00 ± 0.000
	8	0.21 ± 0.077	0.10 ± 0.029	0.14 ± 0.043	0.22 ± 0.054
Nucleated erythrocytes	1	0.07 ± 0.044	0.15 ± 0.071	0.06 ± 0.042	0.02 ± 0.013
	3	0.10 ± 0.034	0.14 ± 0.050	0.04 ± 0.027	0.03 ± 0.026

(a) Mean ± standard error for groups of eight animals; units are $10^3/mm^3$. P values are vs. the vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
*P<0.05
**P<0.01

APPENDIX H

GAVAGE STUDIES OF

4-VINYL-1-CYCLOHEXENE DIEPOXIDE

APPENDIX H. GAVAGE STUDIES

MATERIALS AND METHODS

Preparation and Characterization of Dose Mixtures

The appropriate amounts of 4-vinyl-1-cyclohexene diepoxide and corn oil were mixed (w/v) to give the desired concentrations (Table H1). The stability of 4-vinyl-1-cyclohexene diepoxide in corn oil was determined, after extracting the samples with acetone, by gas chromatography with tetradecane as the internal standard. 4-Vinyl-1-cyclohexene diepoxide in corn oil at a concentration of 60 mg/ml was found to be stable when stored for up to 2 weeks at room temperature and 5° C or for up to 3 hours at room temperature when stored open to light and air at room temperature.

Periodic analysis by gas chromatography of 4-vinyl-1-cyclohexene diepoxide/corn oil dose mixtures was conducted at the study laboratory and at the analytical chemistry laboratory. Dose mixtures were analyzed twice during the 13-week studies. All mixtures were within ±10% of the target concentrations (Table H2).

TABLE H1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies
Preparation		
15 g chemical dissolved in 25 ml corn oil. Lower concentrations prepared by serial dilution	12 g chemical dissolved in 60 ml corn oil. Lower concentrations prepared by serial dilution	97 g chemical placed in mixing cylinder. Corn oil added to final volume of 970 ml. Lower concentrations prepared by serial dilution
Maximum Storage Time		
7 d	16 d	14 d
Storage Conditions		
23° C	Room temperature in foil-wrapped containers	Room temperature in amber glass bottles

TABLE H2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Date Mixed	Concentration of 4-Vinyl-1-cyclohexene Diepoxide in Corn Oil (mg/ml)		Determined as a Percent of Target
	Target	Determined (a)	
08/24/81	6.25	6.85	109.6
	12.5	13.14	105.1
	25	26.1	104.4
	50	50.44	100.9
	100	98.39	98.4
10/09/81	6.25	6.75	108.0
	12.5	12.71	101.7
	25	25.21	100.8
	50	50.63	101.3
	100	103.58	103.6

(a) Results of duplicate analysis

Single-Administration Studies

Groups of five rats of each sex were fasted overnight and then were administered a single dose of 187.5, 375, 750, 1,500, or 3,000 mg/kg 4-vinyl-1-cyclohexene diepoxide in corn oil by gavage. Groups of five mice of each sex were fasted for 4 hours and then were administered 375, 750, 1,500, 3,000, or 6,000 mg/kg 4-vinyl-1-cyclohexene diepoxide on the same schedule. Animals were observed twice per day for 14 days. A necropsy was performed on all animals. Details of animal maintenance are presented in Table H3.

Sixteen-Day Studies

Male and female F344/N rats and B6C3F$_1$ mice were obtained from Charles River Breeding Laboratories and were held for 12 days (rats) or 13 days (mice) before the studies began. The rats were 6 weeks old when placed on study, and the mice were 7 weeks old.

Groups of five rats and five mice of each sex were administered 0, 125, 250, 500, 1,000, or 2,000 mg/kg 4-vinyl-1-cyclohexene diepoxide in corn oil by gavage, 5 days per week, for 12 doses over 16 days.

Animals were housed five per cage. Water and feed were available ad libitum. The rats and mice were observed twice per day and were weighed on day 1, on day 8 or 9, and at the end of the studies. A necropsy was performed on all animals. The liver, thymus, heart, kidney, brain, and lungs were weighed at necropsy. Histologic examinations were performed on all vehicle controls, all animals in the 500 and 1,000 mg/kg groups, and all rats that received 2,000 mg/kg. Details of animal maintenance are presented in Table H3.

Thirteen-Week Studies

Thirteen-week studies were conducted to evaluate the cumulative toxic effects of repeated administration of 4-vinyl-1-cyclohexene diepoxide.

Four- to five-week-old male and female F344/N rats were obtained from Charles River Breeding Laboratories and 6-week-old male and female B6C3F$_1$ mice were obtained from Frederick Cancer Research Facility. Rats were observed for 14 or 15 days and mice for 22 or 23 days and then assigned to weight classes and distributed to dose groups according to tables of random numbers. Rats were 6-7 weeks old when placed on study, and mice were 9 weeks old.

Groups of 10 rats and 10 mice of each sex were administered 0, 62.5, 125, 250, 500, or 1,000 mg/kg 4-vinyl-1-cyclohexene diepoxide in corn oil by gavage, 5 days per week, for 13 weeks.

Animals were observed two times per day; moribund animals were killed. Individual animal weights were recorded once per week. Further details on animal maintenance are described in Table H3.

At the end of the 13-week studies, survivors were killed. Blood was collected from the vena cava of rats and analyzed for hematocrit values, hemoglobin concentration, and erythrocyte, leukocyte, and reticulocyte counts. A necropsy was performed on all animals except those excessively autolyzed or cannibalized. Body weights and liver, thymus, right kidney, heart, brain, right testis, and lung weights were recorded at necropsy. Total bone marrow cellularity in rat femurs was determined.

Histopathologic examinations were performed on all vehicle control and 1,000 mg/kg animals, 500 mg/kg rats, and all animals that died before the end of the studies. The forestomach, fundic stomach, testes, ovaries, and uterus of mice that received 250 and 500 mg/kg were examined microscopically. Tissues and groups examined are listed in Table H3.

TABLE H3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies
EXPERIMENTAL DESIGN		
Size of Study Groups		
5 males and 5 females of each species	5 males and 5 females of each species	10 males and 10 females of each species
Doses		
Rats--187.5, 375, 750, 1,500, or 3,000 mg/kg 4-vinyl-1-cyclohexene diepoxide in corn oil by gavage; *mice*--375, 750, 1,500, 3,000, or 6,000 mg/kg; dose vol	0, 125, 250, 500, 1,000, or 2,000 mg/kg 4-vinyl-1-cyclohexene diepoxide in corn oil by gavage; dose vol	0, 62.5, 125, 250, 500, or 1,000 mg/kg 4-vinyl-1-cyclohexene diepoxide in corn oil by gavage; dose vol--10 ml/kg
Date of First Dose		
3/20/81	Rats--5/26/81; mice--5/27/81	Rats--9/3/81 (male) or 9/4/81 (female); mice--9/1/81 (male) or 9/2/81 (female)
Date of Last Dose		
Not applicable	Rats--6/10/81; mice--6/11/81	Rats--12/2/81 (male) or 12/3/81 (female); mice--11/30/81 (male) or 12/1/81 (female)
Duration of Dosing		
Single dose	12 doses over 16 d	5 d/wk for 13 wk
Type and Frequency of Observation		
Observed 2 × d; weighed initially	Observed 2 × d; weighed initially and 1 × wk thereafter	Same as 16-d studies
Necropsy, Histologic Examinations, and Supplemental Analyses		
Necropsy performed on all animals	Necropsy performed on all animals; histologic examinations performed on all vehicle controls, all animals administered 500 or 1,000 mg/kg, and all rats administered 2,000 mg/kg. Organ weights obtained at necropsy	Necropsy performed on all animals; histologic examinations performed an all vehicle controls, all animals dying during the studies, all animals administered 1,000 mg/kg, and all rats administered 500 mg/kg. Tissues examined include: adrenal glands, brain, cecum, colon, duodenum, esophagus, femur (including marrow), gallbladder (mice), gross lesions and tissue masses with regional lymph nodes, heart, ileum, jejunum, kidneys, liver, lungs and mainstem bronchi, mammary gland, mandibular lymph nodes, nasal cavity and turbinates, pancreas, parathyroid glands, pituitary gland, preputial or clitoral gland (rats), prostate/testes/epididymis or ovaries/uterus, rectum, salivary glands, skin, spleen, stomach, thymus, thyroid gland, trachea, and urinary bladder; stomach and ovaries/uterus or testes examined in mice administered 250 or 500 mg/kg. Organ weights, blood for hematologic examination, and femoral bone marrow for cellularity studies obtained from rats at necropsy
ANIMALS AND ANIMAL MAINTENANCE		
Strain and Species		
F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice	F344/N rats; B6C3F$_1$ mice
Animal Source		
Harlan Industries (Indianapolis, IN)	Charles River Breeding Laboratories (Portage, MI)	Rats--Charles River Breeding Laboratories (Portage, MI); mice--Frederick Cancer Research Facility (Frederick, MD)

TABLE H3. EXPERIMENTAL DESIGN AND MATERIALS AND METHODS IN THE GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (Continued)

Single-Administration Studies	Sixteen-Day Studies	Thirteen-Week Studies
ANIMALS AND ANIMAL MAINTENANCE (Continued)		
Study Laboratory Battelle Columbus Laboratories	Battelle Columbus Laboratories	Battelle Columbus Laboratories
Method of Animal Identification Toe clip	Toe clip	Toe clip
Time Held Before Study 14 d	Rats--12 d; mice--13 d	Rats--14 or 15 d; mice--22 or 23 d
Age When Placed on Study Rats--7 wk; mice--8 wk	Rats--6 wk; mice--7 wk	Rats--6-7 wk; mice--9 wk
Age When Killed Rats--9 wk; mice--10 wk	Rats--9 wk; mice--10 wk	Rats--19-20 wk; mice--22 wk
Necropsy Dates 4/3/81	6/12/81	Rats--12/3/81-12/4/81; mice--12/1/81-12/2/81
Method of Animal Distribution Animals distributed to weight classes and then assigned to cages by one table of random numbers and to groups by another table of random numbers	Same as single-administration studies	Same as single-administration studies
Diet NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum	Same as single-administration studies	Same as single-administration studies
Bedding Absorb-Dri® hardwood chips (Absorb-Dri, Inc., Garfield, NJ)	Absorb-Dri® hardwood chips (Absorb-Dri, Inc., Garfield, NJ)	Absorb-Dri® hardwood chips (Weisheimers, Columbus, OH)
Water Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum	Same as single-administration studies	Same as single-administration studies
Cages Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)	Same as single-administration studies	Same as single-administration studies
Cage Filters Spun-bonded polyester, Dupont 2024® (Snow Filtration, Cincinnati, OH)	Same as single-administration studies	Same as single-administration studies
Animals per Cage 5	5	5
Other Chemicals on Study in the Same Room None	None	None
Animal Room Environment Temp--22°-24° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Temp--22°-24° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h	Temp--21°-23° C; hum--40%-60%; fluorescent light 12 h/d; 15 room air changes/h

RESULTS FOR RATS

Single-Administration Studies

All rats that received 3,000 mg/kg 4-vinyl-1-cyclohexene diepoxide and 1/5 female rats that received 1,500 mg/kg died before the end of the studies (Table H4). Clinical signs were observed on day 1 only; signs in the 1,500 and 3,000 mg/kg groups included rapid respiration, staggering gait, increased eye blinking, and half-closed eyelids; burrowing activity and half-closed eyelids were observed in the 750 mg/kg group. No lesions were observed at necropsy.

Sixteen-Day Studies

All rats that received 2,000 mg/kg died before the end of the studies (Table H5). The final body weights at 1,000 mg/kg were 8% lower than that of vehicle controls for males and 12% lower for females. Compound-related clinical signs included hyperpnea, increased burrowing activity, and half-closed eyelids. The relative kidney weight for females in the 1,000 mg/kg group was significantly greater than that for vehicle controls (Table H6). The relative thymus weight for females in the 1,000 mg/kg group was significantly lower than that for vehicle controls. All rats in the 1,000 and 2,000 mg/kg groups were examined histologically. All rats in the 2,000 mg/kg groups had some degree of bone marrow hemorrhage, hypoplasia, or necrosis. Bone marrow hypoplasia was found in all rats that received 1,000 mg/kg; the severity was greater in females than in males. Epidermal hyperplasia, hyperkeratosis, inflammation, and/or ulcers were found in the forestomach of 5/5 male and 2/5 female rats administered 1,000 mg/kg and 4/5 males and 1/5 females administered 2,000 mg/kg.

TABLE H4. SURVIVAL OF RATS IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Dose (mg/kg)	Survival	
	Male	Female (a)
187.5	5/5	5/5
375	5/5	5/5
750	5/5	5/5
1,500	5/5	(b) 4/5
3,000	(c) 0/5	(c) 0/5

(a) LD_{50} by Spearman-Karber procedure: 1,847 mg/kg (95% confidence interval 1,407-2,423 mg/kg)
(b) Day of death: 1
(c) All deaths occurred within 8 hours of dosing.

TABLE H5. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

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	112 ± 4	187 ± 8	+75 ± 4	
125	5/5	116 ± 6	186 ± 7	+70 ± 2	99.5
250	5/5	103 ± 4	170 ± 7	+67 ± 3	90.9
500	5/5	110 ± 6	183 ± 8	+73 ± 3	97.9
1,000	5/5	115 ± 3	172 ± 6	+57 ± 4	92.0
2,000	(d) 0/5	112 ± 6	(e)	(e)	(e)
FEMALE					
0	5/5	99 ± 2	139 ± 3	+40 ± 1	
125	5/5	97 ± 5	136 ± 5	+39 ± 2	97.8
250	5/5	100 ± 3	139 ± 4	+39 ± 1	100.0
500	5/5	98 ± 4	140 ± 4	+42 ± 2	100.7
1,000	5/5	99 ± 5	122 ± 9	+23 ± 5	87.8
2,000	(f) 0/5	96 ± 3	(e)	(e)	(e)

(a) Number surviving/number initially in the group
(b) Initial group mean body weight ± standard error of the mean
(c) Mean body weight change of the group ± standard error of the mean
(d) Day of death: 2,2,2,3,4
(e) No data are reported due to 100% mortality in this group.
(f) Day of death: 2,2,3,3,5

TABLE H6. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE SIXTEEN-DAY GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Organ	Vehicle Control	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
MALE					
Liver	61.8 ± 1.76	58.8 ± 2.44	62.7 ± 1.36	63.6 ± 2.05	65.9 ± 3.52
Thymus	2.4 ± 0.15	2.3 ± 0.17	2.0 ± 0.14	2.4 ± 0.15	1.9 ± 0.05
Kidney	5.2 ± 0.10	5.3 ± 0.15	4.9 ± 0.24	5.2 ± 0.17	5.9 ± 0.26
Heart	3.9 ± 0.19	3.9 ± 0.11	4.0 ± 0.11	3.9 ± 0.12	4.0 ± 0.24
Brain	9.5 ± 0.36	9.3 ± 0.33	10.2 ± 0.28	9.7 ± 0.28	10.1 ± 0.33
Lungs	8.0 ± 0.32	9.0 ± 0.41	8.3 ± 0.23	*9.8 ± 0.61	8.4 ± 0.29
FEMALE					
Liver	54.0 ± 1.60	51.8 ± 0.99	54.9 ± 2.02	52.4 ± 2.39	58.4 ± 2.36
Thymus	2.6 ± 0.07	2.6 ± 0.15	2.5 ± 0.22	2.3 ± 0.08	**1.9 ± 0.10
Kidney	5.2 ± 0.15	5.1 ± 0.10	5.2 ± 0.07	5.4 ± 0.16	**6.2 ± 0.31
Heart	4.6 ± 0.42	4.2 ± 0.09	4.2 ± 0.07	4.2 ± 0.18	4.1 ± 0.19
Brain	11.8 ± 0.20	12.4 ± 0.42	11.9 ± 0.24	11.8 ± 0.16	*13.6 ± 0.92
Lungs	(b) 9.0 ± 0.14	9.0 ± 0.55	8.9 ± 0.51	8.7 ± 0.09	8.2 ± 0.58

(a) Mean ± standard error in milligrams per gram for groups of five animals unless otherwise specified; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
(b) Lungs of four animals were weighed.
*P<0.05
**P<0.01

Thirteen-Week Studies

Thirty rats died before the end of the studies; 3/10 males and 6/10 females receiving 1,000 mg/kg died as a result of compound administration, whereas all other deaths were gavage related (Table H7). The final mean body weights of rats administered 500 or 1,000 mg/kg were 6% or 23% lower than that of vehicle controls for males and 7% or 20% lower for females. Compound-related clinical signs at 500 and 1,000 mg/kg included burrowing behavior and closed eyes. At 250, 500, and 1,000 mg/kg, excessive salivation was observed. Kidney weight to body weight ratios for males and females receiving 500 and 1,000 mg/kg, liver weight to body weight ratios for males receiving 500 and 1,000 mg/kg and for females receiving 1,000 mg/kg, heart, brain, lung, and testis weight to body weight ratios for males receiving 1,000 mg/kg, and the brain and heart weight to body weight ratios for females receiving 1,000 mg/kg were increased (Table H8). Total bone marrow cellularity and the lymphocyte, granulocyte, and rubricyte counts in bone marrow did not differ between the dosed groups and the vehicle controls (Table H9). The lymphocyte and leukocyte counts in the blood of male rats receiving 1,000 mg/kg were lower than those for vehicle controls (Table H10). The lymphocyte count in the blood of female rats receiving 1,000 mg/kg was lower than that for vehicle controls.

Smaller than normal testes in males or smaller uterine horns in females and thickened and/or whitish forestomach were seen in rats administered 500 or 1,000 mg/kg. Diffuse hyperplasia and hyperkeratosis in the stratified squamous epithelium of the forestomach were seen in almost all rats receiving 125, 250, 500, and 1,000 mg/kg. Renal degeneration or regeneration of the tubular epithelium was seen in 6/10 males and 6/10 females receiving 1,000 mg/kg. Regeneration of the tubular epithelium was also observed at 250 and 500 mg/kg. One rat that received 1,000 mg/kg had degeneration of the tubular epithelium of the testis.

TABLE H7. SURVIVAL AND MEAN BODY WEIGHTS OF RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams) Initial (b)	Final	Change (c)	Final Weight Relative to Vehicle Controls (percent)
MALE					
0	(d) 9/10	125 ± 3	352 ± 9	+228 ± 12	
62.5	(d) 8/10	121 ± 2	371 ± 2	+250 ± 3	105.4
125	(d) 8/10	121 ± 2	360 ± 13	+238 ± 11	102.3
250	(d) 8/10	126 ± 2	349 ± 10	+222 ± 10	99.1
500	(d) 7/10	119 ± 3	330 ± 9	+210 ± 7	93.8
1,000	(e) 5/10	125 ± 3	272 ± 19	+149 ± 18	77.3
FEMALE					
0	(d) 8/10	107 ± 3	206 ± 4	+98 ± 3	
62.5	10/10	106 ± 2	200 ± 3	+94 ± 3	97.1
125	(d) 7/10	106 ± 2	196 ± 4	+91 ± 3	95.1
250	(d) 9/10	106 ± 2	196 ± 4	+91 ± 3	95.1
500	(d) 9/10	108 ± 2	192 ± 3	+84 ± 2	93.2
1,000	(f) 2/10	107 ± 2	165 ± 2	+55 ± 6	80.1

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

TABLE H8. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Organ	Vehicle Control	62.5 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
MALE						
Number weighed	9	8	8	8	7	5
Body weight (b)	356 ± 9.1	373 ± 2.5	357 ± 13.0	347 ± 10.3	329 ± 8.8	**266 ± 21.0
Liver	34.9 ± 0.88	36.0 ± 0.71	37.8 ± 0.92	37.3 ± 0.58	**42.4 ± 1.02	**46.6 ± 0.85
Thymus	0.9 ± 0.05	0.8 ± 0.04	0.9 ± 0.04	1.0 ± 0.04	0.8 ± 0.03	*0.7 ± 0.03
Right kidney	2.9 ± 0.06	3.0 ± 0.06	3.2 ± 0.07	3.1 ± 0.07	**3.5 ± 0.12	**4.3 ± 0.19
Heart	2.5 ± 0.04	*2.7 ± 0.07	2.8 ± 0.06	2.7 ± 0.06	2.7 ± 0.05	**3.5 ± 0.26
Brain	5.5 ± 0.13	5.2 ± 0.08	5.5 ± 0.14	5.6 ± 0.17	5.8 ± 0.10	**7.0 ± 0.51
Lungs	4.4 ± 0.20	4.7 ± 0.24	4.7 ± 0.32	5.5 ± 0.49	4.9 ± 0.24	5.7 ± 0.41
Right testis	4.1 ± 0.09	4.0 ± 0.08	4.2 ± 0.09	4.2 ± 0.13	4.4 ± 0.07	**5.1 ± 0.29
FEMALE						
Number weighed	8	10	7	9	9	2
Body weight (b)	205 ± 4.1	200 ± 3.1	198 ± 4.6	199 ± 4.0	195 ± 3.2	164 ± 2.3
Liver	35.5 ± 0.72	35.4 ± 0.87	36.3 ± 0.63	34.4 ± 0.60	37.5 ± 0.74	**41.4 ± 1.74
Thymus	1.2 ± 0.05	1.3 ± 0.04	1.1 ± 0.05	1.2 ± 0.04	**1.0 ± 0.03	**0.7 ± 0.04
Right kidney	3.3 ± 0.08	3.4 ± 0.06	3.4 ± 0.13	3.5 ± 0.07	**3.8 ± 0.10	**4.6 ± 0.40
Heart	3.3 ± 0.10	3.3 ± 0.12	3.3 ± 0.14	3.3 ± 0.12	3.2 ± 0.07	*4.0 ± 0.03
Brain	8.9 ± 0.16	9.1 ± 0.11	9.1 ± 0.15	8.9 ± 0.18	9.2 ± 0.09	**10.2 ± 0.28
Lungs	6.8 ± 0.44	6.5 ± 0.33	7.0 ± 0.91	6.0 ± 0.30	5.8 ± 0.22	7.4 ± 0.70

(a) Mean ± standard error in milligrams per gram except as noted; P values vs. vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
(b) Absolute necropsy body weight in grams ± standard error
*P<0.05
**P<0.01

TABLE H9. BONE MARROW DIFFERENTIAL COUNT FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Analysis	Vehicle Control	62.5 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
MALE						
Number examined	9	8	8	8	7	5
Total cellularity	7.0 ± 0.33	7.8 ± 0.51	7.5 ± 0.31	6.8 ± 0.64	6.2 ± 0.51	6.1 ± 0.83
Granulocytes	1.91 ± 0.158	2.20 ± 0.138	2.18 ± 0.148	1.96 ± 0.274	1.66 ± 0.162	1.71 ± 0.224
Lymphocytes	1.27 ± 0.171	1.47 ± 0.110	1.94 ± 0.618	1.48 ± 0.183	1.08 ± 0.113	1.02 ± 0.165
Rubricytes	2.78 ± 0.284	3.03 ± 0.264	3.12 ± 0.222	2.53 ± 0.249	2.60 ± 0.270	2.51 ± 0.408
FEMALE						
Number examined	8	10	7	9	9	2
Total cellularity	4.6 ± 0.46	4.1 ± 0.17	4.4 ± 0.43	4.4 ± 0.28	4.0 ± 0.21	4.0 ± 0.45
Granulocytes	1.36 ± 0.172	1.08 ± 0.070	1.22 ± 0.117	1.24 ± 0.118	1.04 ± 0.066	1.04 ± 0.225
Lymphocytes	0.78 ± 0.100	0.67 ± 0.044	0.83 ± 0.135	0.72 ± 0.084	0.72 ± 0.074	0.58 ± 0.100
Rubricytes	1.79 ± 0.166	1.75 ± 0.101	1.73 ± 0.180	1.79 ± 0.169	1.60 ± 0.101	1.72 ± 0.010

(a) Mean ± standard error; all values in units of 10^7 cells per femur. No significant differences were observed by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).

TABLE H10. HEMATOLOGIC DATA FOR RATS IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Analysis	Vehicle Control	62.5 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
MALE						
Number examined (b)	7	8	8	8	7	5
Leukocytes (10^3/µl)	5.4 ± 0.25	5.8 ± 0.33	4.9 ± 0.16	5.0 ± 0.22	5.0 ± 0.24	**3.7 ± 0.36
Lymphocytes (10^3/µl)	4.7 ± 0.30	4.7 ± 0.30	4.2 ± 0.26	4.3 ± 0.25	4.1 ± 0.25	**2.8 ± 0.43
Segmented neutrophils (10^3/µl)	0.59 ± 0.078	*1.05 ± 0.103	0.58 ± 0.110	0.62 ± 0.097	0.85 ± 0.193	0.90 ± 0.167
Monocytes (10^3/µl)	0.04 ± 0.020	0.03 ± 0.016	0.07 ± 0.044	0.01 ± 0.006	0.06 ± 0.022	0.01 ± 0.007
Eosinophils (10^3/µl)	0.03 ± 0.021	0.04 ± 0.021	0.05 ± 0.033	0.01 ± 0.005	0.04 ± 0.024	0.01 ± 0.009
Hematocrit (percent)	44.3 ± 0.54	44.6 ± 0.53	44.4 ± 0.47	44.4 ± 0.51	45.5 ± 0.58	47.1 ± 2.46
Hemoglobin (g/dl)	15.4 ± 0.19	15.4 ± 0.14	15.5 ± 0.16	15.5 ± 0.17	15.8 ± 0.24	16.1 ± 0.80
Mean corpuscular volume (μ^3)	48.7 ± 0.18	48.8 ± 0.25	48.4 ± 0.18	48.5 ± 0.19	49.1 ± 0.26	48.6 ± 0.24
Platelets (10^3/µl)	539 ± 18.3	570 ± 13.4	553 ± 11.9	534 ± 13.4	537 ± 21.0	590 ± 22.0
Erythrocytes (10^6/µl)	9.1 ± 0.13	9.2 ± 0.10	9.2 ± 0.08	9.1 ± 0.11	9.3 ± 0.12	9.6 ± 0.50
Reticulocytes (percent)	1.2 ± 0.23	1.4 ± 0.29	1.1 ± 0.13	0.8 ± 0.18	(c) 1.1 ± 0.26	1.1 ± 0.24
FEMALE						
Number examined (b)	8	10	7	9	8	2
Leukocytes (10^3/µl)	3.8 ± 0.28	2.9 ± 0.25	4.1 ± 0.37	3.0 ± 0.29	2.9 ± 0.12	2.2 ± 0.20
Lymphocytes (10^3/µl)	3.1 ± 0.22	2.4 ± 0.24	3.4 ± 0.35	2.5 ± 0.21	2.3 ± 0.07	*1.6 ± 0.15
Segmented neutrophils (10^3/µl)	0.50 ± 0.089	0.44 ± 0.061	0.61 ± 0.084	0.49 ± 0.116	0.52 ± 0.088	0.56 ± 0.040
Monocytes (10^3/µl)	0.08 ± 0.024	0.04 ± 0.014	0.04 ± 0.017	0.04 ± 0.014	0.03 ± 0.011	0.07 ± 0.006
Eosinophils (10^3/µl)	0.06 ± 0.031	0.03 ± 0.010	0.06 ± 0.024	0.01 ± 0.007	0.05 ± 0.030	0.00 ± 0.000
Hematocrit (percent)	45.5 ± 0.53	45.3 ± 0.35	46.4 ± 0.54	45.4 ± 0.30	44.5 ± 0.59	44.1 ± 0.45
Hemoglobin (g/dl)	15.3 ± 0.21	15.2 ± 0.13	15.6 ± 0.21	15.1 ± 0.13	15.1 ± 0.23	14.5 ± 0.10
Mean corpuscular volume (μ^3)	53.3 ± 0.25	53.3 ± 0.26	53.0 ± 0.38	53.3 ± 0.17	53.4 ± 0.18	54.5 ± 1.50
Platelets (10^3/µl)	555 ± 11.2	547 ± 13.7	597 ± 15.0	562 ± 10.0	*601 ± 9.5	554 ± 16.5
Erythrocytes (10^6/µl)	8.6 ± 0.10	8.5 ± 0.05	8.7 ± 0.12	(c) 8.5 ± 0.07	8.3 ± 0.12	8.1 ± 0.09
Reticulocytes (percent)	1.2 ± 0.15	1.6 ± 0.25	1.3 ± 0.19	1.3 ± 0.17	*2.0 ± 0.17	1.8 ± 0.85

(a) Mean ± standard error; P values vs. vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
(b) Unless otherwise specified
(c) Eight animals were examined.
*P<0.05
**P<0.01

RESULTS FOR MICE

Single-Administration Studies

All mice that received 6,000 mg/kg 4-vinyl-1-cyclohexene diepoxide by gavage, 4/5 male mice and 3/5 female mice that received 3,000 mg/kg, 2/5 male mice that received 1,500 mg/kg, and 1/5 female mice that received 750 mg/kg died before the end of the studies (Table H11). Compound-related clinical signs observed for the 1,500 and 3,000 mg/kg groups included staggering gait and rough hair coats. Clinical signs observed for the 6,000 mg/kg groups included staggering gait and rapid respiration for 3-5 minutes after dosing until death. No lesions were observed at necropsy.

Sixteen-Day Studies

All mice that received 2,000 mg/kg, 2/5 males and 1/5 females that received 1,000 mg/kg, 1/5 males that received 125 mg/kg, and 1/5 male vehicle controls died before the end of the studies (Table H12). The deaths of the female that received 1,000 mg/kg and the male vehicle control were probably due to gavage error. The final mean body weights of dosed and vehicle control mice were comparable. Compound-related clinical signs, observed only in the 2,000 mg/kg groups, included hyperpnea, burrowing behavior, and half-closed eyelids. No compound-related effects on relative organ weights were observed (Table H13). Hyperplasia, hyperkeratosis, and/or ulcers were seen in the forestomach of 3/3 males and 4/4 females that received 1,000 mg/kg and lived to the end of the studies. Degeneration of the testis was seen in 4/5 mice that received 1,000 mg/kg.

TABLE H11. SURVIVAL OF MICE IN THE SINGLE-ADMINISTRATION GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Dose (mg/kg)	Survival	
	Male (a)	Female (b)
375	5/5	5/5
750	5/5	(c) 4/5
1,500	(d) 3/5	5/5
3,000	(e) 1/5	(f) 2/5
6,000	(g) 0/5	(g) 0/5

(a) LD_{50} by probit analysis: 1,862 mg/kg (95% confidence interval 1,080-3,194 mg/kg)
(b) LD_{50} by probit analysis: 2,358 mg/kg (95% confidence interval 1,327-4,704 mg/kg)
(c) Day of death: 10
(d) Day of death: 2,14
(e) Day of death: 1,1,1,14
(f) Day of death: all 1
(g) All deaths occurred within 8 hours of dosing.

TABLE H12. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Dose (mg/kg)	Survival (a)	Mean Body Weights (grams)			Final Weight Relative to Vehicle Controls (percent)
		Initial (b)	Final	Change (c)	
MALE					
0	(d) 4/5	23.0 ± 0.71	23.2 ± 0.63	+0.2 ± 0.75	
125	(e) 4/5	23.2 ± 0.66	23.2 ± 0.55	0.0 ± 0.41	100.0
250	5/5	24.2 ± 0.73	24.8 ± 0.66	+0.6 ± 0.24	106.9
500	5/5	23.8 ± 0.57	24.0 ± 0.55	+0.2 ± 0.37	103.4
1,000	(f) 3/5	22.8 ± 0.66	22.7 ± 0.67	−0.1 ± 0.33	97.8
2,000	(g) 0/5	22.2 ± 0.20	(h)	(h)	(h)
FEMALE					
0	5/5	17.2 ± 0.49	21.2 ± 0.49	+4.0 ± 0.84	
125	5/5	19.0 ± 0.71	20.8 ± 0.20	+1.8 ± 0.73	98.1
250	5/5	18.4 ± 0.68	21.0 ± 0.32	+2.6 ± 0.51	99.1
500	5/5	18.4 ± 0.40	20.8 ± 0.37	+2.4 ± 0.40	98.1
1,000	(d) 4/5	18.2 ± 0.37	21.0 ± 0.00	+2.8 ± 0.48	99.1
2,000	(i) 0/5	17.8 ± 0.37	(h)	(h)	(h)

(a) Number surviving/number initially in group
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean
(d) Death probably due to gavage error
(e) Day of death: 10; cause of death was undetermined.
(f) Day of death: 2,4
(g) Day of death: all 2
(h) No data are reported due to 100% mortality in this group.
(i) Day of death: all 3

TABLE H13. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE SIXTEEN-DAY GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Organ	Vehicle Control	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
MALE					
Number weighed	4	4	5	5	3
Liver	64.1 ± 2.20	58.2 ± 2.00	59.1 ± 1.44	66.6 ± 2.22	71.3 ± 1.86
Thymus	2.1 ± 0.15	**1.3 ± 0.15	*1.4 ± 0.20	*1.5 ± 0.05	1.8 ± 0.07
Kidney	9.9 ± 0.52	10.5 ± 0.44	10.1 ± 0.33	10.3 ± 0.35	7.8 ± 3.27
Heart	5.8 ± 0.26	6.0 ± 0.52	5.4 ± 0.19	6.1 ± 0.42	6.6 ± 0.34
Brain	19.3 ± 0.67	18.4 ± 0.88	17.6 ± 0.56	17.8 ± 0.40	19.9 ± 0.35
Lungs	9.4 ± 1.01	*12.4 ± 0.78	9.2 ± 0.52	10.6 ± 0.84	9.2 ± 0.13
FEMALE					
Number weighed	5	5	5	5	4
Liver	59.6 ± 1.67	*53.6 ± 0.24	59.5 ± 0.75	60.5 ± 1.07	63.2 ± 2.59
Thymus	2.6 ± 0.17	2.9 ± 0.15	2.5 ± 0.19	2.5 ± 0.21	2.5 ± 0.40
Kidney	8.8 ± 0.19	8.4 ± 0.48	8.7 ± 0.27	8.9 ± 0.33	8.8 ± 0.25
Heart	6.0 ± 0.16	5.5 ± 0.21	5.7 ± 0.28	5.7 ± 0.13	6.1 ± 0.56
Brain	22.4 ± 0.68	21.9 ± 0.35	21.7 ± 0.60	21.9 ± 0.30	21.8 ± 0.49
Lungs	10.3 ± 0.77	12.3 ± 0.24	9.1 ± 0.67	9.9 ± 0.34	12.3 ± 0.56

(a) Mean ± standard error in milligrams per gram; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
*$P<0.05$
**$P<0.01$

Thirteen-Week Studies

No compound-related deaths occurred (Table H14). Five of the deaths of females receiving 500 mg/kg were due to a drowning incident; all other deaths were attributed to errors in gavage technique. The final mean body weights of mice that received 500 or 1,000 mg/kg were 13% or 15% lower than that of vehicle controls for males and 3% or 6% lower for females. Nine female mice, one receiving 62.5 mg/kg, two receiving 125 mg/kg, four receiving 250 mg/kg, and two receiving 1,000 mg/kg, delivered litters during week 4 of the studies, about 4 weeks after mice had escaped from cages. The 250 mg/kg female group gained weight compared with vehicle controls and contained the largest number of pregnant females. The lung and liver weight to body weight ratios for males receiving 1,000 mg/kg, the liver weight to body weight ratio for females receiving 1,000 mg/kg, and the kidney weight to body weight ratios for males and females receiving 62.5 mg/kg and higher were significantly greater than those for vehicle controls (Table H15). Compound-related lesions were seen in the forestomach, testis, ovary, and uterus. Diffuse hyperplasia and/or hyperkeratosis involving the stratified squamous epithelium of the forestomach were seen in 1/10 females receiving 62.5 mg/kg, 1/10 males and 1/10 females receiving 125 mg/kg, 9/10 males and 6/10 females receiving 250 mg/kg, 6/10 males and 9/10 females receiving 500 mg/kg, and 8/10 males and 7/10 females receiving 1,000 mg/kg. Multifocal to diffuse testicular degeneration was present in 8/10 males receiving 250 mg/kg, 8/10 receiving 500 mg/kg, and 9/10 receiving 1,000 mg/kg. Diffuse ovarian atrophy was seen in 5/10 females receiving 250 mg/kg, 6/10 receiving 500 mg/kg, and 10/10 receiving 1,000 mg/kg. Uterine atrophy was present in 7/10 mice receiving 1,000 mg/kg.

TABLE H14. SURVIVAL AND MEAN BODY WEIGHTS OF MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

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	22.4 ± 0.4	32.5 ± 0.8	+10.1 ± 0.7	
62.5	10/10	22.6 ± 0.4	33.0 ± 0.9	+10.4 ± 0.8	101.5
125	10/10	22.5 ± 0.3	32.2 ± 0.9	+9.7 ± 1.0	99.1
250	10/10	22.5 ± 0.3	32.0 ± 1.0	+9.5 ± 0.9	98.5
500	10/10	21.9 ± 0.4	28.4 ± 0.9	+6.5 ± 0.6	87.4
1,000	8/10	22.6 ± 0.3	27.5 ± 0.0	+5.1 ± 0.8	84.6
FEMALE					
0	10/10	17.4 ± 0.2	24.5 ± 0.3	+7.1 ± 0.2	
62.5	8/10	17.3 ± 0.3	23.8 ± 0.5	+6.5 ± 0.4	97.1
125	8/10	17.4 ± 0.4	25.2 ± 0.5	+7.8 ± 0.4	102.9
250	9/10	17.3 ± 0.4	25.8 ± 0.7	+8.3 ± 0.7	105.3
500	4/10	17.4 ± 0.5	23.8 ± 0.9	+6.0 ± 0.7	97.1
1,000	10/10	17.1 ± 0.3	23.0 ± 0.6	+5.9 ± 0.4	93.9

(a) Number surviving/number initially in the group; all deaths were judged to be accidental.
(b) Initial group mean body weight ± standard error of the mean. Subsequent calculations are based on animals surviving to the end of the study.
(c) Mean body weight change of the survivors ± standard error of the mean

TABLE H15. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE THIRTEEN-WEEK GAVAGE STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Organ	Vehicle Control	62.5 mg/kg	125 mg/kg	250 mg/kg	500 mg/kg	1,000 mg/kg
MALE						
Number weighed	10	10	10	10	10	8
Body weight (b)	31.9 ± 0.82	32.5 ± 1.11	30.8 ± 1.07	30.7 ± 1.30	*27.9 ± 1.04	28.2 ± 0.87
Liver	56.0 ± 1.27	54.7 ± 1.86	53.0 ± 1.40	55.8 ± 2.16	54.0 ± 0.55	**64.8 ± 3.03
Thymus	1.2 ± 0.10	1.2 ± 0.12	1.2 ± 0.09	1.3 ± 0.11	1.2 ± 0.15	0.8 ± 0.13
Right kidney	8.8 ± 0.23	*9.5 ± 0.21	9.6 ± 0.30	**10.5 ± 0.46	*10.1 ± 0.31	**10.9 ± 0.20
Heart	5.2 ± 0.13	5.0 ± 0.23	5.3 ± 0.34	5.7 ± 0.30	5.2 ± 0.13	5.1 ± 0.28
Brain	14.1 ± 0.40	14.1 ± 0.64	14.8 ± 0.61	15.5 ± 0.69	*16.3 ± 0.53	15.9 ± 0.40
Lungs	7.9 ± 0.40	8.1 ± 0.29	8.7 ± 0.59	9.4 ± 0.64	8.6 ± 0.33	**11.2 ± 0.83
Right testis	3.6 ± 0.16	3.6 ± 0.13	3.7 ± 0.20	3.6 ± 0.13	**2.7 ± 0.24	**1.2 ± 0.10
FEMALE						
Number weighed (c)	10	8	8	9	4	10
Body weight (b)	23.4 ± 0.33	23.8 ± 0.43	24.2 ± 0.61	23.4 ± 0.48	22.8 ± 0.59	22.2 ± 0.53
Liver	50.5 ± 0.58	**57.9 ± 0.83	56.1 ± 1.54	55.3 ± 2.63	54.3 ± 1.49	**60.2 ± 1.37
Thymus	2.0 ± 0.15	2.2 ± 0.33	2.0 ± 0.13	1.7 ± 0.10	2.0 ± 0.07	*1.4 ± 0.11
Right kidney	7.2 ± 0.23	**8.7 ± 0.26	**8.9 ± 0.36	**9.2 ± 0.31	8.3 ± 0.37	**8.8 ± 0.25
Heart	5.0 ± 0.10	5.2 ± 0.14	5.1 ± 0.22	5.2 ± 0.19	5.0 ± 0.19	5.1 ± 0.25
Brain	19.4 ± 0.46	19.3 ± 0.46	19.1 ± 0.49	19.4 ± 0.36	19.4 ± 0.70	19.8 ± 0.39
Lungs	9.8 ± 0.56	9.1 ± 0.37	9.7 ± 0.43	9.5 ± 0.59	9.2 ± 0.63	(d) 12.1 ± 1.05

(a) Mean ± standard error in milligrams per gram except as noted; P values vs. vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
(b) Absolute necropsy body weight in grams ± standard error
(c) Unless otherwise specified
(d) Lungs of nine animals were weighed.
*P<0.05
**P<0.01

APPENDIX I

ORGAN WEIGHTS AND HEMATOLOGY DATA IN THE FOURTEEN-DAY AND THIRTEEN-WEEK DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

TABLE I1. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE FOURTEEN-DAY DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Organ	Vehicle Control	27 mg/Rat	35 mg/Rat	57 mg/Rat	68 mg/Rat
MALE					
Liver	65.2 ± 0.79		59.1 ± 2.44		62.2 ± 1.89
Thymus	2.1 ± 0.07		**1.7 ± 0.06		**1.7 ± 0.07
Kidney	4.9 ± 0.05		4.8 ± 0.17		**5.6 ± 0.11
Heart	3.7 ± 0.10		3.9 ± 0.17		4.0 ± 0.07
Brain	8.2 ± 0.17		8.7 ± 0.29		**9.4 ± 0.10
Lungs	6.9 ± 0.61		7.0 ± 0.34		7.3 ± 0.44
FEMALE					
Liver	54.1 ± 1.92	*45.6 ± 1.69		55.0 ± 2.95	
Thymus	2.6 ± 0.12	2.4 ± 0.19		*1.8 ± 0.24	
Kidney	5.3 ± 0.08	*4.9 ± 0.12		5.5 ± 0.12	
Heart	4.2 ± 0.05	4.1 ± 0.29		4.2 ± 0.16	
Brain	11.3 ± 0.37	11.5 ± 0.21		12.2 ± 0.31	
Lungs	7.4 ± 0.17	*8.7 ± 0.53		8.6 ± 0.30	

(a) Mean ± standard error in milligrams per gram for groups of five animals; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
*P<0.05
**P<0.01

TABLE I2. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE THIRTEEN-WEEK DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Organ	Vehicle Control	3.75 mg/Rat	7.5 mg/Rat	15 mg/Rat	30 mg/Rat	60 mg/Rat
MALE						
Body weight (b)	343 ± 5.0	346 ± 8.2	337 ± 7.8	346 ± 2.5	333 ± 6.2	286 ± 7.6
Liver	40.4 ± 1.13	40.9 ± 0.81	43.0 ± 1.31	40.8 ± 1.12	41.2 ± 0.78	40.6 ± 0.94
Thymus	1.0 ± 0.07	0.9 ± 0.02	1.0 ± 0.04	1.0 ± 0.04	**0.8 ± 0.04	**0.8 ± 0.03
Right kidney	3.6 ± 0.06	3.5 ± 0.07	3.5 ± 0.07	3.4 ± 0.30	3.4 ± 0.30	3.7 ± 0.32
Heart	3.0 ± 0.03	3.0 ± 0.06	3.0 ± 0.07	3.1 ± 0.06	2.9 ± 0.07	**3.3 ± 0.08
Brain	5.6 ± 0.10	5.6 ± 0.11	5.8 ± 0.15	5.5 ± 0.09	5.7 ± 0.10	**6.5 ± 0.10
Lung	5.2 ± 0.14	4.9 ± 0.21	5.2 ± 0.15	5.0 ± 0.16	5.6 ± 0.38	5.2 ± 0.30
Right testis	4.6 ± 0.07	4.5 ± 0.07	4.5 ± 0.08	4.5 ± 0.07	4.6 ± 0.08	**5.3 ± 0.12
FEMALE						
Body weight (b)	202 ± 3.5	203 ± 5.2	205 ± 2.3	197 ± 3.1	197 ± 2.8	**179 ± 2.5
Liver	39.9 ± 0.73	38.7 ± 1.53	40.4 ± 0.89	41.6 ± 0.66	38.7 ± 0.72	40.4 ± 0.85
Thymus	1.4 ± 0.06	1.3 ± 0.06	1.3 ± 0.05	1.4 ± 0.06	1.3 ± 0.08	1.2 ± 0.16
Right kidney	3.9 ± 0.09	3.8 ± 0.06	3.8 ± 0.08	3.9 ± 0.08	3.9 ± 0.11	4.0 ± 0.12
Heart	3.6 ± 0.07	3.7 ± 0.12	3.6 ± 0.12	3.6 ± 0.12	3.6 ± 0.12	3.9 ± 0.15
Brain	9.1 ± 0.17	9.0 ± 0.25	8.7 ± 0.14	9.2 ± 0.23	9.2 ± 0.12	*9.8 ± 0.13
Lung	6.9 ± 0.32	6.7 ± 0.26	6.2 ± 0.15	6.8 ± 0.24	6.5 ± 0.25	6.7 ± 0.10

(a) Mean ± standard error in milligrams per gram except as noted for groups of 10 animals; P values vs. vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
(b) Absolute necropsy body weight in grams
*P<0.05
**P<0.01

TABLE I3. BONE MARROW DIFFERENTIAL COUNT FOR RATS IN THE THIRTEEN-WEEK DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Analysis	Vehicle Control	3.75 mg/Rat	7.5 mg/Rat	15 mg/Rat	30 mg/Rat	60 mg/Rat
MALE						
Total cellularity	8.0 ± 0.28	8.5 ± 0.37	8.3 ± 0.39	7.8 ± 0.16	7.5 ± 0.38	7.9 ± 0.31
Granulocytes	2.3 ± 0.09	2.3 ± 0.08	2.5 ± 0.23	2.0 ± 0.12	2.0 ± 0.13	2.1 ± 0.17
Lymphocytes	1.38 ± 0.099	1.58 ± 0.215	1.63 ± 0.145	1.55 ± 0.106	1.24 ± 0.060	1.68 ± 0.154
Rubricytes	3.41 ± 0.180	3.48 ± 0.276	3.04 ± 0.195	3.06 ± 0.160	3.19 ± 0.189	2.95 ± 0.111
FEMALE						
Total cellularity	4.5 ± 0.16	4.6 ± 0.19	4.6 ± 0.25	4.6 ± 0.31	4.6 ± 0.27	4.1 ± 0.17
Granulocytes	1.10 ± 0.063	1.24 ± 0.119	1.21 ± 0.082	1.09 ± 0.141	1.10 ± 0.068	1.05 ± 0.071
Lymphocytes	0.79 ± 0.065	0.80 ± 0.073	0.88 ± 0.081	0.78 ± 0.060	0.79 ± 0.080	0.73 ± 0.056
Rubricytes	1.89 ± 0.198	1.92 ± 0.116	1.81 ± 0.189	2.06 ± 0.169	2.13 ± 0.190	1.62 ± 0.157

(a) Mean ± standard error for groups of 10 animals; all values in units of 10^7 cells per femur; no significant differences vs. the vehicle controls were observed by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).

TABLE I4. HEMATOLOGIC DATA FOR RATS IN THE THIRTEEN-WEEK DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Analysis	Vehicle Control	3.75 mg/Rat	7.5 mg/Rat	15 mg/Rat	30 mg/Rat	60 mg/Rat
MALE						
Hemoglobin (g/dl)	15.5 ± 0.14	15.4 ± 0.25	15.6 ± 0.24	(b) 15.4 ± 0.16	16.0 ± 0.20	*16.3 ± 0.12
Hematocrit (percent)	45 ± 0.4	45 ± 0.8	45 ± 0.7	45 ± 0.3	46 ± 0.5	47 ± 0.4
Erythrocytes (10^6/mm^3)	9.24 ± 0.09	9.13 ± 0.15	9.24 ± 0.12	9.18 ± 0.07	9.58 ± 0.12	9.44 ± 0.08
Reticulocytes (10^3/mm^3)	109 ± 10.7	111 ± 12.6	117 ± 13.4	88 ± 8.3	104 ± 13.8	115 ± 15.8
Leukocytes (10^3/mm^3)	5.2 ± 0.17	4.9 ± 0.26	4.8 ± 0.15	4.9 ± 0.17	4.9 ± 0.20	4.5 ± 0.28
Segmented neutrophils (percent)	17.0 ± 2.10	17.5 ± 1.68	15.1 ± 1.04	13.7 ± 1.35	15.0 ± 1.14	18.2 ± 1.76
Eosinophils (percent)	1.2 ± 0.59	1.1 ± 0.35	0.8 ± 0.33	1.1 ± 0.41	1.2 ± 0.20	1.6 ± 0.27
Lymphocytes (percent)	81.7 ± 2.06	81.4 ± 1.76	84.1 ± 1.16	85.2 ± 1.62	83.8 ± 1.24	80.2 ± 1.58
Monocytes (percent)	0.1 ± 0.10	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
FEMALE						
Hemoglobin (g/dl)	14.9 ± 0.34	15.7 ± 0.38	15.1 ± 0.09	(b) 15.3 ± 0.10	14.9 ± 0.17	15.3 ± 0.15
Hematocrit (percent)	43 ± 0.8	**46 ± 1.2	44 ± 0.3	45 ± 0.3	43 ± 0.4	45 ± 0.4
Erythrocytes (10^6/mm^3)	8.25 ± 0.157	8.64 ± 0.225	8.37 ± 0.047	8.44 ± 0.062	8.23 ± 0.074	8.47 ± 0.097
Reticulocytes (10^3/mm^3)	150 ± 190	125 ± 21.8	112 ± 11.2	121 ± 13.3	129 ± 14.6	99 ± 16.2
Leukocytes (10^3/mm^3)	4.1 ± 0.24	4.0 ± 0.21	4.1 ± 0.32	4.5 ± 0.21	4.2 ± 0.19	3.9 ± 0.15
Segmented neutrophils (percent)	11.5 ± 1.59	8.2 ± 0.99	11.1 ± 2.20	7.0 ± 1.05	8.8 ± 1.00	13.3 ± 1.31
Eosinophils (percent)	1.7 ± 0.34	0.6 ± 0.22	1.3 ± 0.52	0.9 ± 0.35	0.9 ± 0.18	0.9 ± 0.31
Lymphocytes (percent)	85.1 ± 1.88	90.5 ± 0.90	86.8 ± 2.22	*91.5 ± 1.21	89.6 ± 0.84	85.0 ± 1.48
Monocytes (percent)	1.7 ± 0.54	0.7 ± 0.26	0.8 ± 0.29	0.6 ± 0.40	0.7 ± 0.34	0.8 ± 0.42

(a) Mean ± standard error for groups of 10 animals, unless otherwise specified. P values vs. vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
(b) Eight animals were examined.
*$P<0.05$
**$P<0.01$

TABLE I5. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE FOURTEEN-DAY DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Organ	Vehicle Control	2 mg/ Mouse	3 mg/ Mouse	5 mg/ Mouse	10 mg/ Mouse	19 mg/ Mouse	21 mg/ Mouse
MALE							
Number weighed	5		5	5	5		2
Liver	63.8 ± 2.63		64.2 ± 4.27	66.9 ± 1.13	68.7 ± 1.52		69.4 ± 0.03
Thymus	1.9 ± 0.21		2.0 ± 0.18	1.7 ± 0.17	1.4 ± 0.17		1.1 ± 0.02
Kidney	10.4 ± 0.29		11.6 ± 0.51	11.5 ± 0.34	10.8 ± 0.46		10.8 ± 0.82
Heart	6.0 ± 0.26		6.3 ± 0.42	6.4 ± 0.50	6.6 ± 0.49		5.5 ± 0.26
Brain	17.4 ± 0.27		18.1 ± 0.88	17.9 ± 0.20	17.8 ± 0.41		17.7 ± 0.15
Lungs	9.2 ± 0.98		8.4 ± 0.50	8.6 ± 0.45	8.6 ± 0.28		7.6 ± 0.23
FEMALE							
Number weighed	5	5		5	5	0	
Liver	64.2 ± 2.11	61.7 ± 2.04		62.0 ± 1.18	**72.4 ± 1.25		
Thymus	2.9 ± 0.14	2.7 ± 0.17		*2.3 ± 0.17	**2.0 ± 0.10		
Kidney	8.9 ± 0.51	9.0 ± 0.50		9.6 ± 0.44	9.4 ± 0.24		
Brain	20.4 ± 0.76	21.2 ± 0.76		20.6 ± 0.67	20.6 ± 0.73		
Heart	6.9 ± 0.41	6.4 ± 0.41		6.0 ± 0.28	7.4 ± 0.53		
Lungs	9.9 ± 0.76	9.0 ± 0.15		8.9 ± 0.38	10.5 ± 0.49		

(a) Mean ± standard error in milligrams per gram; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
*P<0.05
**P<0.01

TABLE I6. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE THIRTEEN-WEEK DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Organ	Vehicle Control	0.625 mg/Mouse	1.25 mg/Mouse	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
MALE						
Number weighed	10	9	10	10	9	10
Body weight (b)	26.0 ± 0.46	27.8 ± 0.65	*28.2 ± 0.45	27.8 ± 0.63	*28.3 ± 0.59	26.9 ± 0.41
Liver	52.9 ± 2.11	**60.3 ± 1.06	*58.3 ± 0.35	**60.9 ± 0.70	**62.6 ± 1.55	**60.8 ± 1.10
Thymus	1.5 ± 0.12	1.6 ± 0.36	1.7 ± 0.09	1.8 ± 0.36	1.8 ± 0.40	1.5 ± 0.32
Right kidney	10.1 ± 0.37	10.9 ± 0.24	*11.2 ± 0.29	*11.3 ± 0.19	**11.5 ± 0.30	**12.1 ± 0.23
Heart	5.5 ± 0.13	5.3 ± 0.14	5.6 ± 0.13	5.9 ± 0.16	5.5 ± 0.33	5.8 ± 0.25
Brain	17.4 ± 0.28	16.7 ± 0.23	16.8 ± 0.25	16.8 ± 0.25	16.1 ± 0.64	17.3 ± 0.48
Lung	8.5 ± 0.34	9.3 ± 0.60	9.0 ± 0.34	8.9 ± 0.26	8.1 ± 0.47	**10.3 ± 0.35
Right testis	4.4 ± 0.11	4.1 ± 0.31	4.2 ± 0.12	4.2 ± 0.13	4.2 ± 0.17	4.2 ± 0.14
FEMALE						
Number weighed	10	10	10	10	10	10
Body weight (b)	24.3 ± 0.54	23.8 ± 0.53	24.4 ± 0.42	24.4 ± 0.57	24.5 ± 0.45	24.2 ± 0.31
Liver	57.9 ± 0.69	58.9 ± 0.96	60.1 ± 0.73	62.0 ± 1.34	**64.0 ± 1.30	**67.4 ± 1.57
Thymus	1.9 ± 0.15	2.2 ± 0.18	2.2 ± 0.21	2.0 ± 0.23	2.1 ± 0.16	2.1 ± 0.21
Right kidney	8.5 ± 0.20	9.1 ± 0.20	9.2 ± 0.16	*9.3 ± 0.14	**9.9 ± 0.29	**10.0 ± 0.30
Heart	5.7 ± 0.25	5.9 ± 0.19	5.9 ± 0.18	5.5 ± 0.25	5.7 ± 0.16	5.8 ± 0.18
Brain	19.5 ± 0.41	19.7 ± 0.51	19.6 ± 0.33	19.5 ± 0.32	19.7 ± 0.42	19.7 ± 0.43
Lung	9.6 ± 0.47	9.8 ± 0.36	9.4 ± 0.47	10.1 ± 0.29	11.1 ± 0.55	10.9 ± 0.55

(a) Mean ± standard error in milligrams per gram except as noted; P values vs. vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
(b) Absolute necropsy body weight in grams
*P<0.05
**P<0.01

APPENDIX J

ORGAN WEIGHTS AND HEMATOLOGY DATA IN THE FIFTEEN-MONTH DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

TABLE J1. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR RATS IN THE FIFTEEN-MONTH DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Organ	Vehicle Control	15 mg/Rat	30 mg/Rat
MALE			
Body weight (b)	486 ± 4.5	480 ± 6.8	**442 ± 5.0
Brain	4.2 ± 0.06	4.3 ± 0.06	**4.6 ± 0.06
Kidney	4.2 ± 0.11	4.0 ± 0.04	4.2 ± 0.15
Liver	40.5 ± 1.13	37.1 ± 1.22	38.2 ± 1.25
Right testis	3.7 ± 0.34	3.4 ± 0.14	3.6 ± 0.47
FEMALE			
Body weight (b)	297 ± 4.0	292 ± 7.5	281 ± 7.5
Brain	6.3 ± 0.08	6.4 ± 0.14	6.7 ± 0.15
Uterus	2.3 ± 0.22	2.1 ± 0.14	2.3 ± 0.43
Ovary	0.5 ± 0.05	0.4 ± 0.01	0.5 ± 0.03
Kidney	3.9 ± 0.10	4.0 ± 0.07	4.0 ± 0.10
Liver	37.0 ± 1.86	35.7 ± 0.54	35.2 ± 1.01

(a) Mean ± standard error for groups of 10 animals in milligrams per gram unless otherwise specified; P values are vs. the vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
(b) Absolute body weight in grams
**$P<0.01$

TABLE J2. RESULTS OF HEMATOLOGIC ANALYSES FOR RATS IN THE FIFTEEN-MONTH DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Analysis	Vehicle Control	15 mg/Rat	30 mg/Rat
MALE			
Number examined	10	10	10
Leukocytes (10^3/mm^3)	5.37 ± 0.54	5.57 ± 0.26	5.02 ± 0.44
Lymphocytes (10^3/mm^3)	3.17 ± 0.47	3.38 ± 0.22	2.81 ± 0.29
Segmented neutrophils (10^3/mm^3)	2.11 ± 0.18	2.12 ± 0.09	2.14 ± 0.21
Eosinophils (10^3/mm^3)	0.08 ± 0.02	0.07 ± 0.02	0.07 ± 0.03
Hematocrit (percent)	45.3 ± 0.47	46.9 ± 0.57	45.7 ± 0.90
Hemoglobin (g/dl)	15.2 ± 0.16	15.7 ± 0.17	15.4 ± 0.45
Mean corpuscular hemoglobin (pg)	17.2 ± 0.13	17.2 ± 0.16	17.4 ± 0.28
Mean corpuscular hemoglobin concentration (g/dl)	33.6 ± 0.29	33.5 ± 0.35	33.6 ± 0.59
Mean corpuscular volume (μ^3)	50.9 ± 0.55	51.3 ± 0.54	51.9 ± 0.48
Nucleated erythrocytes (10^3/mm^3)	0.90 ± 0.50	1.80 ± 0.68	0.90 ± 0.35
Platelets (10^3/mm^3)	485 ± 37.6	457 ± 21.7	424 ± 33.1
Erythrocytes (10^6/mm^3)	8.89 ± 0.13	9.14 ± 0.11	8.87 ± 0.26
Reticulocytes (10^6/mm^3)	0.19 ± 0.02	0.17 ± 0.02	0.17 ± 0.01
FEMALE			
Number examined (b)	9	10	10
Leukocytes (10^3/mm^3)	2.82 ± 0.15	2.75 ± 0.17	3.40 ± 0.36
Lymphocytes (10^3/mm^3)	1.71 ± 0.09	1.83 ± 0.08	2.02 ± 0.12
Segmented neutrophils (10^3/mm^3)	1.03 ± 0.09	0.87 ± 0.09	1.29 ± 0.27
Eosinophils (10^3/mm^3)	0.07 ± 0.01	0.05 ± 0.01	0.08 ± 0.02
Hematocrit (percent)	44.1 ± 0.48	44.3 ± 0.56	40.1 ± 2.83
Hemoglobin (g/dl)	15.1 ± 0.12	15.2 ± 0.21	14.0 ± 0.98
Mean corpuscular hemoglobin (pg)	18.3 ± 0.11	18.4 ± 0.09	18.8 ± 0.33
Mean corpuscular hemoglobin concentration (g/dl)	34.2 ± 0.38	34.2 ± 0.18	34.8 ± 0.45
Mean corpuscular volume (μ^3)	53.4 ± 0.47	53.7 ± 0.26	54.3 ± 1.25
Nucleated erythrocytes (10^3/mm^3)	1.11 ± 0.26	2.50 ± 0.81	2.60 ± 1.14
Platelets (10^3/mm^3)	381 ± 17.0	410 ± 24.0	397 ± 32.7
Erythrocytes (10^6/mm^3)	8.23 ± 0.08	8.24 ± 0.11	7.48 ± 0.57
Reticulocytes (10^6/mm^3)	0.14 ± 0.02	0.16 ± 0.01	(c) 0.15 ± 0.02

(a) Mean ± standard error; P values vs. the vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
(b) Unless otherwise specified
(c) Nine animals were examined.

TABLE J3. ORGAN WEIGHT TO BODY WEIGHT RATIOS FOR MICE IN THE FIFTEEN-MONTH DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Organ	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
MALE				
Body weight (b)	45.3 ± 1.71	46.1 ± 1.25	44.4 ± 1.47	*40.4 ± 1.13
Brain	10.5 ± 0.42	10.1 ± 0.46	10.8 ± 0.38	11.6 ± 0.24
Kidney	12.2 ± 0.31	11.6 ± 0.41	11.3 ± 0.34	12.0 ± 0.15
Liver	49.3 ± 3.13	(c) 46.9 ± 1.17	46.6 ± 1.22	53.5 ± 2.02
Right testis	2.5 ± 0.11	2.6 ± 0.12	2.4 ± 0.12	2.5 ± 0.13
FEMALE				
Body weight (b)	39.8 ± 1.72	39.5 ± 1.39	45.7 ± 2.53	38.1 ± 2.15
Brain	12.2 ± 0.57	12.5 ± 0.48	10.8 ± 0.57	13.2 ± 0.66
Uterus	14.0 ± 2.14	17.7 ± 1.66	**4.4 ± 0.50	**5.9 ± 1.30
Ovary	(c) 0.7 ± 0.13	0.4 ± 0.02	0.4 ± 0.06	(c) 0.5 ± 0.07
Kidney	7.6 ± 0.23	7.7 ± 0.23	7.4 ± 0.35	8.3 ± 0.19
Liver	47.2 ± 1.42	48.2 ± 1.31	45.7 ± 2.06	50.6 ± 1.86

(a) Mean ± standard error in milligrams per gram for groups of 10 animals unless otherwise specified; P values are vs. the vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
(b) Absolute body weight in grams
(c) Nine animals were weighed.
*$P<0.05$
**$P<0.01$

TABLE J4. RESULTS OF HEMATOLOGIC ANALYSES FOR MICE IN THE FIFTEEN-MONTH DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Analysis	Vehicle Control	2.5 mg/Mouse	5 mg/Mouse	10 mg/Mouse
MALE				
Leukocytes (10^3/mm^3)	3.92 ± 0.409	4.26 ± 0.358	4.52 ± 0.517	**11.34 ± 2.734
Lymphocytes (10^3/mm^3)	2.95 ± 0.286	3.14 ± 0.280	3.18 ± 0.323	*5.06 ± 0.717
Segmented neutrophils (10^3/mm^3)	0.90 ± 0.149	0.98 ± 0.124	1.25 ± 0.230	*5.93 ± 2.277
Eosinophils (10^3/mm^3)	0.07 ± 0.022	0.14 ± 0.045	0.09 ± 0.025	0.24 ± 0.083
Hematocrit (percent)	43.4 ± 0.62	45.2 ± 0.92	44.9 ± 0.74	**34.6 ± 1.70
Hemoglobin (g/dl)	14.4 ± 0.27	15.1 ± 0.25	14.8 ± 0.27	**11.4 ± 0.59
Mean corpuscular hemoglobin (pg)	14.6 ± 0.20	14.6 ± 0.10	14.5 ± 0.16	14.6 ± 0.32
Mean corpuscular hemoglobin concentration (g/dl)	33.2 ± 0.30	33.6 ± 0.30	33.0 ± 0.33	32.8 ± 0.44
Mean corpuscular volume (μ^3)	44.2 ± 0.36	43.5 ± 0.40	44.0 ± 0.26	44.7 ± 1.14
Platelets (10^3/mm^3)	864 ± 15.3	828 ± 46.0	831 ± 50.2	927 ± 66.8
Erythrocytes (10^6/mm^3)	9.83 ± 0.133	10.38 ± 0.221	10.18 ± 0.138	**7.83 ± 0.484
Reticulocytes (10^6/mm^3)	0.20 ± 0.019	0.19 ± 0.024	0.19 ± 0.015	**0.46 ± 0.067
FEMALE				
Leukocytes (10^3/mm^3)	4.08 ± 0.347	3.34 ± 0.221	2.98 ± 0.338	3.86 ± 0.702
Lymphocytes (10^3/mm^3)	3.12 ± 0.289	2.44 ± 0.144	**2.19 ± 0.217	**2.13 ± 0.120
Segmented neutrophils (10^3/mm^3)	0.83 ± 0.065	0.82 ± 0.093	0.72 ± 0.151	1.61 ± 0.706
Eosinophils (10^3/mm^3)	0.12 ± 0.027	0.07 ± 0.023	0.08 ± 0.020	0.11 ± 0.037
Hematocrit (percent)	45.3 ± 0.30	44.6 ± 0.52	43.7 ± 0.56	*42.1 ± 1.49
Hemoglobin (g/dl)	15.0 ± 0.17	14.7 ± 0.16	14.3 ± 0.22	**13.7 ± 0.47
Mean corpuscular hemoglobin (pg)	14.7 ± 0.07	15.0 ± 0.14	14.5 ± 0.17	14.7 ± 0.18
Mean corpuscular hemoglobin concentration (g/dl)	33.3 ± 0.34	33.1 ± 0.36	32.8 ± 0.15	32.6 ± 0.28
Mean corpuscular volume (μ^3)	44.0 ± 0.42	45.3 ± 0.26	44.2 ± 0.47	45.0 ± 0.47
Platelets (10^3/mm^3)	669 ± 50.9	661 ± 30.2	726 ± 53.4	714 ± 19.4
Erythrocytes (10^6/mm^3)	10.21 ± 0.090	9.84 ± 0.110	9.88 ± 0.150	*9.37 ± 0.400
Reticulocytes (10^6/mm^3)	0.20 ± 0.015	0.21 ± 0.016	0.19 ± 0.015	0.28 ± 0.041

(a) Mean ± standard error for groups of 10 animals; P values are vs. the vehicle controls by Dunnett's test (Dunnett, 1980) or Williams' test (Williams, 1971, 1972).
*$P<0.05$
**$P<0.01$

APPENDIX K

CHEMICAL CHARACTERIZATION, ANALYSIS, AND DOSE PREPARATION OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE FOR THE TOXICOLOGY STUDIES

APPENDIX K. CHEMICAL CHARACTERIZATION

Procurement and Characterization of 4-Vinyl-1-cyclohexene Diepoxide

4-Vinyl-1-cyclohexene diepoxide (labeled Bakelite Epoxy Resin ERL-4206) was obtained in one lot (lot no. TF3-91614) from Union Carbide Corporation (Danbury, CT) as a clear, pale yellow liquid. Purity and identity analyses were conducted at Midwest Research Institute (MRI) (Kansas City, MO). MRI reports on the analyses performed in support of the 4-vinyl-1-cyclohexene diepoxide studies are on file at the National Institute for Environmental Health Sciences.

The study chemical was identified as 4-vinyl-1-cyclohexene diepoxide by infrared, ultraviolet/visible, and nuclear magnetic resonance spectroscopy. The infrared spectrum (Figure K1) was consistent with the structure and with the literature spectrum (Serboli, 1966); the nuclear magnetic resonance (Figure K2) and ultraviolet/visible spectra were consistent with those expected for the structure of 4-vinyl-1-cyclohexene diepoxide.

The purity of lot no. TF3-91614 was determined by elemental analysis, Karl Fischer water analysis, potentiometric titration of the epoxide group in chloroform (by in situ generation of hydrogen iodide from excess tetrabutylammonium iodide and 0.1 N perchloric acid), thin-layer chromatography, and gas chromatography. Thin-layer chromatography was performed with two solvent systems: diethyl ether:hexanes (75:25) (system 1) and toluene:ethyl acetate (50:50) (system 2). Gas chromatography was performed with flame ionization detection and a nitrogen carrier at 70 ml/minute and with either a 10% Carbowax 20M-TPA column (system 1) or a 20% SP2100/0.1% Carbowax 1500 column (system 2).

The results of elemental analyses were slightly low for carbon; those for hydrogen were in agreement with the theoretical value. Karl Fischer analysis indicated the presence of 0.37% water. Titration of the epoxide group indicated a purity of 97.0%. Thin-layer chromatography indicated three minor and one trace impurity by system 1; system 2 indicated five trace impurities. Gas chromatography by system 1 indicated seven impurities, six before and one after the major peak. The impurities before the major peak, seen as three groups of unresolved peaks, had areas 0.91%, 0.11%, and 0.41% relative to that of the major peak, and the impurity after the major peak had a relative area of 0.30%. Gas chromatography by system 2 indicated seven impurities, five before and two after the major peak. The impurities before the major peak, seen as two groups of unresolved peaks, had relative areas of 0.79% and 0.30%; the two impurities after the major peak were unresolved with an area 0.13% relative to the major peak area. Six additional impurities, three before and three after the major peak, had individual areas less than 0.1% of the major peak area. No attempt was made to identify any of the impurities detected by gas chromatography. The isomeric configuration of the 4-vinyl-1-cyclohexene diepoxide study material was determined by carbon-13 nuclear magnetic resonance spectroscopy. Four distinct enantiomeric pairs of 4-vinyl-1-cyclohexene diepoxide were detected. Results indicated that the *anti*-configurated stereoisomers were present at a concentration of approximately 2:1 relative to the *syn*-configurated stereoisomers.

Stability studies performed by gas chromatography with system 2 and tetradecane as an internal standard indicated that 4-vinyl-1-cyclohexene diepoxide is stable as a bulk chemical when stored protected from light for at least 2 weeks at temperatures up to 60° C. Periodic analysis of 4-vinyl-1-cyclohexene diepoxide by gas chromatography and titration of the epoxide group indicated that no deterioration occurred during the studies.

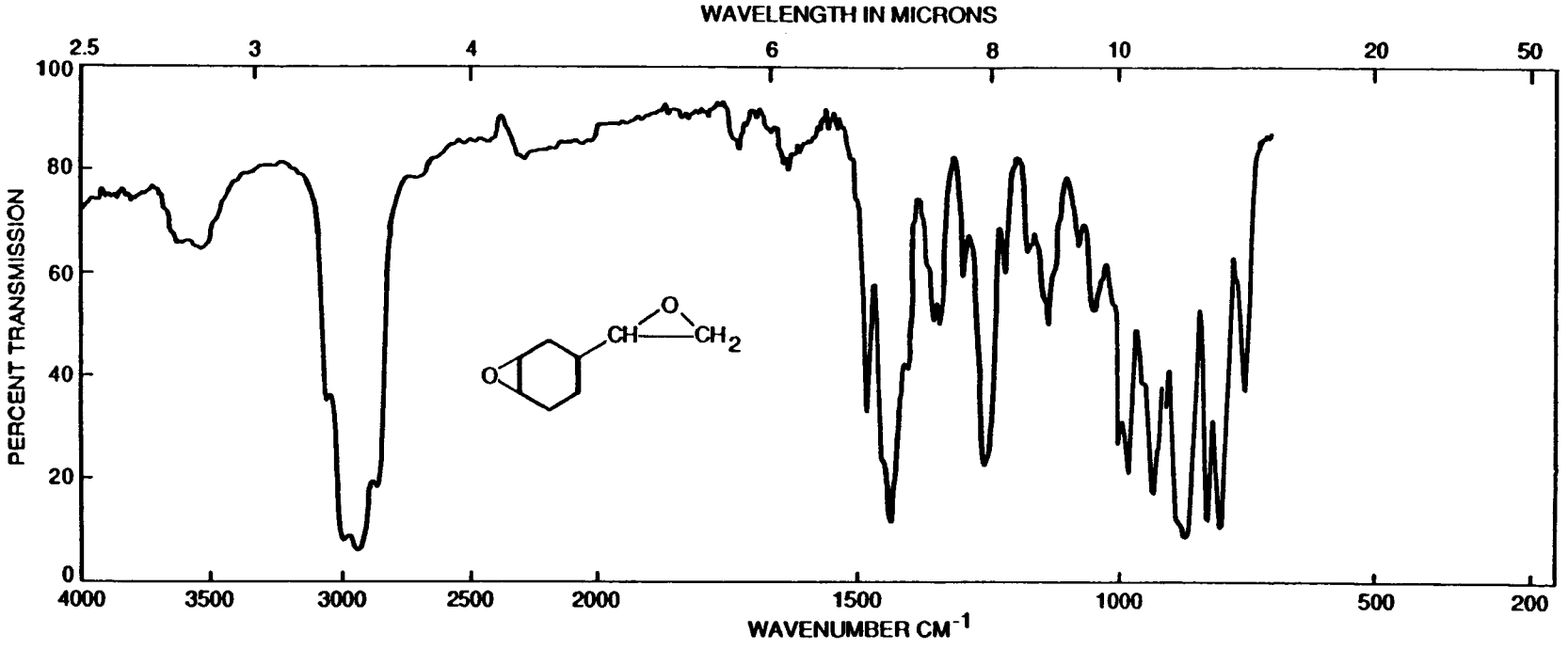

FIGURE K1. INFRARED ABSORPTION SPECTRUM OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (LOT NO. TF3-91614)

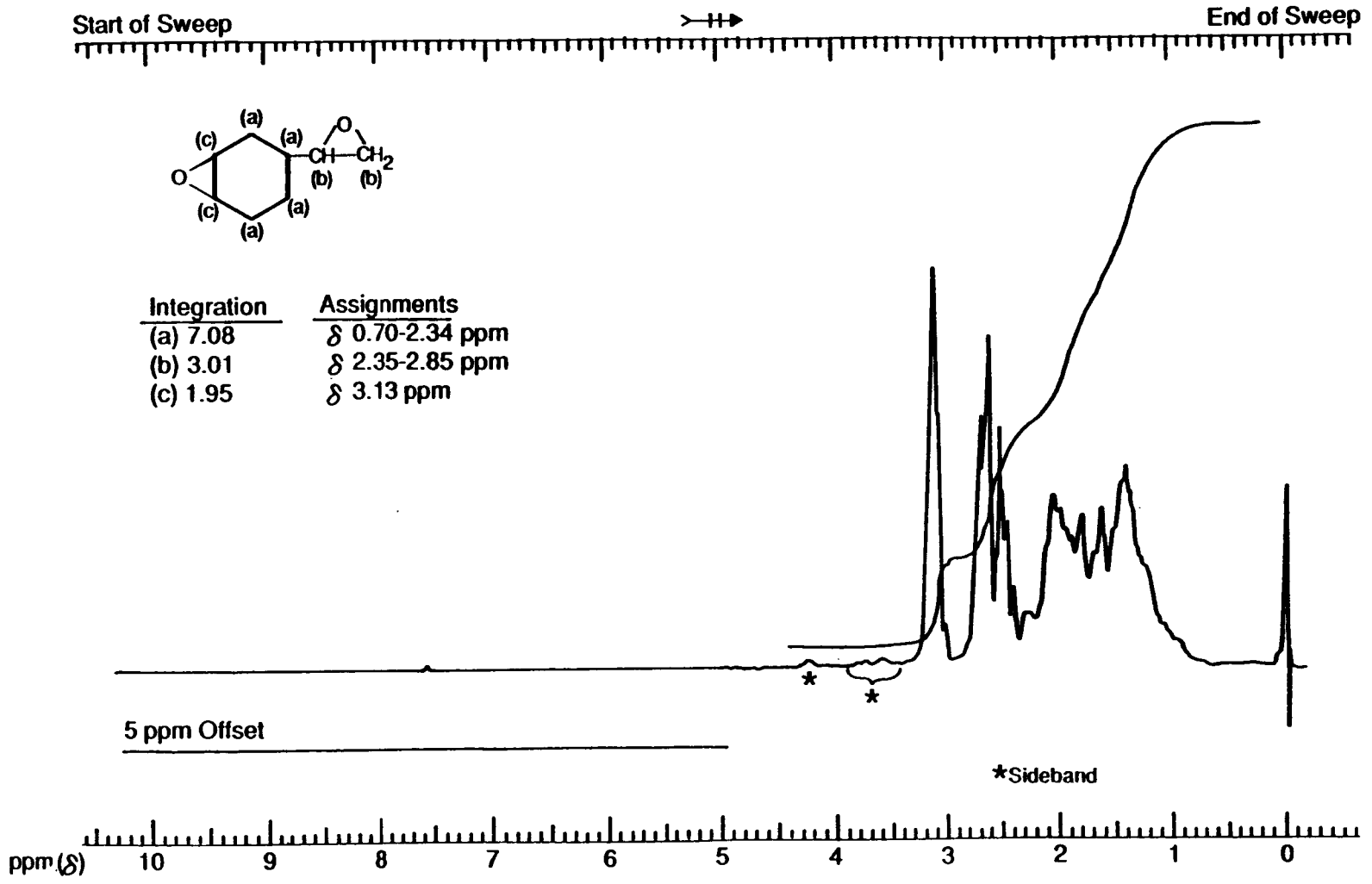

FIGURE K2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (LOT NO. TF3-91614)

Preparation and Characterization of Dose Mixtures for the Dermal Studies

The appropriate amounts of 4-vinyl-1-cyclohexene diepoxide and acetone for the dermal application studies (Table K1) were mixed (w/v) to give the desired concentrations. The stability of 4-vinyl-1-cyclohexene diepoxide in acetone was determined by gas chromatography with the same column as previously described for system 2, with 30 ml/minute nitrogen, and with tetradecane as the internal standard. 4-Vinyl-1-cyclohexene diepoxide in acetone at a concentration of 500 mg/ml was found to be stable for at least 2 weeks when stored in the dark at room temperature, at 5° C, or for 3 hours open to light and air at room temperature.

Periodic analysis by gas chromatography of 4-vinyl-1-cyclohexene diepoxide/acetone dose mixtures were conducted at the study laboratory and at the analytical chemistry laboratory. Dose mixtures were analyzed twice during the 13-week studies. All mixtures were within ±10% of the target concentrations (Table K2).

During the 2-year studies, the dose mixtures were analyzed at approximately 8-week intervals. For the 4-vinyl-1-cyclohexene diepoxide dermal studies, the mixtures were formulated within ±10% of the target concentrations approximately 93% (39/42) of the time throughout the studies; the three samples outside the ±10% were within ±13% of the target concentrations (Table K3). Results of periodic referee analysis performed by the analytical chemistry laboratory indicated generally good agreement with the results from the study laboratory (Table K4).

TABLE K1. PREPARATION AND STORAGE OF DOSE MIXTURES IN THE DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Single-Administration Studies	Fourteen-Day Studies	Thirteen-Week Studies	Fifteen-Month and Two-Year Studies
Preparation			
Specified weight of chemical mixed with acetone to appropriate volume. Lower concentrations prepared by serial dilution.	Same as single-administration studies.	Same as single-administration studies.	Same as single-administration studies.
Maximum Storage Time			
2 wk	2 wk	2 wk	2 wk
Storage Conditions			
Foil-wrapped glass vials at 4° C	Foil-wrapped glass vials at 23° C	Amber glass bottles at 23° C	Amber glass bottles at 4° C

TABLE K2. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE THIRTEEN-WEEK DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Date Mixed	Concentration of 4-Vinyl-1-cyclohexene Diepoxide in Acetone (mg/ml)		Determined as a Percent of Target
	Target	Determined (a)	
09/08/81	6.25	6.1	97.6
	12.5	13.1	104.8
	25	25.8	103.2
	50	53.9	107.8
	100	98.2	98.2
	200	211.4	105.7
10/26/81	6.25	6.64	106.2
	12.5	12.68	101.4
	25	25.54	102.2
	50	50.1	100.2
	100	102.8	102.8
	200	202.0	101.0

(a) Results of duplicate analysis

TABLE K3. RESULTS OF ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Date Mixed	Concentration of 4-Vinyl-1-cyclohexene Diepoxide in Acetone for Target Concentration (mg/ml) (a)		
	25	50	100
09/18/82	24.8	47.4	97.6
11/18/82	24.7	49.3	99.5
		51.2	
12/23/82	25.8	50.2	99.7
03/03/83	25.6	51.3	103.2
04/22/83	(b) 28.3	(b) 55.8	(b) 111.2
04/27/83	(c) 25.8	(c) 52.0	(c) 102.2
06/24/83	22.8	51.0	98.2
08/12/83	25.3	50.7	100.3
10/14/83	22.8	46.0	90.1
12/09/83	24.6	50.7	99.8
02/03/84	26.2	50.9	101.0
03/23/84	25.3	49.1	95.1
05/25/84	24.8	51.2	100.5
07/20/84	25.7	50.7	98.6
09/17/84		49.4	96.9
Mean (mg/ml)	25.1	50.3	99.4
Standard deviation	1.41	2.14	4.60
Coefficient of variation (percent)	5.6	4.3	4.6
Range (mg/ml)	22.8-28.3	46.0-55.8	90.1-111.2
Number of samples	13	15	14

(a) Results of duplicate analysis
(b) Out of specifications; not used in studies.
(c) Remix; not included in the mean.

TABLE K4. RESULTS OF REFEREE ANALYSIS OF DOSE MIXTURES IN THE TWO-YEAR DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE

Date Mixed	Target Concentration (mg/ml)	Determined Concentration (mg/ml)	
		Study Laboratory (a)	Referee Laboratory (b)
03/03/83	50	51.3	53.3
08/12/83	100	100.3	101.0
02/03/84	50	50.9	50.5
07/20/84	25	25.7	25.9

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

APPENDIX L

GENETIC TOXICOLOGY OF

4-VINYL-1-CYCLOHEXENE DIEPOXIDE

METHODS

Salmonella Protocol: Testing was performed as reported by Ames et al. (1975) with modifications listed below and described in greater detail by Haworth et al. (1983) and Mortelmans et al. (1986). Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). The study chemical was incubated with the *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, and TA1537) either in buffer or S9 mix (metabolic activation enzymes and cofactors from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver) for 20 minutes at 37° C before the addition of soft agar supplemented with L-histidine and D-biotin and subsequent plating on minimal glucose agar plates. Incubation was continued for an additional 48 hours.

Chemicals were tested in four strains. Each test consisted of triplicate plates of concurrent positive and negative controls and of at least five doses of the study chemical. The high dose was limited by toxicity or solubility but did not exceed 10 mg/plate. All assays were repeated.

A positive response was defined as a reproducible, dose-related increase in histidine-independent (revertant) colonies in any one strain/activation combination. An equivocal response was defined as an increase in revertants which was not dose related, not reproducible, or of insufficient magnitude to support a determination of mutagenicity. A response was considered negative when no increase in revertant colonies was observed after chemical treatment.

Mouse Lymphoma Protocol: The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). All study chemicals were supplied as coded aliquots from Radian Corporation (Austin, TX). The highest dose of the study compound was determined by solubility or toxicity and did not exceed 5 mg/ml. Mouse L5178Y/TK lymphoma cells were maintained at 37° C as suspension cultures in Fischer's medium supplemented with 2 mM L-glutamine, 110 µg/ml sodium pyruvate, 0.05% pluronic F68, antibiotics, and heat-inactivated horse serum; normal cycling time was about 10 hours. To reduce the number of spontaneously occurring trifluorothymidine (Tft)-resistant cells, subcultures were exposed once to medium containing thymidine, hypoxanthine, methotrexate, and glycine for 1 day, to thymidine, hypoxanthine, and glycine for 1 day, and to normal medium for 3-5 days. For cloning, horse serum content was increased and Noble agar was added. Freshly prepared S9 metabolic activation factors were obtained from the liver of either Aroclor 1254-induced or noninduced male F344 rats.

All doses within an experiment, including concurrent positive and solvent controls, were replicated. Treated cultures contained 6×10^6 cells in 10 ml of medium. This volume included the S9 fraction in those experiments performed with metabolic activation. Incubation with the study chemical continued for 4 hours, after which time the medium plus chemical was removed and the cells were resuspended in 20 ml of fresh medium and incubated for an additional 2 days to express the mutant phenotype. Cell density was monitored so that log phase growth was maintained. After the 48-hour expression period, 3×10^6 cells were plated in medium and soft agar supplemented with Tft for selection of Tft-resistant cells ($TK^{+/+}$), and 600 cells were plated in nonselective medium and soft agar to determine cloning efficiency. Plates were incubated at 37° C under 5% carbon dioxide for 10-12 days. All data were evaluated statistically for both trend and peak response. Both responses had to be significant ($P<0.05$) for a chemical to be considered capable of inducing Tft resistance; a single significant response led to an "equivocal" conclusion, and the absence of both a trend and a peak response resulted in a "negative" call.

Minimum criteria for accepting an experiment as valid and a detailed description of the statistical analysis and data evaluation are presented in Myhr et al. (1985). This assay was initially performed without S9; if a clearly positive response was not obtained, the experiment was repeated with induced S9.

Chinese Hamster Ovary Cytogenetics Assays: Testing was performed as reported by Galloway et al. (1985) and is described briefly below. Chemicals were sent to the laboratories as coded aliquots from Radian Corporation (Austin, TX). Chemicals were tested in cultured Chinese hamster ovary (CHO) cells for induction of sister chromatid exchanges (SCEs) and chromosomal aberrations both in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine (BrdU)-substituted DNA. Each test consisted of concurrent solvent and positive controls and of at least three doses of the study chemical; the high dose was limited by toxicity or solubility but did not exceed 5 mg/ml.

In the SCE test without S9, CHO cells were incubated for 26 hours with the study chemical in McCoy's 5A medium supplemented with 10% fetal bovine serum, L-glutamine (2 mM), and antibiotics. BrdU was added 2 hours after culture initiation. After 26 hours, the medium containing the study chemical was removed and replaced with fresh medium plus BrdU and colcemid, and incubation was continued for 2 more hours. Cells were then harvested by mitotic shake-off, fixed, and stained with Hoechst 33258 and Giemsa. In the SCE test with S9, cells were incubated with the chemical, serum-free medium, and S9 for 2 hours. The medium was then removed and replaced with medium containing BrdU and no study chemical; incubation proceeded for an additional 26 hours, with colcemid present for the final 2 hours. Harvesting and staining were the same as for cells treated without S9.

In the chromosomal aberration test without S9, cells were incubated in McCoy's 5A medium with the study chemical for 8 hours; colcemid was added, and incubation was continued for 2 hours. The cells were then harvested by mitotic shake-off, fixed, and stained with Giemsa. For the chromosomal aberration test with S9, cells were treated with the study chemical and S9 for 2 hours, after which the treatment medium was removed and the cells were incubated for 10 hours in fresh medium, with colcemid present for the final 2 hours. Cells were harvested in the same manner as for the treatment without S9.

For the SCE test, if significant chemical-induced cell cycle delay was seen, incubation time was lengthened to ensure a sufficient number of scorable cells. The harvest time for the chromosomal aberration test was based on the cell cycle information obtained in the SCE test; if cell cycle delay was anticipated, the incubation period was extended approximately 5 hours.

Cells were selected for scoring on the basis of good morphology and completeness of karyotype (21 ± 2 chromosomes). All slides were scored blind, and those from a single test were read by the same person. For the SCE test, 50 second-division metaphase cells were usually scored for frequency of SCEs per cell from each dose; 25, 50, or 100 first-division metaphase cells were scored at each dose for the chromosomal aberration test. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the slopes of the dose-response curves and the individual dose points. An SCE frequency 20% above the concurrent solvent control value was chosen as a statistically conservative positive response. The probability of this level of difference occurring by chance at one dose point is less than 0.01; the probability for such a chance occurrence at two dose points is less than 0.001. Chromosomal aberration data are presented as percentage of cells with aberrations. As with SCEs, both the dose-response curve and individual dose points were statistically analyzed. A statistically significant ($P<0.003$) trend test or a significantly increased dose point ($P<0.05$) was sufficient to indicate a chemical effect.

RESULTS

Treatment with 100-10,000 µg/plate 4-vinyl-1-cyclohexene diepoxide produced a significant, dose-related increase in revertant colonies in *S. typhimurium* strains TA98, TA100, and TA1535 with and without Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver S9; in strain TA1537, the response in the absence of S9 was equivocal, but with S9, a significant increase in mutant colonies was observed (Mortelmans et al., 1986; Table L1). 4-Vinyl-1-cyclohexene diepoxide, over a dose range of 25-200 µg/ml, induced a highly significant, dose-related increase in Tft resistance in mouse L5178Y/TK lymphoma cells without S9 activation (Table L2). This increase in resistant colonies was seen in cultures with good total growth relative to negative controls; the test was not performed with S9. In tests for chromosomal effects with cultured CHO cells, 4-vinyl-1-cyclohexene diepoxide, at doses as low as 1.12 µg/ml for the SCE test and 37 µg/ml for the chromosome aberration test, produced a highly significant increase in both SCEs and chromosomal aberrations in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 (Tables L3 and L4). Some chemical-induced cell cycle delay was observed, particularly in the chromosomal aberration test without S9, but most of the increases in SCEs were achieved in the absence of overt toxicity.

TABLE L1. MUTAGENICITY OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE IN *SALMONELLA TYPHIMURIUM* (a)

Strain	Dose (µg/plate)	Revertants/Plate (b)					
		−S9		+S9 (hamster)		+S9 (rat)	
		Trial 1	Trial 2	Trial 1	Trial 2	Trial 1	Trial 2
TA100	0	131 ± 14.7	103 ± 5.7	147 ± 9.0	120 ± 7.2	152 ± 8.2	103 ± 1.5
	100	169 ± 6.8	193 ± 4.0	166 ± 8.4	154 ± 8.6	154 ± 9.5	164 ± 11.4
	333	255 ± 13.6	285 ± 13.1	218 ± 4.5	188 ± 10.5	250 ± 6.5	236 ± 4.3
	1,000	433 ± 12.9	482 ± 9.9	360 ± 13.6	325 ± 10.7	462 ± 27.9	458 ± 11.7
	3,333	614 ± 51.9	685 ± 50.4	687 ± 22.8	741 ± 21.0	683 ± 55.0	915 ± 27.2
	10,000	615 ± 71.0	801 ± 82.3	831 ± 65.5	1,197 ± 49.3	741 ±107.4	1,263 ± 30.7
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		259 ± 14.4	323 ± 11.4	1,148 ± 58.9	1,410 ± 29.6	567 ± 27.7	608 ± 14.5
TA1535	0	25 ± 3.0	22 ± 3.8	12 ± 2.4	8 ± 0.3	15 ± 1.0	14 ± 2.5
	100	31 ± 5.8	39 ± 4.6	17 ± 1.2	18 ± 4.9	13 ± 3.7	24 ± 2.6
	333	57 ± 3.2	60 ± 4.4	40 ± 1.5	41 ± 7.3	39 ± 3.5	42 ± 1.2
	1,000	120 ± 5.1	120 ± 9.7	95 ± 9.3	95 ± 15.2	99 ± 2.4	111 ± 3.0
	3,333	252 ± 9.5	240 ± 5.8	249 ± 12.3	235 ± 5.5	293 ± 9.5	317 ± 10.7
	10,000	307 ± 11.2	381 ± 19.6	396 ± 21.7	409 ± 48.4	440 ± 19.0	465 ± 22.0
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		284 ± 2.3	330 ± 9.2	389 ± 2.5	308 ± 25.5	144 ± 9.4	188 ± 6.9
TA1537	0	5 ± 1.2	9 ± 1.5	7 ± 0.9	5 ± 2.0	6 ± 0.9	8 ± 0.3
	100	9 ± 2.3	7 ± 3.2	7 ± 2.6	5 ± 1.2	14 ± 1.5	10 ± 1.7
	333	5 ± 0.3	5 ± 2.0	6 ± 1.0	5 ± 0.7	11 ± 2.4	12 ± 2.1
	1,000	7 ± 0.6	11 ± 2.5	10 ± 1.9	6 ± 0.7	9 ± 1.3	14 ± 1.2
	3,333	11 ± 4.0	13 ± 2.8	14 ± 1.2	7 ± 0.9	18 ± 0.9	20 ± 0.9
	10,000	18 ± 0.6	19 ± 5.7	28 ± 0.3	15 ± 1.2	20 ± 0.6	22 ± 2.3
Trial summary		Equivocal	Equivocal	Positive	Equivocal	Positive	Positive
Positive control (c)		329 ± 28	339 ± 3.4	537 ± 17.7	512 ± 13.4	205 ± 2.3	238 ± 12.2
TA98	0	15 ± 1.0	19 ± 1.9	32 ± 2.6	30 ± 0.9	34 ± 2.9	21 ± 2.4
	100	22 ± 2.1	28 ± 1.9	32 ± 2.7	31 ± 3.8	34 ± 4.0	28 ± 4.9
	333	22 ± 3.7	28 ± 1.9	30 ± 4.9	37 ± 3.5	27 ± 1.7	33 ± 4.4
	1,000	42 ± 2.8	41 ± 5.5	48 ± 2.6	42 ± 2.2	40 ± 1.8	37 ± 2.4
	3,333	87 ± 1.8	94 ± 10.7	90 ± 4.7	67 ± 3.8	79 ± 7.0	92 ± 4.4
	10,000	106 ± 12.2	133 ± 15.6	160 ± 5.0	124 ± 16.7	139 ± 8.3	118 ± 5.2
Trial summary		Positive	Positive	Positive	Positive	Positive	Positive
Positive control (c)		225 ± 85.9	631 ± 21.4	1,093 ± 63.3	886 ± 22.6	498 ± 33.0	394 ± 14.8

(a) Study performed at SRI International. The detailed protocol is presented in Haworth et al. (1983), and the data are presented in Mortelmans et al. (1986). Cells and study compound or solvent (distilled water) were incubated in the absence of exogenous metabolic activation (−S9) or with Aroclor 1254-induced S9 from male Syrian hamster liver or male Sprague Dawley rat liver. High dose was limited by toxicity or solubility, but did not exceed 10 mg/plate; 0 µg/plate dose is the solvent control.

(b) Revertants are presented as mean ± the standard error from three plates.

(c) Positive control; 2-aminoanthracene was used with all strains in the presence of S9. In the absence of metabolic activation, 4-nitro-o-phenylenediamine was used with TA98, sodium azide used with TA100 and TA1535, and 9-aminoacridine was used with TA1537.

TABLE L2. INDUCTION OF TRIFLUOROTHYMIDINE RESISTANCE IN MOUSE L5178Y LYMPHOMA CELLS BY 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a,b)

Compound	Concentration (μg/ml)	Cloning Efficiency (percent)	Relative Total Growth (percent)	Tft-Resistant Cells	Mutant Fraction (c)
Trial 1					
Distilled water (d)		57.0 ± 3.2	100.3 ± 5.0	82.3 ± 5.8	48.3 ± 3.2
4-Vinyl-1-cyclohexene diepoxide	25	46.5 ± 1.5	60.5 ± 7.5	216.0 ± 31.0	(e) 156.5 ± 27.5
	50	33.0 ± 3.0	42.5 ± 6.5	267.5 ± 37.5	(e) 273.0 ± 62.0
	100	16.5 ± 3.5	14.5 ± 6.5	416.0 ± 2.0	(e) 895.0 ± 180.0
	(f) 200	14	9	338	804
	400	Lethal	--	--	--
Methyl methanesulfonate (f)	15	19	18	231	413
Trial 2					
Distilled water (g)		75.0 ± 6.7	99.8 ± 8.3	215.5 ± 15.4	96.0 ± 2.7
4-Vinyl-1-cyclohexene diepoxide	25	82.5 ± 1.5	95.0 ± 13.0	432.5 ± 13.5	(e) 175.0 ± 3.0
	50	60.5 ± 1.5	69.0 ± 15.0	496.5 ± 16.5	(e) 274.5 ± 2.5
	100	54.0 ± 0.0	49.5 ± 3.5	952.0 ± 2.0	(e) 590.0 ± 4.0
	200	19.0 ± 4.0	6.5 ± 1.5	870.0 ± 45.0	(e) 1,595.0 ± 416.0
	400	Lethal	--	--	--
Methyl methanesulfonate	15	23.0 ± 3.0	16.0 ± 1.0	469.5 ± 5.5	699.5 ± 112.5

(a) Study performed at Inveresk Research International. The experimental protocol is presented in detail by Myhr et al. (1985) and follows the basic format of Clive et al. (1979). The highest dose of study compound is determined by solubility or toxicity and may not exceed 5 mg/ml. All doses are tested in duplicate, except as noted; the average for the tests is presented in the table. Cells (6×10^5/ml) were treated for 4 hours at 37° C in medium, washed, resuspended in medium, and incubated for 48 hours at 37° C. After expression, 3×10^6 cells were plated in medium and soft agar supplemented with trifluorothymidine (Tft) for selection of Tft-resistant cells, and 600 cells were plated in nonselective medium and soft agar to determine the cloning efficiency.

(b) Mean ± standard error from replicate trials of approximately 1×10^6 cells each. All data are evaluated statistically for both trend and peak response ($P<0.05$ for at least one of the three highest dose sets). Both responses must be significantly ($P<0.05$) positive for a chemical to be considered capable of inducing Tft resistance. If only one of these responses is significant, the call is "equivocal"; the absence of both trend and peak response results in a "negative" call.

(c) Mutant fraction (frequency) is a ratio of the Tft-resistant cells to the cloning efficiency, divided by 3 (to arrive at MF per 1×10^6 cells treated); MF = mutant fraction.

(d) Data presented are the average of three tests.

(e) Significant positive response; occurs when the relative mutant fraction (average MF of treated culture/average MF of solvent control) is greater than or equal to 1.6.

(f) Data presented are from one test.

(g) Data presented are the average of four tests.

TABLE L3. INDUCTION OF SISTER CHROMATID EXCHANGES IN CHINESE HAMSTER OVARY CELLS BY 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

Compound	Dose (μg/ml)	Total Cells	No. of Chromosomes	No. of SCEs	SCEs/ Chromosome	SCEs/ Cell	Hours in BrdU	Relative SCEs/Cell (percent) (b)
−S9 (c) Summary: Positive								
Dimethyl sulfoxide		50	1,050	600	0.57	12.0	25.8	
4-Vinyl-1-cyclohexene diepoxide	1.12	50	1,046	808	0.77	16.2	25.8	135.0
	3.73	50	1,047	1,646	1.57	32.9	25.8	274.2
	11.2	50	1,047	1,891	1.81	37.8	25.8	315.0
Mitomycin C	0.001	50	1,049	711	0.68	14.2	25.8	118.3
	0.01	5	105	238	2.27	47.6	25.8	396.7
+S9 (e) Summary: Positive								
Dimethyl sulfoxide		50	1,051	579	0.55	11.6	25.8	
4-Vinyl-1-cyclohexene diepoxide	37.3	50	1,045	1,471	1.41	29.4	25.8	253.4
	112	50	1,052	1,928	1.83	38.6	25.8	332.8
	373	5	105	596	5.68	119.2	(d) 32.5	1,027.6
Cyclophosphamide	0.35	50	1,049	775	0.74	15.5	25.8	133.6
	2	5	105	168	1.60	33.6	25.8	289.7

(a) Study performed at Litton Bionetics, Inc. SCE = sister chromatid exchange; BrdU = bromodeoxyuridine. A detailed description of the SCE protocol is presented by Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent (dimethyl sulfoxide) as described in (c) and (e) below and cultured for sufficient time to reach second metaphase division. Cells were then collected by mitotic shake-off, fixed, air dried, and stained.
(b) SCEs/cell of culture exposed to study chemical relative to those of culture exposed to solvent
(c) In the absence of S9, Chinese hamster ovary cells were incubated with study compound or solvent for 2 hours at 37° C. Then BrdU was added, and incubation was continued for 24 hours. Cells were washed, fresh medium containing BrdU and colcemid was added, and incubation was continued for 2-3 hours.
(d) Because some chemicals induce a delay in the cell division cycle, harvest times are occasionally extended to maximize the proportion of second division cells available for analysis.
(e) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, and medium containing BrdU was added. Cells were incubated for a further 26 hours, with colcemid present for the final 2-3 hours. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.

TABLE L4. INDUCTION OF CHROMOSOMAL ABERRATIONS IN CHINESE HAMSTER OVARY CELLS BY 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (a)

−S9 (b)					+S9 (c)				
Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs	Dose (µg/ml)	Total Cells	No. of Abs	Abs/ Cell	Percent Cells with Abs
Harvest time: 22.8 h (d)					Harvest time: 10.5 h				
Dimethyl sulfoxide					Dimethyl sulfoxide				
	100	6	0.06	3.0		100	5	0.05	5.0
4-Vinyl-1-cyclohexene diepoxide					4-Vinyl-1-cyclohexene diepoxide				
37.8	100	95	0.95	43.0	447	100	49	0.49	33.0
50.3	50	151	3.02	82.0	503	100	69	0.69	45.0
62.9	25	195	7.80	100.0	548	50	46	0.92	60.0
Summary: Positive					Summary: Positive				
Mitomycin C					Cyclophosphamide				
0.05	50	49	0.98	50.0	50	50	32	0.64	38.0

(a) Study performed at Litton Bionetics, Inc. Abs = aberrations. A detailed presentation of the technique for detecting chromosomal aberrations is found in Galloway et al. (1985). Briefly, Chinese hamster ovary cells were incubated with study compound or solvent as indicated in (b) and (c). Cells were arrested in first metaphase by addition of colcemid and harvested by mitotic shake-off, fixed, and stained in 6% Giemsa.
(b) In the absence of S9, cells were incubated with study compound or solvent for 8-10 hours at 37° C. Cells were then washed, and fresh medium containing colcemid was added for an additional 2-3 hours followed by harvest.
(c) In the presence of S9, cells were incubated with study compound or solvent for 2 hours at 37° C. Cells were then washed, medium was added, and incubation was continued for 8-10 hours. Colcemid was added for the last 2-3 hours of incubation before harvest. S9 was from the liver of Aroclor 1254-induced male Sprague Dawley rats.
(d) Because of significant chemical-induced cell cycle delay, incubation time prior to addition of colcemid was lengthened to provide sufficient metaphases at harvest.

APPENDIX M

AUDIT SUMMARY

APPENDIX M. AUDIT SUMMARY

The pathology specimens, experimental data, study documents, and draft of NTP Technical Report No. 362 for the 2-year studies of 4-vinyl-1-cyclohexene diepoxide in rats and mice were audited for the National Institute of Environmental Health Sciences (NIEHS) at the National Toxicology Program (NTP) Archives by quality assurance resource support contractors. The audit included review of:

(1) All records concerning animal receipt, quarantine, randomization, and disposition prior to study start.
(2) All inlife records including protocol, correspondence, animal husbandry, environmental conditions, dosing, external masses, mortality, animal identification, and serology for 2-year study animals.
(3) Body weight and clinical observation data; all data were scanned before individual data for a random 10% sample of animals in each study group were reviewed in detail.
(4) All chemistry records.
(5) All postmortem records for individual animals concerning date of death, disposition code, condition code, tissue accountability, correlation of masses or clinical signs recorded at or near the last inlife observation with gross observations and microscopic diagnoses, and correlation between gross observations and microscopic diagnoses.
(6) All wet tissue bags for inventory and wet tissues from a random 20% sample of 2-year study animals in each group, plus other relevant cases, to evaluate the integrity of identity for individual animals and to examine for untrimmed potential lesions.
(7) Blocks and slides of tissues from a random 20% sample of 2-year study animals from each group, plus animals with less than complete or correct identification, to examine for proper match and inventory.
(8) Necropsy record forms for data entry errors and all microscopic diagnoses for a random 20% sample of animals, plus all redlined diagnoses on the preliminary pathology tables, to verify incorporation of changes into the final pathology tables.
(9) The extent of correlation between the data, factual information, and procedures for the 2-year studies as presented in the draft Technical Report and the study records available at the NTP Archives.

Procedures and events for the exposure phase of the studies were documented adequately by the archival records, with the exception that temperature and humidity records for 1 month of the rat studies were not available at the Archives. Review of data for the entire exposure phase of each study indicated that protocol procedures for animal care were followed adequately. Records documenting dose preparation, storage, analysis, and administration to animals were complete, consistent, and accurate. Recalculation of approximately 10% of the group mean body weights showed differences in 6/56 values, ranging from 0.1% to 2.4%. Appropriate changes have been incorporated into the Technical Report. Of the external masses observed during the last months of life, 347/351 in rats and 486/493 in mice correlated with necropsy observations. The disposition code and date of death recorded at necropsy for each unscheduled-death animal (214 rats and 236 mice) had matching entries in the inlife records, except for 2 high dose male mice that were documented by study records to have been switched sometime before necropsy. This discrepancy had no influence on overall survival values or pathology data. Twelve high dose female mice were killed during week 85 rather than 10 during week 84 as indicated in the draft Technical Report. The disposition codes for two animals and the survival table have been amended in the final Technical Report.

Individual animal identifiers (clipped toes) were present and correct in the residual tissue bags for 66/78 rats and 105/128 mice examined. Review of the entire data trail for the 12 rats and 23 mice with less than complete and correct identifiers indicated that the integrity of their individual animal identity had been maintained, but their feet had not been saved. A total of 11 untrimmed potential lesions were found in the wet tissues of 78 rats examined (3 corresponded to masses noted in life), and 6 were found in 128 mice examined; 2 involved target organs in rats. Intestinal segments ranging

from 1 to 20 cm in length were not completely opened for 36/36 rats and 68/76 mice examined; no potential lesions were evident by external examination. All gross observations made at necropsy were correlated with microscopic diagnoses. Tissue blocks and slides matched each other properly. All post-Pathology Working Group changes in diagnoses had been incorporated into the final pathology tables.

Full details about these and other audit findings are presented in audit reports that are on file at the NIEHS. This summary describes the extent to which the data and factual information presented in the Technical Report are supported by records at the NTP Archives.