

NATIONAL TOXICOLOGY PROGRAM  
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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<sub>1</sub> 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<sub>1</sub> MICE**  
**(DERMAL STUDIES)**

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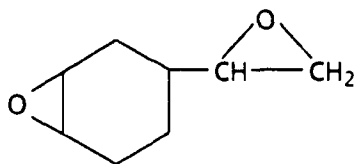
**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**Public Health Service**  
**National Institutes of Health**

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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<sub>1</sub> 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<sub>1</sub> 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<sub>1</sub> 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.

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\*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**

| <b>Male F344/N Rats</b>  | <b>Female F344/N Rats</b>   | <b>Male B6C3F<sub>1</sub> Mice</b>  | <b>Female B6C3F<sub>1</sub> Mice</b>  |
|--|---|---|---|
| <b>Dose</b><br>0, 15, or 30 mg/animal<br>4-vinyl-1-cyclohexene<br>diepoxide in acetone, 5 d/wk                       | 0, 15, or 30 mg/animal<br>4-vinyl-1-cyclohexene<br>diepoxide in acetone, 5 d/wk         | 0, 2.5, 5, or 10 mg/animal<br>4-vinyl-1-cyclohexene<br>diepoxide in acetone, 5 d/wk | 0, 2.5, 5, or 10 mg/animal<br>4-vinyl-1-cyclohexene<br>diepoxide in acetone, 5 d/wk   |
| <b>Body weights in the 2-year study</b><br>High dose lower than vehicle<br>controls                                  | High dose lower than vehicle<br>controls  | Mid and high dose lower<br>than vehicle controls                                    | High dose lower than vehicle<br>controls  |
| <b>Survival rates in the 2-year study</b><br>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;<br>10/50 (wk 85)   |
| <b>Nonneoplastic effects</b><br>Acanthosis and sebaceous<br>gland hypertrophy of the skin                            | Acanthosis and sebaceous<br>gland hypertrophy of the skin                               | Acanthosis, hyperkeratosis,<br>and necrotizing inflamma-<br>tion of the skin        | Acanthosis, hyperkeratosis,<br>and necrotizing inflamma-<br>tion of the skin; follicular<br>atrophy and tubular hyper-<br>plasia of the ovary   |
| <b>Neoplastic effects</b><br>Skin neoplasms: basal cell<br>(2/50; 4/50; 8/50); squamous<br>cell (0/50; 33/50; 36/50) | Skin neoplasms: basal cell<br>(2/50; 5/50; 5/50); squamous<br>cell (0/50; 16/50; 34/50) | Skin neoplasms: squamous<br>cell carcinomas (0/50; 14/50;<br>40/50; 43/50)          | Skin neoplasms: squamous<br>cell carcinomas (0/50; 6/50;<br>37/50; 43/50); ovary: granu-<br>losa cell neoplasms, benign<br>mixed tumors, or luteomas<br>(combined) (1/50; 0/49; 17/49;<br>18/50)<br>Other possible effect--lung:<br>alveolar/bronchiolar adeno-<br>mas or carcinomas (com-<br>bined) (4/50; 9/50; 11/50;<br>7/50) |
| <b>Level of evidence of carcinogenic activity</b><br>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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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

**Physical and Chemical Properties**

**Use, Production, and Exposure**

**Absorption, Distribution, Metabolism, and Disposition**

**Toxicity**

**Immunotoxicity**

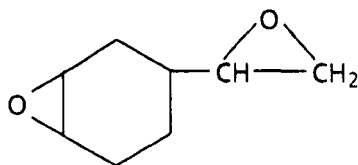
**Genetic Toxicology**

**Carcinogenicity**

**Study Rationale**

# 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<sup>3</sup>) 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 [<sup>14</sup>C]4-vinyl-1-cyclohexene diepoxide in female F344/N rats and B6C3F<sub>1</sub> 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-<sup>14</sup>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 monoepoxymonoglycols, 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<sub>50</sub> 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<sub>50</sub> for rats is 2,130 mg/kg, and the inhalation LC<sub>50</sub> 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<sub>1</sub> 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<sub>1</sub> mice. The doses applied were 1.25, 2.5, or 5 mg in 0.1 ml of vehicle.

# I. INTRODUCTION

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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



# I. INTRODUCTION

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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<sub>1</sub> 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**

**FOURTEEN-DAY DERMAL STUDIES**

**THIRTEEN-WEEK DERMAL STUDIES**

**FIFTEEN-MONTH AND TWO-YEAR STUDIES**

**Study Design**

**Source and Specifications of Animals**

**Animal Maintenance**

**Clinical Examinations and Pathology**

**Statistical Methods**

## II. MATERIALS AND METHODS

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### 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  $\pm 10\%$  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  $\pm 10\%$  of the target concentrations approximately 93% of the time throughout the studies; the other mixtures were within  $\pm 13\%$  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<sub>1</sub> 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<sub>1</sub> 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   |
|---|---|--|--|
| <b>EXPERIMENTAL DESIGN</b>  |   |  |  |
| <b>Size of Study Groups</b><br>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   |
| <b>Doses</b><br>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)   |
| <b>Date of First Dose</b><br>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   |
| <b>Date of Last Dose</b><br>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)   |
| <b>Duration of Dosing</b><br>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  |
| <b>Type and Frequency of Observation</b><br>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   |
| <b>Necropsy, Histologic Examinations, and Supplemental Analyses</b><br>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 sternbrae 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   |
|---|---|--|--|
| <b>EXPERIMENTAL DESIGN</b>  |   |  |  |
| <b>Necropsy, Histologic Examinations, and Supplemental Analyses (Continued)</b> |   |  |  |
|   | 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 non-application 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 |
| <b>ANIMALS AND ANIMAL MAINTENANCE</b>   |   |  |  |
| <b>Strain and Species</b><br>F344/N rats; B6C3F <sub>1</sub> mice               | F344/N rats; B6C3F <sub>1</sub> mice              | F344/N rats; B6C3F <sub>1</sub> mice   | F344/N rats; B6C3F <sub>1</sub> mice   |
| <b>Animal Source</b><br>Harlan Industries (Indianapolis, IN)                    | Charles River Breeding Laboratories (Portage, MI) | Frederick Cancer Research Facility (Frederick, MD)   | Charles River Breeding Laboratories (Portage, MI)  |
| <b>Study Laboratory</b><br>Battelle Columbus Laboratories                       | Battelle Columbus Laboratories                    | Battelle Columbus Laboratories   | Battelle Columbus Laboratories   |
| <b>Method of Animal Identification</b><br>Toe clip                              | Toe clip  | Toe clip   | Toe clip   |
| <b>Time Held Before Study</b><br>14 d   | Rats--19 d; mice--21 d                            | Rats--21-22 d; mice--22-23 d   | 18 d   |
| <b>Age When Placed on Study</b><br>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   |
| <b>Age When Killed</b><br>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   |
| <b>Necropsy Dates</b><br>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  |
|--|--|--|---|
| <b>ANIMALS AND ANIMAL MAINTENANCE (Continued)</b>  |  |  |   |
| <b>Method of Animal Distribution</b>   |  |  |   |
| 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   |
| <b>Diet</b>  |  |  |   |
| 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   |
| <b>Bedding</b>   |  |  |   |
| 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   |
| <b>Water</b>   |  |  |   |
| 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   |
| <b>Cages</b>   |  |  |   |
| Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)  | Same as single-administration studies  | Same as single-administration studies  | Same as single-administration studies   |
| <b>Cage Filters</b>  |  |  |   |
| Spun-bonded polyester, Dupont 2024® (Snow Filtration, Cincinnati, OH)  | Same as single-administration studies  | Same as single-administration studies  | Same as single-administration studies   |
| <b>Animals per Cage</b>  |  |  |   |
| 1  | 1  | 1  | 1   |
| <b>Other Chemicals on Study in the Same Room</b>   |  |  |   |
| None   | None   | None   | None  |
| <b>Animal Room Environment</b>   |  |  |   |
| 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 |

## II. MATERIALS AND METHODS

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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<sub>1</sub> 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- $\mu$ l 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- $\mu$ l 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.



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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<sub>1</sub> (C57BL/6N, female × C3H/HeN MTV<sup>-</sup>, 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 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.

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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

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analysis of tumor incidence, and reported P values are one-sided. The procedures described above also were used to evaluate selected non-neoplastic 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 eval-

uate 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**

### III. RESULTS: RATS

#### 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) |          |            | Final Weight Relative to Vehicle Controls (percent) |
|---------------|--------------|---------------------------|----------|------------|---|
|               |              | Initial (b)               | Final    | Change (c) |   |
| <b>MALE</b>   |              |                           |          |            |   |
| 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)   |
| <b>FEMALE</b> |              |                           |          |            |   |
| 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) |         |            | Final Weight Relative to Vehicle Controls (percent) |
|---------------|--------------|---------------------------|---------|------------|---|
|               |              | Initial (b)               | Final   | Change (c) |   |
| <b>MALE</b>   |              |                           |         |            |   |
| 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  |
| <b>FEMALE</b> |              |                           |         |            |   |
| 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) |    |     |      | Female (mg/rat) |      |     |      |
|-------------------------------|---------------|----|-----|------|-----------------|------|-----|------|
|                               | 0             | 15 | 30  | 60   | 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  | 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) |     |     | Female (mg/rat) |    |      |
|-----------------------------|---------------|-----|-----|-----------------|----|------|
|                             | 0             | 15  | 30  | 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    |

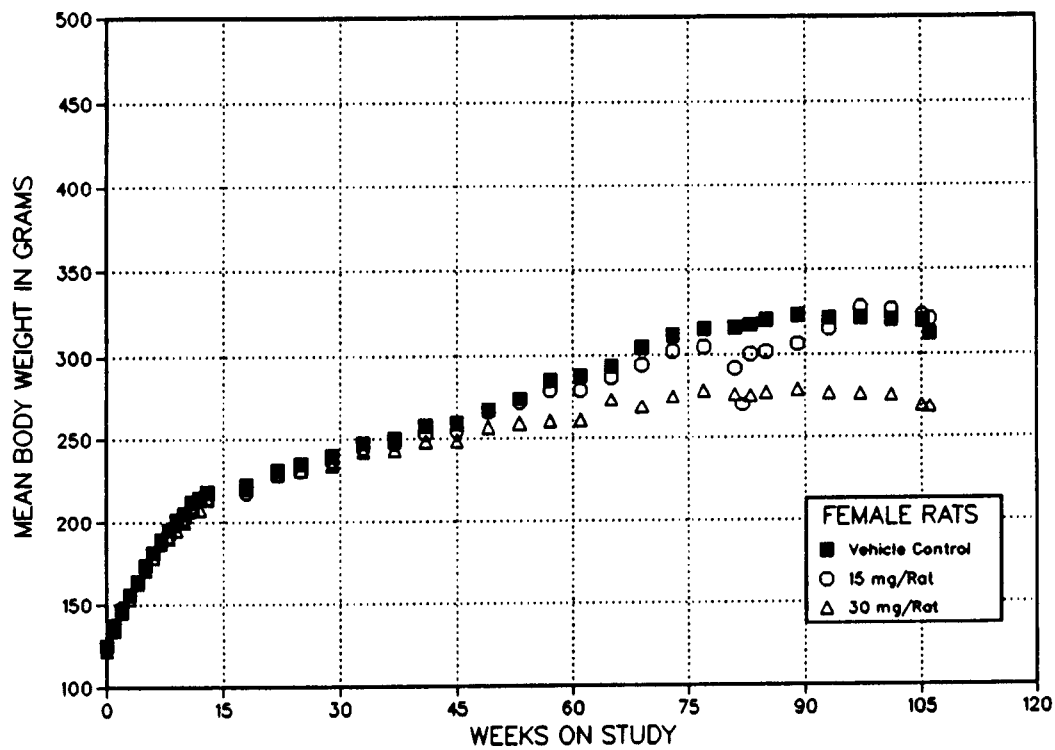
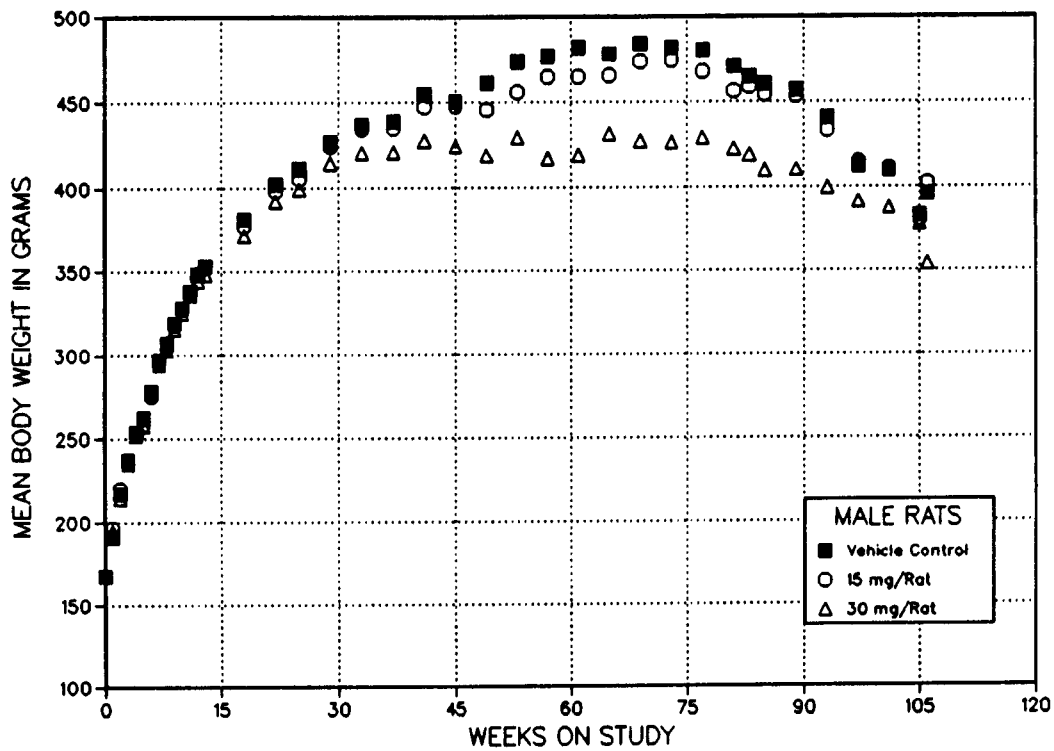
(a) Ten animals were examined in each group.  
 \*P<0.05 vs. controls  
 \*\*P<0.01 vs. controls



**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 |
| <b>MALE</b>   |                 |                |                 |                                   |                |                 |                                   |                |
| 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                                | 58             | 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              |
| <b>FEMALE</b> |                 |                |                 |                                   |                |                 |                                   |                |
| 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.

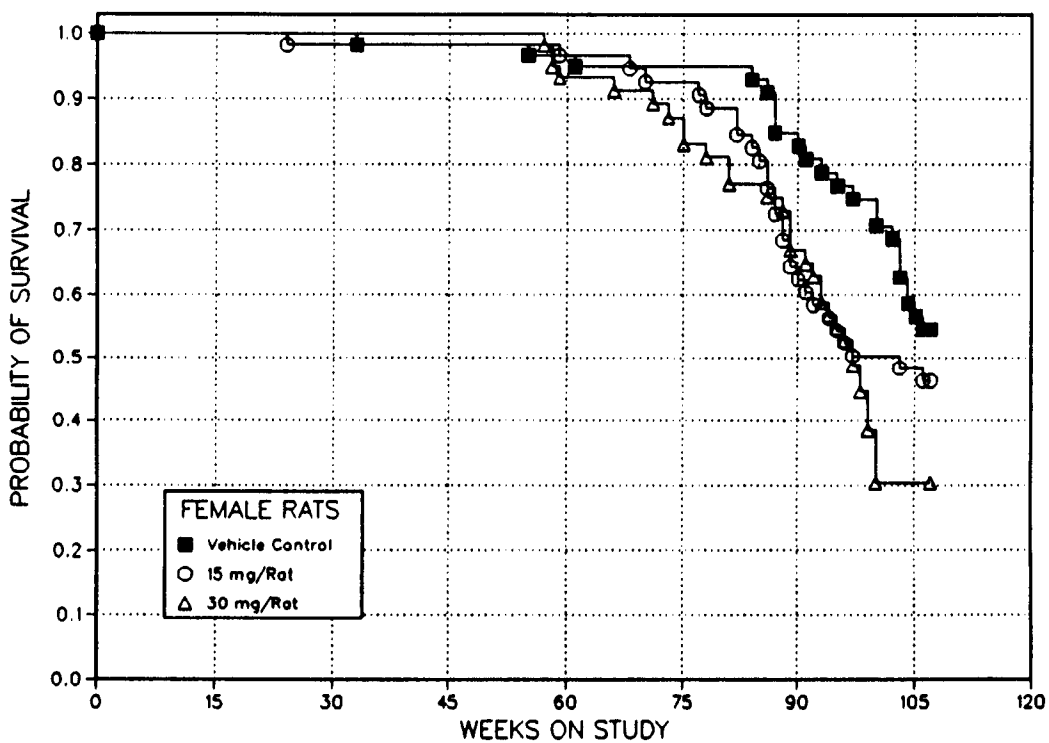
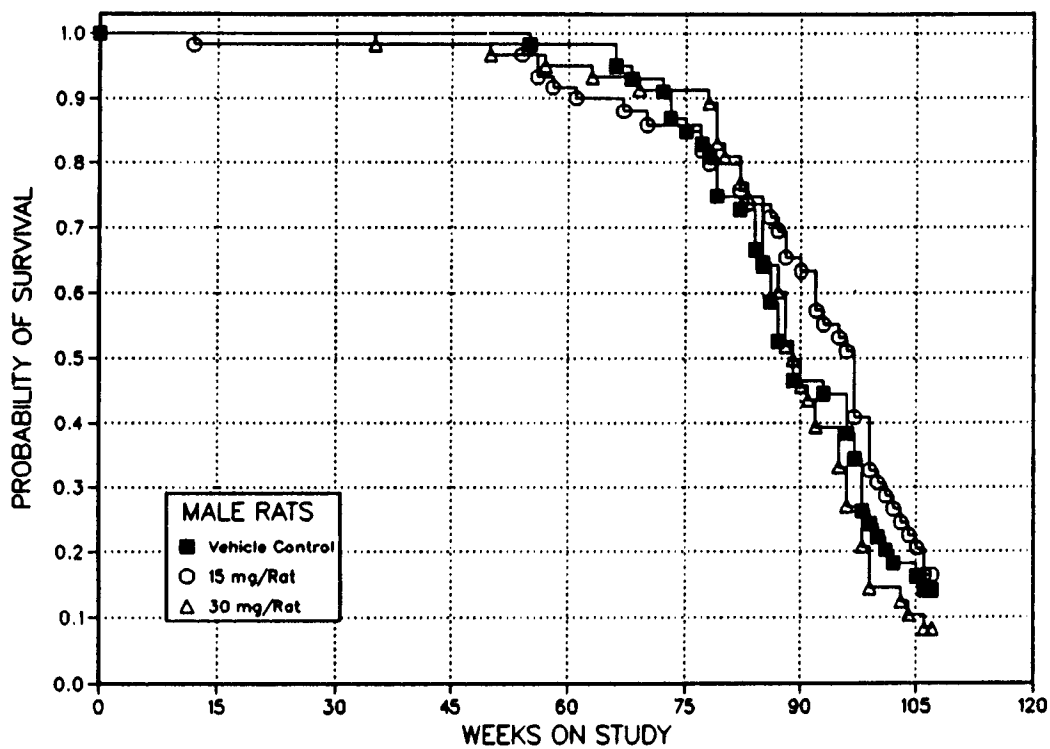
Summaries of the incidences of neoplasms and nonneoplastic lesions, individual animal tumor diagnoses, statistical analyses of primary tumors that occurred with an incidence of at least 5% in at least one animal group, and historical control incidences for the neoplasms mentioned in this section are 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 |
|---|-----------------|-----------|-----------|
| <b>MALE (a)</b>                           |                 |           |           |
| 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     |
| <b>FEMALE (a)</b>                         |                 |           |           |
| 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**

### III. RESULTS: RATS

*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   |
|---|-----------------|-------------|-------------|
| <b>MALE</b>   |                 |             |             |
| <b>Application Site (Scapula or Back)</b>                                 |                 |             |             |
| <b>Sebaceous Gland Adenoma</b>  |                 |             |             |
| Overall Rates   | 0/50 (0%)       | 2/50 (4%)   | 1/50 (2%)   |
| <b>Basal Cell Adenoma</b>   |                 |             |             |
| 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     |
| <b>Basal Cell Carcinoma</b>   |                 |             |             |
| 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     |
| <b>Basal Cell Adenoma or Basal Cell Carcinoma</b>                         |                 |             |             |
| 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     |
| <b>Squamous Cell Papilloma (c)</b>  |                 |             |             |
| 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     |
| <b>Squamous Cell Carcinoma (d)</b>  |                 |             |             |
| 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     |
| <b>Nonapplication Site</b>  |                 |             |             |
| <b>Basal Cell Adenoma</b>   |                 |             |             |
| Overall Rates   | 1/50 (2%)       | 0/50 (0%)   | 0/50 (0%)   |
| <b>Basal Cell Carcinoma</b>   |                 |             |             |
| Overall Rates   | 1/50 (2%)       | 1/50 (2%)   | 0/50 (0%)   |
| <b>Trichoepithelioma</b>  |                 |             |             |
| Overall Rates   | 0/50 (0%)       | 0/50 (0%)   | 1/50 (2%)   |
| <b>Trichoepithelioma, Basal Cell Adenoma, or Basal Cell Carcinoma (e)</b> |                 |             |             |
| 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       |
|---|-----------------|-------------|-----------------|
| <b>FEMALE</b>   |                 |             |                 |
| <b>Application Site</b>   |                 |             |                 |
| <b>Basal Cell Carcinoma</b>   |                 |             |                 |
| 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         |
| <b>Sebaceous Gland Adenoma</b>  |                 |             |                 |
| Overall Rates   | 1/50 (2%)       | 1/50 (2%)   | 1/50 (2%)       |
| <b>Squamous Cell Carcinoma (f)</b>  |                 |             |                 |
| 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         |
| <b>Nonapplication Site</b>  |                 |             |                 |
| <b>Basal Cell Adenoma</b>   |                 |             |                 |
| Overall Rates   | 1/50 (2%)       | 1/50 (2%)   | 0/50 (0%)       |
| <b>Sebaceous Gland Adenoma, Basal Cell Adenoma, or Basal Cell Carcinoma (h)</b> |                 |             |                 |
| 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.

### III. RESULTS: MICE

#### 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<br>(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<sub>50</sub> 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<br>(mg/mouse) | Survival (a) | Mean Body Weights (grams) |             |             | Final Weight Relative<br>to Vehicle Controls<br>(percent) |
|--------------------|--------------|---------------------------|-------------|-------------|---|
|                    |              | Initial (b)               | Final       | Change (c)  |   |
| <b>MALE</b>        |              |                           |             |             |   |
| 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)   |
| <b>FEMALE</b>      |              |                           |             |             |   |
| 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) |    |     |    | Female (mg/mouse) |    |     |    |
|-----------------------------|-----------------|----|-----|----|-------------------|----|-----|----|
|                             | 0               | 5  | 10  | 21 | 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 16).

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) |            |            | Final Weight Relative to Vehicle Controls (percent) |
|-----------------|--------------|---------------------------|------------|------------|---|
|                 |              | Initial (b)               | Final      | Change (c) |   |
| <b>MALE</b>     |              |                           |            |            |   |
| 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  |
| <b>FEMALE</b>   |              |                           |            |            |   |
| 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) |     |    |     | Female (mg/rat) |     |     |     |
|-------------------------------|---------------|-----|----|-----|-----------------|-----|-----|-----|
|                               | 0             | 2.5 | 5  | 10  | 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)

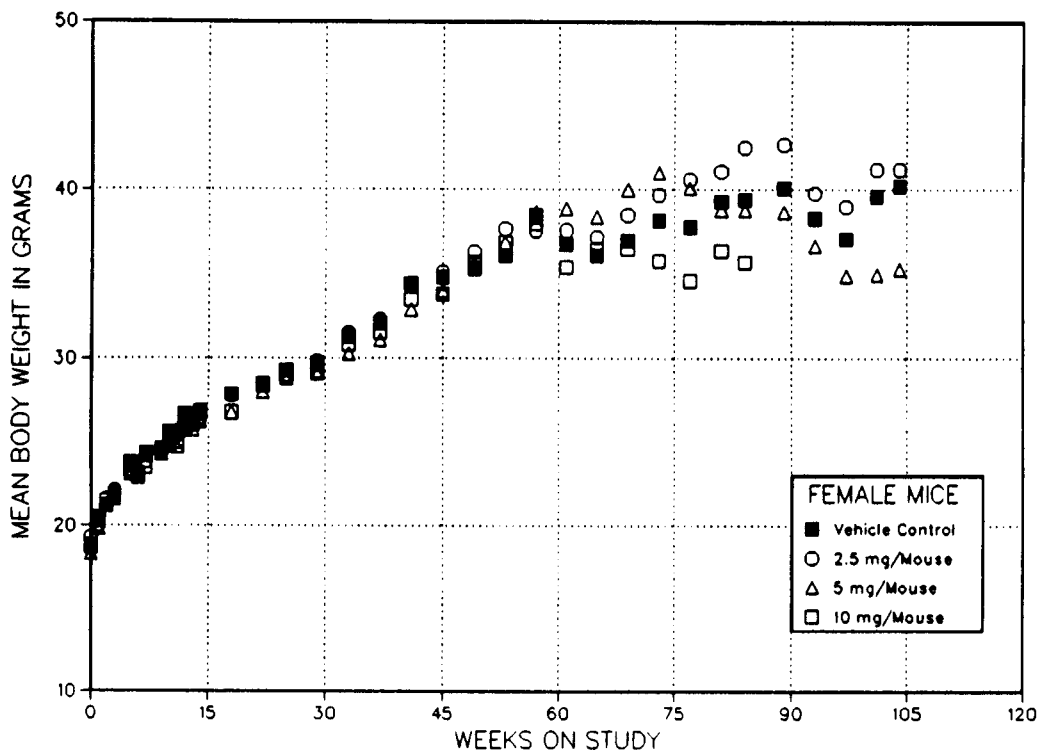
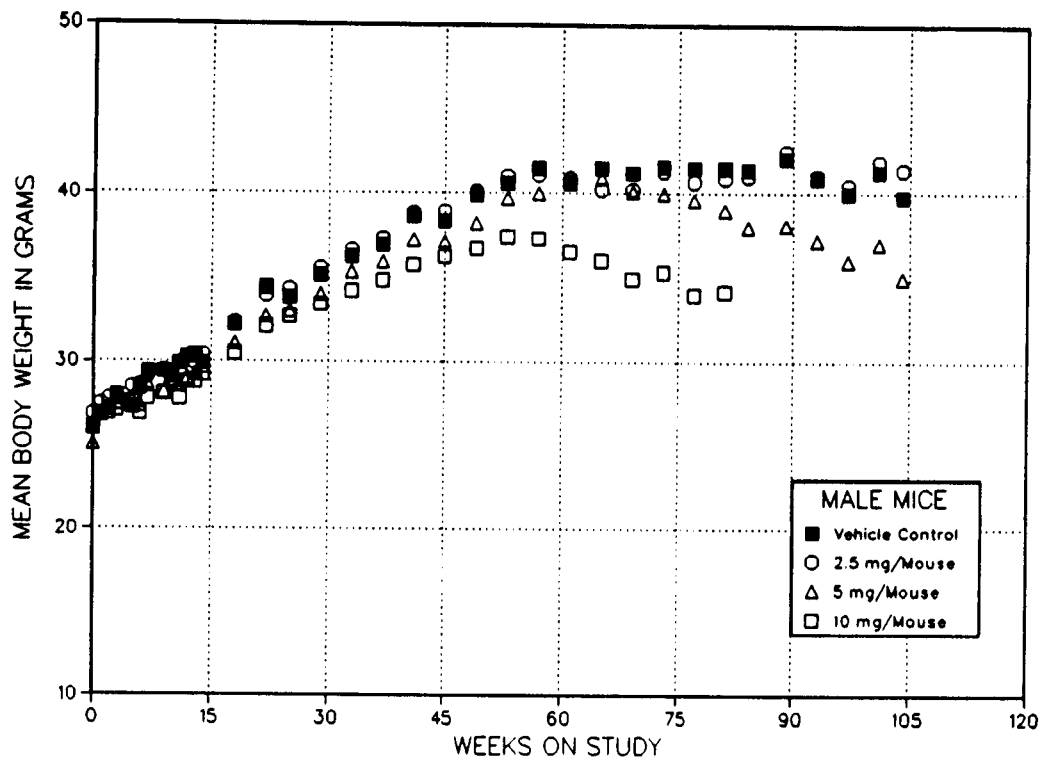
| Lesion                                  | Male (mg/mouse) |     |      |     | Female (mg/mouse) |     |     |      |
|---|-----------------|-----|------|-----|-------------------|-----|-----|------|
|   | 0               | 2.5 | 5    | 10  | 0                 | 2.5 | 5   | 10   |
| Acanthosis                              | 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 |
| <b>MALE</b>   |                 |                |                 |                                |                |                 |                                |                |                 |                                |                |
| 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              |                 |                                |                |
| <b>FEMALE</b> |                 |                |                 |                                |                |                 |                                |                |                 |                                |                |
| 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**

### III. RESULTS: MICE

#### 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

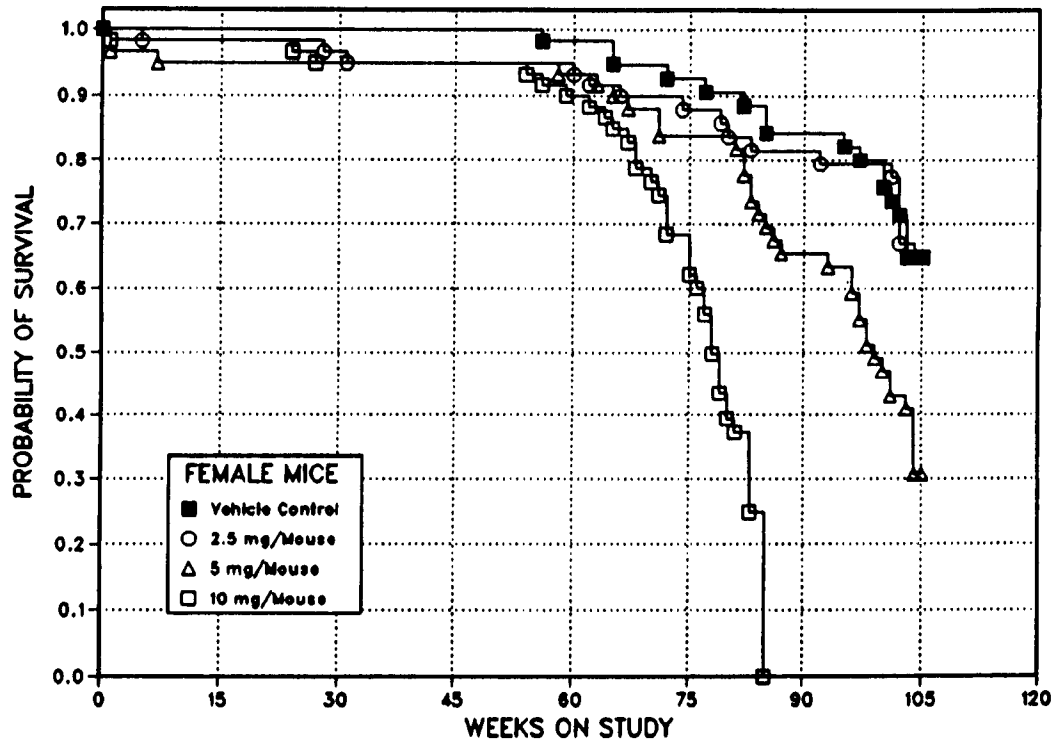
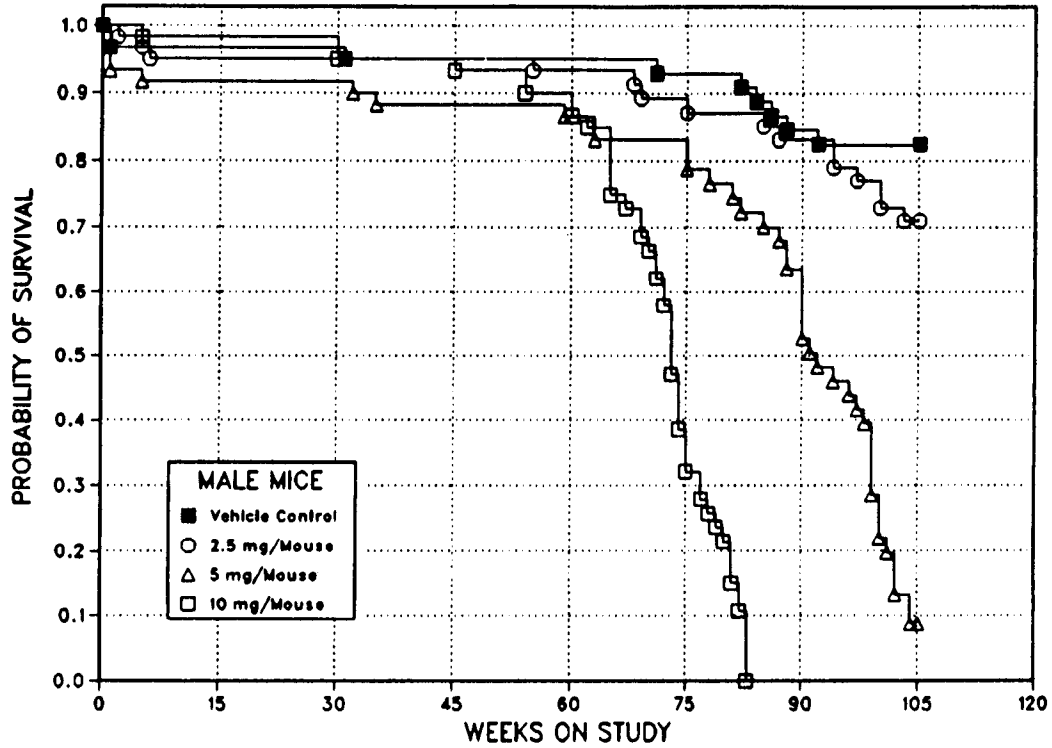
|   | Vehicle Control | 2.5 mg/Mouse | 5 mg/Mouse | 10 mg/Mouse |
|---|-----------------|--------------|------------|-------------|
| <b>MALE (a)</b>                           |                 |              |            |             |
| Animals initially in study                | 50              | 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      |
| <b>FEMALE (a)</b>                         |                 |              |            |             |
| 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**

### III. RESULTS: MICE

*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 |
|---|-----------------|--------------|--------------|-------------|
| <b>MALE</b>                               |                 |              |              |             |
| <b>Application Site (Scapula or Back)</b> |                 |              |              |             |
| <b>Squamous Cell Carcinoma (b)</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     |
| <b>FEMALE</b>                             |                 |              |              |             |
| <b>Application Site (Scapula or Back)</b> |                 |              |              |             |
| <b>Squamous Cell Carcinoma (c)</b>        |                 |              |              |             |
| 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<sub>1</sub> 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) |
|---|-----------------|--------------|-------------|-----------------|
| <b>Luteoma</b>  |                 |              |             |                 |
| Overall Rates   | 1/50 (2%)       | 0/49 (0%)    | 0/49 (0%)   | 0/50 (0%)       |
| <b>Benign Mixed Tumor</b>   |                 |              |             |                 |
| 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         |
| <b>Granulosa Cell Tumor</b>   |                 |              |             |                 |
| 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         |
| <b>Malignant Granulosa Cell Tumor</b>   |                 |              |             |                 |
| Overall Rates   | 0/50 (0%)       | 0/49 (0%)    | 2/49 (4%)   | 2/50 (4%)       |
| <b>Granulosa Cell Tumor or Malignant Granulosa Cell Tumor</b>                                   |                 |              |             |                 |
| 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         |
| <b>Luteoma, Granulosa Cell Tumor, or Benign Mixed Tumor</b>                                     |                 |              |             |                 |
| 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         |
| <b>Luteoma, Granulosa Cell Tumor, Benign Mixed Tumor, or Malignant Granulosa Cell Tumor (d)</b> |                 |              |             |                 |
| 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%)

### III. RESULTS: MICE

**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) |
|--|-----------------|--------------|-------------|-----------------|
| <b>Alveolar Epithelial Hyperplasia</b>               |                 |              |             |                 |
| Overall Rates  | 1/50 (2%)       | 1/50 (2%)    | 0/50 (0%)   | 1/50 (2%)       |
| <b>Alveolar/Bronchiolar Adenoma</b>                  |                 |              |             |                 |
| Overall Rates  | 3/50 (6%)       | 5/50 (10%)   | 8/50 (16%)  | 6/50 (12%)      |
| <b>Alveolar/Bronchiolar Carcinoma</b>                |                 |              |             |                 |
| Overall Rates  | 1/50 (2%)       | 4/50 (8%)    | 3/50 (6%)   | 1/50 (2%)       |
| <b>Alveolar/Bronchiolar Adenoma or Carcinoma (c)</b> |                 |              |             |                 |
| 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  $\pm$  SD): 107/1,676 (6%  $\pm$  4%)

### III. RESULTS: GENETIC TOXICOLOGY

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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

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### 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<sub>1</sub> 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<sub>50</sub> studies in rats, in single-dose dermal LD<sub>50</sub> 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

## IV. DISCUSSION AND CONCLUSIONS

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

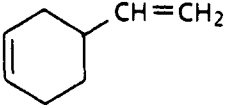
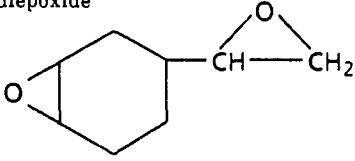
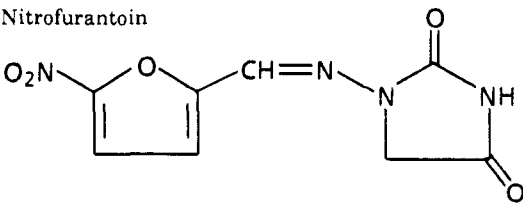
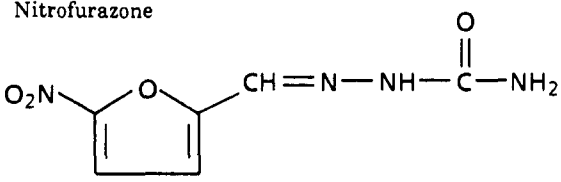
were performed by the NTP in rats and mice of each sex by the gavage route of administration (NTP, 1986a). The chemical was administered at doses of 200 or 400 mg/kg for 103 weeks. There was clear evidence of carcinogenicity for female mice, as shown by markedly increased incidences of benign and malignant 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<sub>1</sub> 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


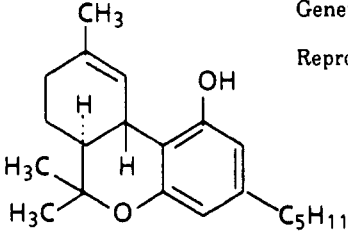
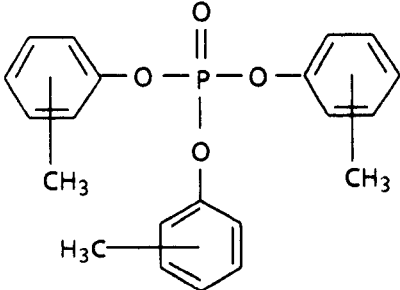
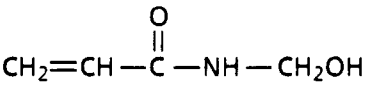
Chemical carcinogens have been divided into three classes: genotoxic carcinogens (e.g., alkylating agents, polycyclic aromatic hydrocarbons, nitrosamines), nongenotoxic carcinogens (e.g., promoters, cytotoxic agents, immunosuppressor agents, solid state agents), and unclassified carcinogens that do not 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  |   |
|---|---|---|
| <p>1,3-Butadiene</p> $\text{CH}_2 = \text{CH} - \text{CH} = \text{CH}_2$  | <p>Sites of carcinogenicity<br/>NTP TR 288 (NTP, 1984)</p> <p>Pharmacokinetics<br/>Genetic toxicology</p> <p>Reproductive toxicology</p>            | <p>Male mouse--heart, lymphomas, lung, stomach;<br/>female mouse--heart, lymphomas, lung,<br/>stomach, mammary gland, ovary</p> <p>Ongoing<br/>SA: selected<br/>ML: -<br/>DL: -<br/>CY: on test</p> <p>Developmental toxicity in mice</p> |
| <p>4-Vinylcyclohexene</p>                | <p>Sites of carcinogenicity<br/>NTP TR 303 (NTP, 1986a)</p> <p>Chemical disposition<br/>Genetic toxicology</p> <p>Reproductive toxicology</p>       | <p>Male rat, female rat, male mouse--inadequate<br/>studies; female mouse--ovary</p> <p>Ongoing<br/>SA: -<br/>ML: +<br/>CY: +/+</p> <p>Continuous breeding: on test</p>   |
| <p>4-Vinyl-1-cyclohexene diepoxide</p>  | <p>Sites of carcinogenicity<br/>NTP TR 362</p> <p>Chemical disposition<br/>Immunotoxicity<br/>Genetic toxicology</p> <p>Reproductive toxicology</p> | <p>Male rat--skin; female rat--skin; male mouse--<br/>skin; female mouse--skin, ovary</p> <p>Ongoing<br/>+<br/>SA: +<br/>ML: +<br/>CY: +/+</p> <p>Not selected</p>  |
| <p>Nitrofurantoin</p>                  | <p>Sites of carcinogenicity<br/>NTP TR 341 (NTP, 1989b)</p> <p>Genetic toxicology</p> <p>Reproductive toxicology</p>                                | <p>Male rat--kidney; female rat--none;<br/>male mouse--none; female mouse--<br/>ovary</p> <p>SA: +<br/>ML: +<br/>DL: -<br/>CY: +/+</p> <p>Continuous breeding: on test</p>  |
| <p>Nitrofurazone</p>                   | <p>Sites of carcinogenicity<br/>NTP TR 337 (NTP, 1988)</p> <p>Genetic toxicology</p> <p>Reproductive toxicology</p>                                 | <p>Male rat--equivocal; female rat--<br/>mammary gland; male mouse--none;<br/>female mouse--ovary</p> <p>SA: +<br/>ML: +<br/>CY: +/+</p> <p>Developmental toxicity with<br/>maternal toxicity in mice and rabbits</p>                     |



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

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

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

## IV. DISCUSSION AND CONCLUSIONS

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on the following information on genetic and non-genetic 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 inter-strand 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*<sup>Ha</sup> 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*<sup>Ha</sup> 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.

## IV. DISCUSSION AND CONCLUSIONS

### 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.

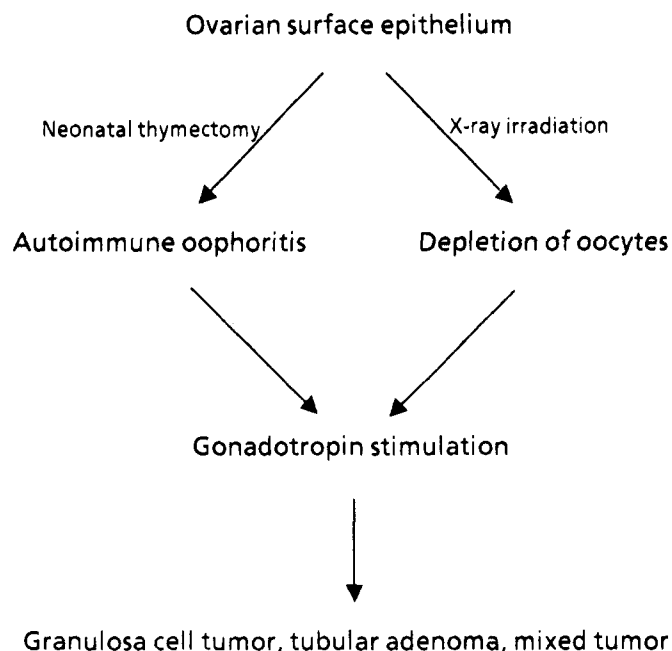
Nishizuka et al. (1976) proposed a scheme of ovarian neoplasm formation (Figure 5) resulting from oocyte depletion and subsequent possible progression stimulated by gonadotropins. Whether the ovarian atrophy and loss of oocytes observed in 4-vinyl-1-cyclohexene diepoxide-exposed mice was due to an autoimmune 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<sub>1</sub> 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

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**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        |
| <b>ALIMENTARY SYSTEM</b>                  |                 |           |           |
| 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 |
|--|-----------------|-----------|-----------|
| <b>CARDIOVASCULAR SYSTEM</b>                       |                 |           |           |
| Heart  | (50)            | (50)      | (50)      |
| Carcinoma, metastatic, skin                        |                 |           | 1 (2%)    |
| Leukemia mononuclear                               | 10 (20%)        | 5 (10%)   | 13 (26%)  |
| Squamous cell carcinoma, metastatic, skin          |                 | 1 (2%)    |           |
| <b>ENDOCRINE SYSTEM</b>                            |                 |           |           |
| 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%)    |           |
| <b>GENERAL BODY SYSTEM</b>                         |                 |           |           |
| None   |                 |           |           |
| <b>GENITAL SYSTEM</b>                              |                 |           |           |
| 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 |
|--|-----------------|-----------|-----------|
| <b>HEMATOPOIETIC SYSTEM</b>                            |                 |           |           |
| 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%)          |           |           |
| <b>INTEGUMENTARY SYSTEM</b>                            |                 |           |           |
| 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%)    |           |
| 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 |
|---|-----------------|-----------|-----------|
| <b>MUSCULOSKELETAL SYSTEM</b>                                     |                 |           |           |
| Skeletal muscle   | *(50)           | *(50)     | *(50)     |
| Diaphragm, carcinoma, metastatic, skin                            |                 |           | 1 (2%)    |
| Diaphragm, intercostal, squamous cell carcinoma, metastatic, skin |                 | 1 (2%)    |           |
| <b>NERVOUS SYSTEM</b>   |                 |           |           |
| 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%)    |           |
| <b>RESPIRATORY SYSTEM</b>   |                 |           |           |
| 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%)          |           |           |
| <b>SPECIAL SENSES SYSTEM</b>                                      |                 |           |           |
| Eye   | *(50)           | *(50)     | *(50)     |
| Leukemia mononuclear  | 1 (2%)          |           | 1 (2%)    |
| Zymbal gland  | *(50)           | *(50)     | *(50)     |
| Adenoma   |                 |           | 1 (2%)    |
| Carcinoma   |                 |           | 1 (2%)    |
| <b>URINARY SYSTEM</b>   |                 |           |           |
| 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%)    |
| <b>SYSTEMIC LESIONS</b>   |                 |           |           |
| 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 |
|--|-----------------|-----------|-----------|
| <b>ANIMAL DISPOSITION SUMMARY</b>                                  |                 |           |           |
| 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         |
| <b>TUMOR SUMMARY</b>   |                 |           |           |
| 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--<br>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                        | 0       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|                                       | 5 6 6 6 7 7 7 7 7 7 7 7 8 8 8 8 8 8 8 8 8 8       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| CARCASS ID                            | 4 2 3 1 0 0 1 2 3 3 4 4 2 0 4 3 4 5 4 0 2 2 2 1 0 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|                                       | 0 9 7 1 8 9 5 3 2 6 3 7 4 2 1 4 6 0 5 5 1 0 7 3 3 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|                                       | 1   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>ALIMENTARY SYSTEM</b>              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 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 |   |   |   |
| Mesothelioma malignant                |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Pharynx                               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Palate, papilloma squamous            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Salivary glands                       | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear                  | X   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Stomach                               | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach, forestomach                  | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Mesothelioma malignant                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Stomach, glandular                    | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leiomyosarcoma                        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Mesothelioma malignant                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Tooth                                 |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>CARDIOVASCULAR SYSTEM</b>          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Blood vessel                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Heart                                 | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear                  | X   |   |   |   |   |   |   |   |   | X | X |   | X |   |   |   | X |   |   | X |   |   |   |   |
| <b>ENDOCRINE SYSTEM</b>               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 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               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Bilateral, pheochromocytoma benign    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Islets, pancreatic                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Adenoma                               | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Pituitary gland                       | +   | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear                  | X   |   |   |   |   |   |   |   |   | X | X |   |   |   |   |   |   |   | X |   |   |   |   |   |
| Pars distalis, adenoma                |   |   | 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                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Follicular cell, adenoma              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Follicular cell, carcinoma            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>GENERAL BODY SYSTEM</b>            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| None                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>GENITAL SYSTEM</b>                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Ductus deferens                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Epididymis                            | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Mesothelioma malignant                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Preputial gland                       | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Prostate                              | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Testes                                | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear                  | X   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   | X |   |   |   |   |   | X |   |
| Mesothelioma malignant                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Bilateral, interstitial cell, adenoma | X   |   |   |   |   |   |   |   |   |   | X | X | X |   | X | X | X |   | X | X |   | X | X | X |
| Interstitial cell, adenoma            |   |   | X |   | X |   | 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           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|--|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
|  | 5 6 6 6 7 7 7 7 7 7 7 7 8 8 8 8 8 8 8 8 8 8           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CARCASS ID                             | 4 2 3 1 0 0 1 2 3 3 4 4 2 0 4 3 4 5 4 0 2 2 2 1 0     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 1       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>HEMATOPOIETIC SYSTEM</b>            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood                                  | + X +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                   | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone marrow                            | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Femoral, leukemia mononuclear          | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Sternal, leukemia mononuclear          | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node                             | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Inguinal, leukemia mononuclear         | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mediastinal, leukemia mononuclear      | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pancreatic, leukemia mononuclear       | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mandibular                 | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                   | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mesenteric                 | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                   | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Spleen                                 | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                   | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mesothelioma malignant                 | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thymus                                 | + + M + + + + + + + + I + + + + A + + + + + + + + + + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                   | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thymoma benign                         | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>INTEGUMENTARY SYSTEM</b>            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mammary gland                          | + + M + + + + + + + + + + + + M + + + + + + + + + +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenocarcinoma                         | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fibroadenoma                           | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Skin                                   | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Basal cell adenoma                     | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Basal cell carcinoma                   | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Subcutaneous tissue, fibroma           | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Subcutaneous tissue, sarcoma           | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>MUSCULOSKELETAL SYSTEM</b>          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone                                   | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>NERVOUS SYSTEM</b>                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Brain                                  | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Carcinoma, metastatic, pituitary gland | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                   | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>RESPIRATORY SYSTEM</b>              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lung                                   | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Chordoma                               | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                   | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Nose                                   | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                   | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Trachea                                | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                   | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>SPECIAL SENSES SYSTEM</b>           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Eye                                    | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                   | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>URINARY SYSTEM</b>                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kidney                                 | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                   | X           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mesothelioma malignant                 | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Urethra                                | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Urinary bladder                        | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                   | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mesothelioma malignant                 | +           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |



**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                                     | 0         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|--|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
|  | 1 5 5 5 5 6 6 7 7 7 7 8 8 8 8 8 8 8 9 9         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CARCASS ID   | 2 4 6 6 8 1 7 0 7 7 8 2 2 3 6 7 8 8 0 2         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 2 7 8 7 1 5 9 0 5 3 0 8 9 4 4 4 6 8 0 9         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 1         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>ALIMENTARY SYSTEM</b>                           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Esophagus  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intestine large                                    | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intestine large, cecum                             | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intestine large, colon                             | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Carcinoma  | M X + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intestine large, rectum                            | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Carcinoma  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intestine small                                    | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intestine small, duodenum                          | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intestine small, ileum                             | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                               | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intestine small, jejunum                           | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Liver  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Carcinoma, metastatic, islets, pancreatic          | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                               | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin          | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mesentery  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Carcinoma, metastatic, intestine large             | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mesothelioma malignant                             | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin          | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pancreas   | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Carcinoma, metastatic, intestine large             | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                               | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin          | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pharynx  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Salivary glands                                    | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                               | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin          | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stomach  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stomach, forestomach                               | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                               | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stomach, glandular                                 | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin          | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Tongue   | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Papilloma squamous                                 | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Tooth  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>CARDIOVASCULAR SYSTEM</b>                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood vessel                                       | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Heart  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                               | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin          | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>ENDOCRINE SYSTEM</b>                            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adrenal gland                                      | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adrenal gland, cortex                              | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                               | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medulla, squamous cell carcinoma, metastatic, skin | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adrenal gland, medulla                             | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                               | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pheochromocytoma benign                            | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bilateral, pheochromocytoma benign                 | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Islets, pancreatic                                 | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenoma  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Carcinoma  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Parathyroid gland                                  | M M + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenoma  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pituitary gland                                    | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                               | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pars distalis, adenoma                             | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pars distalis, carcinoma                           | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thyroid gland                                      | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| C cell, adenoma                                    | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| C cell, adenoma, multiple                          | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Follicular cell, adenoma                           | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Follicular cell, carcinoma                         | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>GENERAL BODY SYSTEM</b>                         |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| None   | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>URINARY SYSTEM</b>                              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kidney   | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                               | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin          | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Urinary bladder                                    | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                               | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mesothelioma malignant                             | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |









**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 | 5 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| CARCASS ID                            | 5 0 7 3 9 2 8 9 9 9 0 2 2 3 5 5 5 5 7 7 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|                                       | 6                                       | 5 | 5 | 4 | 8 | 5 | 7 | 8 | 6 | 7 | 7 | 5 | 8 | 4 | 5 | 6 | 8 | 4 | 6 | 4 |
|                                       | 6                                       | 7 | 1 | 5 | 8 | 3 | 2 | 0 | 7 | 6 | 0 | 5 | 7 | 9 | 2 | 3 | 6 | 8 | 8 |   |
|                                       | 1                                       | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |
| <b>ALIMENTARY SYSTEM</b>              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 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 |   |
| Mesentery                             |   |   |   |   |   |   |   |   | + | + | X |   |   |   |   | + |   | X |   |   |
| Carcinoma, metastatic, skin           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 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                                |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |
| <b>CARDIOVASCULAR SYSTEM</b>          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Blood vessel                          | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| Heart                                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Carcinoma, metastatic, skin           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X | X | X |   |
| Leukemia mononuclear                  |   |   |   |   |   |   |   | X |   |   | X |   |   |   |   |   |   |   | X |   |
| <b>ENDOCRINE SYSTEM</b>               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Adrenal gland                         | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| Adrenal gland, cortex                 | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| Leukemia mononuclear                  |   |   |   |   |   |   |   | X |   |   | 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 | + | + | + | + | + | + | + | + | + | + |   |
| Adenoma                               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | M |   |
| 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 |   |
| Pars distalis, adenoma, multiple      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Thyroid gland                         | +                                       | A | + | A | + | + | + | A | + | A | + | + | + | A | + | + | + | + | + |   |
| Leukemia mononuclear                  |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   | X |   |   |   |   |
| C cell, adenoma                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |
| Follicular cell, adenoma              |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>GENERAL BODY SYSTEM</b>            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| None                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>GENITAL SYSTEM</b>                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Ductus deferens                       | +                                       | + | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + |   |
| Epididymis                            | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| 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 |   |

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

| WEEKS ON STUDY                        | 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1               |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | TOTAL TISSUES TUMORS |
|---------------------------------------|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|----------------------|
|                                       | 8 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 9 0 0 0 0 0 0 0 0               |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| CARCASS ID                            | 2               |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
|                                       | 4 4 6 8 6 5 6 7 8 5 6 6 4 9 7 8 4 5 6 7 7 7 7 8 8 8 8             |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
|                                       | 7 3 5 2 0 4 4 8 1 8 2 9 6 0 7 3 4 6 1 4 1 3 4 5 9                 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
|                                       | 1               |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| <b>ALIMENTARY SYSTEM</b>              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Esophagus                             | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 49                   |
| Intestine large                       | + A + + + + A +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 44                   |
| Intestine large, cecum                | + A A + + + + A +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 40                   |
| Mesothelioma malignant                | + A A + + + + A + + + + + + + + + + + M + + + + + + + + + + +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Intestine large, colon                | + A + + + + A +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 40                   |
| Mesothelioma malignant                | + A + + + + A +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Intestine large, rectum               | + A + + + + A +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 44                   |
| Mesothelioma malignant                | + A + + + + A +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 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                | + A A + + + + A +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Intestine small, jejunum              | + A A + + + + A +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 42                   |
| Leukemia mononuclear                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Mesothelioma malignant                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Liver                                 | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Leukemia mononuclear                  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 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                    |
| <b>CARDIOVASCULAR SYSTEM</b>          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Blood vessel                          | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2                    |
| Heart                                 | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Carcinoma, metastatic, skin           | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Leukemia mononuclear                  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 13                   |
| <b>ENDOCRINE SYSTEM</b>               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Adrenal gland                         | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Adrenal gland, cortex                 | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Leukemia mononuclear                  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 11                   |
| Adrenal gland, medulla                | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Leukemia mononuclear                  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 9                    |
| Pheochromocytoma malignant            | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2                    |
| Islets, pancreatic                    | + A +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 46                   |
| Adenoma                               | + A +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 3                    |
| Parathyroid gland                     | + M + M + + + + + + + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 45                   |
| Adenoma                               | + M + M + + + + + + + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Pituitary gland                       | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 48                   |
| Leukemia mononuclear                  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 10                   |
| Fars distalis, adenoma                | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 26                   |
| Fars distalis, adenoma, multiple      | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Thyroid gland                         | + + A + + + + A +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 43                   |
| Leukemia mononuclear                  | + + A + + + + A +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 3                    |
| C cell, adenoma                       | + + A + + + + A +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2                    |
| Follicular cell, adenoma              | + + A + + + + A +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 3                    |
| <b>GENERAL BODY SYSTEM</b>            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| None                                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| <b>GENITAL SYSTEM</b>                 |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Ductus deferens                       | + M + + + + + + + +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Epididymis                            | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 48                   |
| Penis                                 | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Preputial gland                       | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Adenoma                               | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Prostate                              | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Leukemia mononuclear                  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2                    |
| Testes                                | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Leukemia mononuclear                  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 3                    |
| Mesothelioma malignant                | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Bilateral, interstitial cell, adenoma | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 25                   |
| Interstitial cell, adenoma            | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 14                   |

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

| WEEKS ON STUDY  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--|
| CARCASS ID  | 3 | 5 | 5 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |  |
|   | 5 | 0 | 7 | 3 | 9 | 2 | 8 | 9 | 9 | 9 | 0 | 2 | 2 | 3 | 5 | 5 | 5 | 5 | 5 | 5 | 7 | 7 | 8 | 8 | 8 | 8 | 8 | 8 | 8 |  |
| <b>HEMATOPOIETIC SYSTEM</b>                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Blood   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Bone marrow   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Femoral, leukemia mononuclear                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Lymph node  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Mediastinal, carcinoma, metastatic, skin              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Mediastinal, leukemia mononuclear                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Lymph node, mandibular                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Lymph node, mesenteric                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Spleen  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Mesothelioma malignant                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Thymus  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>INTEGUMENTARY SYSTEM</b>                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Mammary gland   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Fibroadenoma  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Skin  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Keratoacanthoma                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Trichoepithelioma                                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Back, squamous cell carcinoma                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Scapula, basal cell adenoma                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Scapula, basal cell carcinoma                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Scapula, basal cell carcinoma, multiple               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Scapula, basal cell carcinoma, metastatic, skin       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Scapula, carcinoma                                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Scapula, keratoacanthoma                              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Scapula, papilloma squamous                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Scapula, squamous cell carcinoma                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Scapula, squamous cell carcinoma, multiple            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Sebacous gland, scapula, adenoma                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Subcutaneous tissue, scapula, fibrosarcoma            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>MUSCULOSKELETAL SYSTEM</b>                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Bone  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Skeletal muscle                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Diaphragm, carcinoma, metastatic, skin                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>NERVOUS SYSTEM</b>                                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Brain   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>RESPIRATORY SYSTEM</b>                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Lung  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Carcinoma, metastatic                                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Carcinoma, metastatic, skin                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Pheochromocytoma malignant, metastatic, adrenal gland |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Squamous cell carcinoma, metastatic, skin             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Nose  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Trachea   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>SPECIAL SENSES SYSTEM</b>                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Eye   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Harderian gland                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Zymbal gland  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Adenoma   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Carcinoma   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>URINARY SYSTEM</b>                                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Kidney  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Carcinoma, metastatic, skin                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Mesothelioma malignant                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Renal tubule, adenoma                                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Urinary bladder                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Mesothelioma malignant                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |

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

| WEEKS ON STUDY  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | TOTAL TISSUES TUMORS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----------------------|
| CARCASS ID  | 8 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |                      |
|   | 9 | 0 | 0 | 1 | 2 | 2 | 5 | 5 | 5 | 6 | 6 | 6 | 8 | 8 | 8 | 8 | 8 | 9 | 9 | 9 | 3 | 4 | 6 | 7 | 7 | 7 |                      |
| <b>HEMATOPOIETIC SYSTEM</b>                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| Blood   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
| Bone marrow   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 49                   |
| Femoral, leukemia mononuclear                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 11                   |
| Lymph node  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 50                   |
| Mediastinal, carcinoma, metastatic, skin              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Mediastinal, leukemia mononuclear                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 4                    |
| Lymph node, mandibular                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 50                   |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 10                   |
| Lymph node, mesenteric                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 3                    |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
| Spleen  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 49                   |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 15                   |
| Mesothelioma malignant                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Thymus  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 42                   |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 3                    |
| <b>INTEGUMENTARY SYSTEM</b>                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| Mammary gland   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 42                   |
| Fibroadenoma  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Skin  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 50                   |
| Keratoacanthoma                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Trichoepithelioma                                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Back, squamous cell carcinoma                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Scapula, basal cell adenoma                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 4                    |
| Scapula, basal cell carcinoma                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
| Scapula, basal cell carcinoma, multiple               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Scapula, basal cell carcinoma, metastatic, skin       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Scapula, carcinoma                                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Scapula, keratoacanthoma                              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 6                    |
| Scapula, papilloma squamous                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 12                   |
| Scapula, squamous cell carcinoma                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 12                   |
| Scapula, squamous cell carcinoma, multiple            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 24                   |
| Sebaceous gland, scapula, adenoma                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Subcutaneous tissue, scapula, fibrosarcoma            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| <b>MUSCULOSKELETAL SYSTEM</b>                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| Bone  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 50                   |
| Skeletal muscle                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Diaphragm, carcinoma, metastatic, skin                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| <b>NERVOUS SYSTEM</b>                                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| Brain   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 49                   |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 6                    |
| <b>RESPIRATORY SYSTEM</b>                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| Lung  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 50                   |
| Carcinoma, metastatic                                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Carcinoma, metastatic, skin                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 15                   |
| Pheochromocytoma malignant, metastatic, adrenal gland |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Squamous cell carcinoma, metastatic, skin             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Nose  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 49                   |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
| Trachea   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 48                   |
| <b>SPECIAL SENSES SYSTEM</b>                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| Eye   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 6                    |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Harderian gland                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Zymbal gland  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
| Adenoma   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Carcinoma   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| <b>URINARY SYSTEM</b>                                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| Kidney  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 49                   |
| Carcinoma, metastatic, skin                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 13                   |
| Mesothelioma malignant                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Renal tubule, adenoma                                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Urinary bladder                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 49                   |
| Leukemia mononuclear                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 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 |
|--|-----------------|-------------|-----------|
| <b>Adrenal Medulla: Pheochromocytoma</b>                               |                 |             |           |
| 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  |
| <b>Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma</b> |                 |             |           |
| 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  |
| <b>Preputial Gland: Adenoma</b>  |                 |             |           |
| 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   |
| <b>Preputial Gland: Adenoma or Squamous Papilloma</b>                  |                 |             |           |
| 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   |
| <b>Pancreatic Islets: Adenoma</b>                                      |                 |             |           |
| 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   |
| <b>Pancreatic Islets: Adenoma or Carcinoma</b>                         |                 |             |           |
| 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   |
|--|-----------------|-------------|-------------|
| <b>Mammary Gland: Fibroadenoma or Adenocarcinoma</b>                       |                 |             |             |
| 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  |
| <b>Pituitary Gland/Pars Distalis: Adenoma</b>                              |                 |             |             |
| 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   |
| <b>Pituitary Gland/Pars Distalis: Adenoma or Carcinoma</b>                 |                 |             |             |
| 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   |
| <b>Skin (Application Site): Basal Cell Adenoma</b>                         |                 |             |             |
| 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   |
| <b>Skin (Application Site): Basal Cell Carcinoma</b>                       |                 |             |             |
| 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   |
| <b>Skin (Application Site): Basal Cell Adenoma or Basal Cell Carcinoma</b> |                 |             |             |
| 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  |
|--|-----------------|-----------|------------|
| <b>Skin (Application Site): Basal Cell Adenoma or Sebaceous Gland Adenoma</b>                        |                 |           |            |
| 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    |
| <b>Skin (Application Site): Basal Cell Adenoma, Sebaceous Gland Adenoma, or Basal Cell Carcinoma</b> |                 |           |            |
| 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    |
| <b>Skin (All Sites): Basal Cell Adenoma</b>  |                 |           |            |
| 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    |
| <b>Skin (All Sites): Basal Cell Carcinoma</b>  |                 |           |            |
| 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    |
| <b>Skin (All Sites): Basal Cell Adenoma or Carcinoma</b>   |                 |           |            |
| 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    |
| <b>Skin (All Sites): Trichoepithelioma, Basal Cell Adenoma, or Sebaceous Gland Adenoma</b>           |                 |           |            |
| 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   |
|--|-----------------|-------------|-------------|
| <b>Skin (All Sites): Trichoepithelioma, Basal Cell Adenoma, Sebaceous Gland Adenoma, or Basal Cell Carcinoma</b> |                 |             |             |
| 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     |
| <b>Skin (All Sites): Keratoacanthoma</b>   |                 |             |             |
| 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     |
| <b>Skin (Application Site): Squamous Cell Papilloma (g,h)</b>  |                 |             |             |
| 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     |
| <b>Skin (Application Site): Squamous Cell Carcinoma (h)</b>  |                 |             |             |
| 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     |
| <b>Testis: Interstitial Cell Adenoma</b>   |                 |             |             |
| 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    |
| <b>Thyroid Gland: C-Cell Adenoma</b>   |                 |             |             |
| 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   |
|--|-----------------|-------------|-------------|
| <b>Thyroid Gland: C-Cell Adenoma or Carcinoma</b>          |                 |             |             |
| 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    |
| <b>Thyroid Gland: Follicular Cell Adenoma</b>              |                 |             |             |
| 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     |
| <b>Thyroid Gland: Follicular Cell Adenoma or Carcinoma</b> |                 |             |             |
| 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     |
| <b>Hematopoietic System: Mononuclear Leukemia</b>          |                 |             |             |
| 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    |
| <b>All Sites: Benign Tumors</b>                            |                 |             |             |
| 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    |
| <b>All Sites: Malignant Tumors</b>                         |                 |             |             |
| 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   |
|---------------------------------|-----------------|-------------|-------------|
| <b>All Sites: All Tumors</b>    |                 |             |             |
| 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)**

|   | <u>Incidence in Controls</u> |                     |                            |
|---|------------------------------|---------------------|----------------------------|
|   | <u>Benign</u>                | <u>Malignant</u>    | <u>Benign or Malignant</u> |
| No 2-year dermal studies using acetone as a vehicle are included in the historical data base. |                              |                     |                            |
| <b>Overall Historical Incidence for Untreated Controls</b>                                    |                              |                     |                            |
| 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)**

|   | <u>Incidence in Controls</u> |                  |                               |
|---|------------------------------|------------------|-------------------------------|
|   | <u>Papilloma</u>             | <u>Carcinoma</u> | <u>Papilloma or Carcinoma</u> |
| No 2-year dermal studies using acetone as a vehicle are included in the historical data base. |                              |                  |                               |
| <b>Overall Historical Incidence for Untreated Controls</b>                                    |                              |                  |                               |
| 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        |
| <b>ALIMENTARY SYSTEM</b>             |                 |           |           |
| 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 |
|--|-----------------|-----------|-----------|
| <b>ALIMENTARY SYSTEM (Continued)</b>         |                 |           |           |
| Tooth  | (2)             | (5)       |           |
| Dysplasia                                    |                 | 1 (20%)   |           |
| Peridontal tissue, inflammation, suppurative | 2 (100%)        | 4 (80%)   |           |
| <b>CARDIOVASCULAR SYSTEM</b>                 |                 |           |           |
| 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%)    |
| <b>ENDOCRINE SYSTEM</b>                      |                 |           |           |
| 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%)    |
| <b>GENERAL BODY SYSTEM</b>                   |                 |           |           |
| None   |                 |           |           |
| <b>GENITAL SYSTEM</b>                        |                 |           |           |
| 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 |
|---|-----------------|-----------|-----------|
| <b>GENITAL SYSTEM (Continued)</b>         |                 |           |           |
| 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%)    |
| <b>HEMATOPOIETIC SYSTEM</b>               |                 |           |           |
| 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%)    |           |
| <b>INTEGUMENTARY SYSTEM</b>               |                 |           |           |
| 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%)  |
| <b>MUSCULOSKELETAL SYSTEM</b>             |                 |           |           |
| Bone                                      | (50)            | (50)      | (50)      |
| Cranium, fibrous osteodystrophy           | 13 (26%)        | 12 (24%)  | 4 (8%)    |
| Femur, fibrous osteodystrophy             | 13 (26%)        | 12 (24%)  | 4 (8%)    |
| <b>NERVOUS SYSTEM</b>                     |                 |           |           |
| 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 |
|--|-----------------|-----------|-----------|
| <b>RESPIRATORY SYSTEM</b>                    |                 |           |           |
| 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%)    |           |
| <b>SPECIAL SENSES SYSTEM</b>                 |                 |           |           |
| Eye  | (7)             | (3)       | (6)       |
| Degeneration                                 | 3 (43%)         | 2 (67%)   | 6 (100%)  |
| <b>URINARY SYSTEM</b>                        |                 |           |           |
| 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

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**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        |
| <b>ALIMENTARY SYSTEM</b>             |                 |           |           |
| 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%)    |
| <b>CARDIOVASCULAR SYSTEM</b>         |                 |           |           |
| Heart                                | (50)            | (50)      | (50)      |
| Leukemia mononuclear                 | 7 (14%)         | 1 (2%)    | 7 (14%)   |
| <b>ENDOCRINE SYSTEM</b>              |                 |           |           |
| 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%)    |
| <b>GENERAL BODY SYSTEM</b>           |                 |           |           |
| 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 |
|---|-----------------|-----------|-----------|
| <b>GENITAL SYSTEM</b>                               |                 |           |           |
| 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%)    |           |
| <b>HEMATOPOIETIC SYSTEM</b>                         |                 |           |           |
| 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%)          |           |           |
| <b>INTEGUMENTARY SYSTEM</b>                         |                 |           |           |
| 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 |
|--|-----------------|-----------|-----------|
| <b>MUSCULOSKELETAL SYSTEM</b>              |                 |           |           |
| Skeletal muscle                            | *(50)           | *(50)     | *(50)     |
| Abdominal, rhabdomyosarcoma                | 1 (2%)          |           |           |
| <b>NERVOUS SYSTEM</b>                      |                 |           |           |
| Brain                                      | (50)            | (50)      | (50)      |
| Carcinoma, metastatic, pituitary gland     | 3 (6%)          | 3 (6%)    | 3 (6%)    |
| Leukemia mononuclear                       | 2 (4%)          |           | 1 (2%)    |
| <b>RESPIRATORY SYSTEM</b>                  |                 |           |           |
| 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%)          |           |           |
| <b>SPECIAL SENSES SYSTEM</b>               |                 |           |           |
| None                                       |                 |           |           |
| <b>URINARY SYSTEM</b>                      |                 |           |           |
| 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%)    |           |
| <b>SYSTEMIC LESIONS</b>                    |                 |           |           |
| Multiple organs                            | *(50)           | *(50)     | *(50)     |
| Leukemia mononuclear                       | 12 (24%)        | 17 (34%)  | 13 (26%)  |
| Lymphoma malignant histiocytic             | 1 (2%)          |           |           |
| Hemangiosarcoma                            |                 |           | 1 (2%)    |
| <b>ANIMAL DISPOSITION SUMMARY</b>          |                 |           |           |
| 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        |
| <b>TUMOR SUMMARY</b>                       |                 |           |           |
| 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: VEHICLE CONTROL**  
(Continued)

| WEEKS ON STUDY                          | 0 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|---|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
|   | 3 5 6 8 8 8 8 8 9 9 9 9 9 0 0 0 0 0 0 0 0   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CARCASS ID                              | 1 0 0 0 1 1 0 1 0 1 1 0 0 0 1 0 0 0 0 0 0 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | 0 7 9 9 0 0 8 0 8 0 1 6 6 9 0 9 8 9 7 8 9 7 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | 3 6 2 8 9 7 1 2 9 5 0 5 7 9 4 1 4 6 7 6 4 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | 1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>HEMATOPOIETIC SYSTEM</b>             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone marrow                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Femoral, leukemia mononuclear           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Femoral, lymphoma malignant histiocytic |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node                              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Inguinal, leukemia mononuclear          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mediastinal, leukemia mononuclear       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mandibular                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mesenteric                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Spleen                                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thymus                                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thymoma malignant                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>INTEGUMENTARY SYSTEM</b>             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mammary gland                           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenocarcinoma                          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fibroadenoma                            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Fibroadenoma, multiple                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Skin                                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Basal cell adenoma                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Back, sebaceous gland, adenoma          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Subcutaneous tissue, fibroma            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>MUSCULOSKELETAL SYSTEM</b>           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone                                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Skeletal muscle                         |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Abdominal, rhabdomyosarcoma             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>NERVOUS SYSTEM</b>                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Brain                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Carcinoma, metastatic, pituitary gland  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>RESPIRATORY SYSTEM</b>               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lung                                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Nose                                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Trachea                                 |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>SPECIAL SENSES SYSTEM</b>            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Eye                                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>URINARY SYSTEM</b>                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kidney                                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Urinary bladder                         |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |





**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                     | 0   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|------------------------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|                                    | 2 5 6 7 7 7 8 8 8 8 8 8 8 8 8 8 8 8 9 9 9 9   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| CARCASS ID                         | 4 9 8 0 7 8 2 2 4 5 6 6 7 7 8 8 8 8 9 9 0 1   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|                                    | 2 1 2 2 2 2 1 1 1 2 2 1 2 1 2 1 2 2 1 1 2 2   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|                                    | 2 9 1 1 2 1 8 9 9 2 1 8 0 9 2 8 0 2 8 9 0 2   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|                                    | 7 3 4 2 5 1 1 8 0 9 7 3 2 1 3 8 5 8 9 7 4 4 6 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|                                    | 1   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>ALIMENTARY SYSTEM</b>           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Esophagus                          | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large                    | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, cecum             | +   | + | + | M | + | + | A | + | A | + | + | + | + | + | + | + | + | + | + | + | + |
| Intestine large, coion             | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| 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                              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | + |
| <b>CARDIOVASCULAR SYSTEM</b>       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Heart                              | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear               |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |
| <b>ENDOCRINE SYSTEM</b>            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 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               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Pars distalis, adenoma             |   |   |   |   | X |   |   |   | X |   |   |   | X |   | X |   | X |   | X | X | X |
| Pars distalis, carcinoma           |   |   |   |   |   |   |   |   |   | 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 |   |   |   |   |   |   |   |   |   |   |   |
| <b>GENERAL BODY SYSTEM</b>         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| None                               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>GENITAL SYSTEM</b>              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Clitoral gland                     | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma                            |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Ovary                              | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear               |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |
| Luteoma                            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Uterus                             | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Carcinoma                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Polyp stromal                      |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |
| Polyp stromal, multiple            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Sarcoma stromal                    |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>HEMATOPOIETIC SYSTEM</b>        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Bone marrow                        | +   | + | + | + | + | + | + | + | + | A | + | + | + | + | + | + | + | + | + | + | + |
| Femoral, leukemia mononuclear      |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |
| Lymph node                         | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Mediastinal, leukemia mononuclear  |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |
| Pancreatic, leukemia mononuclear   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Lymph node, mandibular             | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Spleen                             | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Leukemia mononuclear               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Thymus                             | +   | + | M | + | + | + | M | + | + | + | + | M | + | + | + | + | M | + | + | M | + |
| Leukemia mononuclear               |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |

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

| WEEKS ON STUDY                     | 1                     | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1  | 1  |
|------------------------------------|-----------------------|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----|----|
|                                    | 3                     | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7  | 7  |
| CARCASS ID                         | 1                     | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2  | 2  |
|                                    | 8                     | 9 | 8 | 8 | 8 | 9 | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2  |    |
|                                    | 4                     | 5 | 2 | 5 | 6 | 2 | 4 | 0 | 1 | 3 | 6 | 7 | 8 | 9 | 0 | 3 | 5 | 6 | 8 | 9 | 0 | 1 | 2 | 6 | 0 |   |   |   |    |    |
|                                    | 1                     | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1  |    |
|                                    | TOTAL: TISSUES TUMORS |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |
| <b>ALIMENTARY SYSTEM</b>           |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |
| 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    |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1  |    |
| Salivary glands                    | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 50 |    |
| Stomach                            | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 50 |    |
| Stomach, forestomach               | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 48 |    |
| Stomach, glandular                 | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 48 |    |
| Tongue                             |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1  |    |
| Papilloma squamous                 |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1  |    |
| Tooth                              |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1  |    |
| <b>CARDIOVASCULAR SYSTEM</b>       |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |
| Heart                              | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 50 |    |
| Leukemia mononuclear               |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1  |    |
| <b>ENDOCRINE SYSTEM</b>            |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |
| Adrenal gland                      | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 48 |    |
| Adrenal gland, cortex              | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 48 |    |
| Adenoma                            |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1  |    |
| Leukemia mononuclear               |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1  |    |
| Adrenal gland, medulla             | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 48 |    |
| Leukemia mononuclear               |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1  |    |
| Pheochromocytoma benign            |                       |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |    | 2  |
| Bilateral, pheochromocytoma benign |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |    | 1  |
| Islets, pancreatic                 | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 48 |    |
| Adenoma                            |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1  |    |
| Parathyroid gland                  | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 48 |    |
| Adenoma                            |                       |   | X |   |   |   |   |   |   | M |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    | 1  |
| Pituitary gland                    | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 49 |    |
| Leukemia mononuclear               |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 3  |    |
| Pars distalis, adenoma             |                       | 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 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    | 12 |
| C-cell, carcinoma                  |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 3  |    |
| <b>GENERAL BODY SYSTEM</b>         |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |
| None                               |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |
| <b>GENITAL SYSTEM</b>              |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |
| Clitoral gland                     | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 50 |    |
| Adenoma                            | X                     | X |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   | X  | 7  |
| Ovary                              |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    | 49 |
| Leukemia mononuclear               |                       | I |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    | 1  |
| Luteoma                            |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1  |    |
| Uterus                             | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 50 |    |
| Carcinoma                          |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1  |    |
| Polyp stromal                      |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 7  |    |
| Polyp stromal, multiple            | X                     |   |   |   |   |   |   |   |   | X |   | X |   |   |   |   |   | X | X |   |   |   |   |   |   |   |   |   |    | 1  |
| Sarcoma stromal                    |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1  |    |
| <b>HEMATOPOIETIC SYSTEM</b>        |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |
| Bone marrow                        | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 49 |    |
| Femoral, leukemia mononuclear      |                       |   |   |   |   | X |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   | X  | 6  |
| Lymph node                         | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 50 |    |
| Mediastinal, leukemia mononuclear  |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 3  |    |
| Pancreatic, leukemia mononuclear   |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2  |    |
| Lymph node, mandibular             |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2  |    |
| Leukemia mononuclear               |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    | 50 |
| Lymph node, mandibular             |                       |   | X |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   | X  | 7  |
| Spleen                             | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 50 |    |
| Leukemia mononuclear               |                       |   | X |   |   | X |   | X | X |   | X | X | X | X | X |   |   |   |   | X |   |   |   |   |   | X | X | X | X  | 17 |
| Thymus                             | +                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 43 |    |
| Leukemia mononuclear               |                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 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                                      | 0             |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|---|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
|   | 5 5 5 5 6 7 7 7 7 8 8 8 8 8 8 8 9 9 9 9             |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CARCASS ID  | 3             |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | 1 1 4 3 0 5 0 1 0 0 2 3 2 3 2 1 4 4 1 2             |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | 0 8 0 4 9 0 3 7 6 5 5 3 0 2 3 2 5 1 9 1             |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | 1             |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>ALIMENTARY SYSTEM</b>                            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 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                                | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Neoplastic nodule                                   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pancreas  | + + + + + + + + + + A + + + + X A + + + + + + + + - |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                                | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pharynx   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Salivary glands                                     | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stomach   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stomach, forestomach                                | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stomach, glandular                                  | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Tongue  | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Papilloma squamous                                  | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Tooth   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>CARDIOVASCULAR SYSTEM</b>                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Heart   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                                | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>ENDOCRINE SYSTEM</b>                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adrenal gland                                       | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adrenal gland, cortex                               | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                                | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adrenal gland, medulla                              | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                                | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pheochromocytoma benign                             | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Islets, pancreatic                                  | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenoma   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Parathyroid gland                                   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pituitary gland                                     | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                                | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pars distalis, adenoma                              | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pars distalis, carcinoma                            | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thyroid gland                                       | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| C-cell, adenoma                                     | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| C-cell, carcinoma                                   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Follicular cell, adenoma                            | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>GENERAL BODY SYSTEM</b>                          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| None  | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>GENITAL SYSTEM</b>                               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Clitoral gland                                      | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenoma   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Sarcoma   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Ovary   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                                | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Uterus  | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                                | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Polyp stromal                                       | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>HEMATOPOIETIC SYSTEM</b>                         |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                                | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone marrow   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Femoral, leukemia mononuclear                       | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node  | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Axillary, squamous cell carcinoma, metastatic, skin | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Inguinal, leukemia mononuclear                      | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mediastinal, leukemia mononuclear                   | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pancreatic, leukemia mononuclear                    | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mandibular                              | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                                | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mesenteric                              | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hemangiosarcoma                                     | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Spleen  | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Leukemia mononuclear                                | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thymus  | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thymoma benign                                      | +         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |



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

| WEEKS ON STUDY                             | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |   |   |   |  |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--|
|  | 5 | 5 | 5 | 5 | 6 | 7 | 7 | 7 | 7 | 7 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 9 | 9 | 9 | 9 | 9 | 9 |   |   |  |
|  | 7 | 8 | 8 | 9 | 6 | 1 | 3 | 5 | 5 | 8 | 1 | 1 | 6 | 8 | 9 | 9 | 9 | 9 | 1 | 2 | 3 | 3 | 4 | 5 | 6 | 7 |   |   |   |   |  |
| CARCASS ID                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |   |   |  |
|  | 1 | 1 | 4 | 3 | 0 | 5 | 0 | 1 | 0 | 0 | 2 | 3 | 2 | 3 | 2 | 1 | 4 | 4 | 1 | 2 | 2 | 0 | 1 | 4 | 4 |   |   |   |   |   |  |
|  | 0 | 8 | 0 | 4 | 9 | 0 | 3 | 7 | 6 | 5 | 5 | 3 | 0 | 2 | 3 | 2 | 5 | 1 | 9 | 1 | 9 | 8 | 3 | 4 | 9 |   |   |   |   |   |  |
|  | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |   |  |
| <b>INTEGUMENTARY SYSTEM</b>                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Mammary gland                              | + |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Adenocarcinoma                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Fibroadenoma                               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Skin                                       | + |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Back, squamous cell carcinoma              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Scapula, basal cell carcinoma              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Scapula, papilloma squamous                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Scapula, squamous cell carcinoma           |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   | X |   |   |   |   |   |   |   | X |   |   |   |   |   |  |
| Scapula, squamous cell carcinoma, multiple |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   | X |   | X | X | X |   | X | X |   |  |
| Sebaceous gland, scapula, adenoma          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Subcutaneous tissue, lipoma                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>MUSCULOSKELETAL SYSTEM</b>              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Bone                                       | + |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>NERVOUS SYSTEM</b>                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Brain                                      | + |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Carcinoma, metastatic, pituitary gland     |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |  |
| <b>RESPIRATORY SYSTEM</b>                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Lung                                       | + |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                       |   |   |   |   |   |   |   |   |   |   |   |   |   | X | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Squamous cell carcinoma, metastatic, skin  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |  |
| Nose                                       | + |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Trachea                                    | + |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>SPECIAL SENSES SYSTEM</b>               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Eye  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Harderian gland                            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>URINARY SYSTEM</b>                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Kidney                                     | + |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Leukemia mononuclear                       |   |   |   |   |   |   |   |   |   |   | A |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Urinary bladder                            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |



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

| WEEKS ON STUDY                             | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1  | 1  | TOTAL:<br>TISSUES<br>TUMORS |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----|----|-----------------------------|
| 9  | 9 | 9 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0  |    |                             |
| 7  | 8 | 8 | 9 | 9 | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0  |    |                             |
| CARCASS ID                                 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3  | 3  |                             |
| <b>INTEGUMENTARY SYSTEM</b>                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |                             |
| Mammary gland                              | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +  | 50 |                             |
| Adenocarcinoma                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    | 1  |                             |
| Fibroadenoma                               |   |   |   |   | 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 |   |   |   |   |   |   |   |    | 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  |                             |
| <b>MUSCULOSKELETAL SYSTEM</b>              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |                             |
| Bone                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +  | 50 |                             |
| <b>NERVOUS SYSTEM</b>                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |                             |
| Brain                                      | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +  | 50 |                             |
| Carcinoma, metastatic, pituitary gland     |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    | 3  |                             |
| Leukemia mononuclear                       |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    | 1  |                             |
| <b>RESPIRATORY SYSTEM</b>                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |                             |
| 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 |                             |
| <b>SPECIAL SENSES SYSTEM</b>               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |                             |
| Eye  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    | 3  |                             |
| Harderian gland                            |   |   |   |   | + |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    | 2  |                             |
| <b>URINARY SYSTEM</b>                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |    |    |                             |
| 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  |
|--|-----------------|-------------|------------|
| <b>Adrenal Medulla: Pheochromocytoma</b>                               |                 |             |            |
| 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   |
| <b>Adrenal Medulla: Pheochromocytoma or Malignant Pheochromocytoma</b> |                 |             |            |
| 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   |
| <b>Clitoral Gland: Adenoma</b>   |                 |             |            |
| 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    |
| <b>Clitoral Gland: Adenoma or Carcinoma</b>                            |                 |             |            |
| 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   |
| <b>Mammary Gland: Fibroadenoma</b>                                     |                 |             |            |
| 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   |
| <b>Mammary Gland: Adenocarcinoma</b>                                   |                 |             |            |
| 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   |
|--|-----------------|-------------|-------------|
| <b>Mammary Gland: Fibroadenoma or Adenocarcinoma</b>                             |                 |             |             |
| 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    |
| <b>Pituitary Gland/Pars Distalis: Adenoma</b>                                    |                 |             |             |
| 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    |
| <b>Pituitary Gland/Pars Distalis: Carcinoma</b>                                  |                 |             |             |
| 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    |
| <b>Pituitary Gland/Pars Distalis: Adenoma or Carcinoma</b>                       |                 |             |             |
| 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    |
| <b>Skin (Application Site): Basal Cell Carcinoma (f)</b>                         |                 |             |             |
| 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     |
| <b>Skin (Application Site): Sebaceous Gland Adenoma, or Basal Cell Carcinoma</b> |                 |             |             |
| 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       |
|---|-----------------|-------------|-----------------|
| <b>Skin (All Sites): Basal Cell Adenoma or Carcinoma</b>                                      |                 |             |                 |
| 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         |
| <b>Skin (All Sites): Sebaceous Gland Adenoma, Basal Cell Adenoma, or Basal Cell Carcinoma</b> |                 |             |                 |
| 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         |
| <b>Skin (Application Site): Squamous Cell Carcinoma (f)</b>                                   |                 |             |                 |
| 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         |
| <b>Thyroid Gland: C-Cell Adenoma</b>  |                 |             |                 |
| 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         |
| <b>Thyroid Gland: C-Cell Carcinoma</b>  |                 |             |                 |
| 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         |
| <b>Thyroid Gland: C-Cell Adenoma or Carcinoma</b>   |                 |             |                 |
| 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    |
|---|-----------------|--------------|--------------|
| <b>Uterus: Stromal Polyp</b>                      |                 |              |              |
| 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      |
| <b>Hematopoietic System: Mononuclear Leukemia</b> |                 |              |              |
| 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      |
| <b>All Sites: Benign Tumors</b>                   |                 |              |              |
| 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     |
| <b>All Sites: Malignant Tumors</b>                |                 |              |              |
| 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      |
| <b>All Sites: All Tumors</b>                      |                 |              |              |
| 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)**

|   | <u>Incidence in Controls</u> |                    |                     |
|---|------------------------------|--------------------|---------------------|
|   | Benign                       | Malignant          | Benign or Malignant |
| No 2-year dermal studies using acetone as a vehicle are included in the historical data base. |                              |                    |                     |
| <b>Overall Historical Incidence for Untreated Controls</b>                                    |                              |                    |                     |
| 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)**

|   | <u>Incidence in Controls</u> |                |                        |
|---|------------------------------|----------------|------------------------|
|   | Papilloma                    | Carcinoma      | Papilloma or Carcinoma |
| No 2-year dermal studies using acetone as a vehicle are included in the historical data base. |                              |                |                        |
| <b>Overall Historical Incidence for Untreated Controls</b>                                    |                              |                |                        |
| 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)**

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**Incidence of Papillomas or Carcinomas in Controls**

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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%              |
| <b>Range (d)</b> |                    |
| High             | 1/49               |
| Low              | 0/50               |

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(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 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        |
| <b>ALIMENTARY SYSTEM</b>             |                 |           |           |
| 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 |
|--|-----------------|-----------|-----------|
| <b>ALIMENTARY SYSTEM (Continued)</b>         |                 |           |           |
| Tooth  | (2)             | (1)       | (2)       |
| Dysplasia                                    | 1 (50%)         |           |           |
| Gingiva, hyperplasia, squamous               |                 |           | 1 (50%)   |
| Peridontal tissue, inflammation, suppurative | 1 (50%)         | 1 (100%)  | 1 (50%)   |
| <b>CARDIOVASCULAR SYSTEM</b>                 |                 |           |           |
| 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%)    |
| <b>ENDOCRINE SYSTEM</b>                      |                 |           |           |
| 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%)    |
| <b>GENERAL BODY SYSTEM</b>                   |                 |           |           |
| None   |                 |           |           |
| <b>GENITAL SYSTEM</b>                        |                 |           |           |
| 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%)        |           |           |
| <b>HEMATOPOIETIC SYSTEM</b>                  |                 |           |           |
| 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 |
|---|-----------------|-----------|-----------|
| <b>HEMATOPOIETIC SYSTEM (Continued)</b>       |                 |           |           |
| 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%)    |
| <b>INTEGUMENTARY SYSTEM</b>                   |                 |           |           |
| 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%)  |
| <b>MUSCULOSKELETAL SYSTEM</b>                 |                 |           |           |
| 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%)          |           |           |
| <b>NERVOUS SYSTEM</b>                         |                 |           |           |
| Brain   | (50)            | (50)      | (50)      |
| Compression                                   | 12 (24%)        | 7 (14%)   | 5 (10%)   |
| Infarct                                       | 1 (2%)          |           | 1 (2%)    |
| <b>RESPIRATORY SYSTEM</b>                     |                 |           |           |
| 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 |
|--------------------------------------|-----------------|-----------|-----------|
| <b>SPECIAL SENSES SYSTEM</b>         |                 |           |           |
| Eye                                  | (5)             | (3)       | (3)       |
| Degeneration                         | 4 (80%)         | 2 (67%)   | 2 (67%)   |
| Harderian gland                      |                 |           | (2)       |
| Inflammation, chronic                |                 |           | 2 (100%)  |
| <b>URINARY SYSTEM</b>                |                 |           |           |
| 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

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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          |
| <b>ALIMENTARY SYSTEM</b>                            |                 |              |            |             |
| 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%)          |              |            |             |
| <b>CARDIOVASCULAR SYSTEM</b>                        |                 |              |            |             |
| Heart   | (50)            | (50)         | (50)       | (50)        |
| Lymphoma malignant lymphocytic                      |                 |              | 1 (2%)     |             |
| Lymphoma malignant mixed                            |                 | 1 (2%)       |            |             |
| Squamous cell carcinoma, metastatic, skin           |                 |              | 3 (6%)     | 4 (8%)      |
| <b>ENDOCRINE SYSTEM</b>                             |                 |              |            |             |
| 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 |
|---|-----------------|--------------|------------|-------------|
| <b>ENDOCRINE SYSTEM (Continued)</b>   |                 |              |            |             |
| 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%)     |             |
| <b>GENERAL BODY SYSTEM</b>  |                 |              |            |             |
| Tissue, NOS   | *(50)           | *(50)        | *(50)      | *(50)       |
| Squamous cell carcinoma, metastatic, skin                                       |                 |              | 1 (2%)     |             |
| <b>GENITAL SYSTEM</b>   |                 |              |            |             |
| 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%)      |
| <b>HEMATOPOIETIC SYSTEM</b>   |                 |              |            |             |
| 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 |
|--|-----------------|--------------|------------|-------------|
| <b>HEMATOPOIETIC SYSTEM (Continued)</b>              |                 |              |            |             |
| 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%)       |            |             |
| <b>INTEGUMENTARY SYSTEM</b>                          |                 |              |            |             |
| 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%)     |
| <b>MUSCULOSKELETAL SYSTEM</b>                        |                 |              |            |             |
| Skeletal muscle                                      | *(50)           | *(50)        | *(50)      | *(50)       |
| Diaphragm, squamous cell carcinoma, metastatic, skin |                 |              | 1 (2%)     |             |
| Hindlimb, hemangiosarcoma                            |                 | 1 (2%)       |            |             |
| <b>NERVOUS SYSTEM</b>                                |                 |              |            |             |
| None   |                 |              |            |             |
| <b>RESPIRATORY SYSTEM</b>                            |                 |              |            |             |
| 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%)    |
| <b>SPECIAL SENSES SYSTEM</b>                         |                 |              |            |             |
| 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 |
|--|-----------------|--------------|------------|-------------|
| <b>URINARY SYSTEM</b>                          |                 |              |            |             |
| 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%)          |              |            |             |
| <b>SYSTEMIC LESIONS</b>                        |                 |              |            |             |
| 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%)      |
| <b>ANIMAL DISPOSITION SUMMARY</b>              |                 |              |            |             |
| 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          |
| <b>TUMOR SUMMARY</b>                           |                 |              |            |             |
| 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 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|---|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
|   | 1 1 1 3 1 2 4 6 8 0 0 2 5 5 5 5 5 5 5 5 5         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CARCASS ID                                    | 4 4 0 1 4 2 0 2 3 1 1 3 0 0 0 0 0 0 1 1 1         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | 8 1 2 3 2 5 3 2 1 1 5 3 1 4 5 6 7 8 9 0 2 4 6 7 8 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | - 1         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>ALIMENTARY SYSTEM</b>                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 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                               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hepatocellular carcinoma                      | X X X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hepatocellular carcinoma, multiple            | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hepatocellular adenoma                        | X X X X X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hepatocellular adenoma, multiple              | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mesentery                                     | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lipoma  | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pancreas                                      | + M +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Salivary glands                               | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stomach                                       | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stomach, forestomach                          | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Papilloma squamous                            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stomach, glandular                            | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Carcinoid tumor malignant                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Tooth   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Odontoma                                      | -   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>CARDIOVASCULAR SYSTEM</b>                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Heart   | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>ENDOCRINE SYSTEM</b>                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adrenal gland                                 | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Capsule, adenoma                              | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adrenal gland, cortex                         | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adrenal gland, medulla                        | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Islets, pancreatic                            | + M M +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenoma                                       | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Parathyroid gland                             | M +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pituitary gland                               | + I M + + M + + + + + + + + + + + + + + + + +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pars distalis, adenoma                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pars intermedia, adenoma                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thyroid gland                                 | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>GENERAL BODY SYSTEM</b>                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Tissue, NOS                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>GENITAL SYSTEM</b>                         |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Epididymis                                    | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Preputial gland                               | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prostate                                      | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Seminal vesicle                               | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Testes  | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hemangiosarcoma                               | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>HEMATOPOIETIC SYSTEM</b>                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood   | -   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone marrow                                   | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Femoral, hemangioma                           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node                                    | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mandibular                        | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mesenteric                        | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant undifferentiated cell type |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Spleen  | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hemangiosarcoma                               | X X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed                      | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thymus  | I + M + M + + + M + + + + + I M + + + M + + + + + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>INTEGUMENTARY SYSTEM</b>                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mammary gland                                 | M M M M M M + M M M M M + M M M M M M + M M M M   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Skin  | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>MUSCULOSKELETAL SYSTEM</b>                 |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone  | +       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>NERVOUS SYSTEM</b>                         |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 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                              | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CARCASS ID                                  | 4 | 4 | 0 | 1 | 4 | 2 | 0 | 2 | 3 | 1 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |   |   |   |
|   | 1 | 1 | 1 | 3 | 1 | 2 | 4 | 6 | 8 | 0 | 0 | 2 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |   |   |   |
| <b>RESPIRATORY SYSTEM</b>                   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Lung  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |   |   |
| Alveolar/bronchiolar adenoma                |   |   |   |   |   |   |   | X |   |   |   |   | X | X |   |   |   | X |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Alveolar/bronchiolar adenoma, multiple      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Alveolar/bronchiolar carcinoma              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Hepatocellular carcinoma, metastatic, liver |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Lymphoma malignant mixed                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Nose  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| Trachea                                     | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| <b>SPECIAL SENSES SYSTEM</b>                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Harderian gland                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Adenoma                                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Adenoma                                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Adenoma                                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>URINARY SYSTEM</b>                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Kidney                                      | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |
| Urinary bladder                             | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangiosarcoma                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |







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

| WEEKS ON STUDY                             | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |  |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--|
| CARCASS ID                                 | 2 | 5 | 6 | 5 | 8 | 9 | 5 | 5 | 7 | 4 | 4 | 7 | 0 | 0 | 3 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |  |
|  | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |  |
|  | 2 | 3 | 5 | 4 | 6 | 4 | 4 | 3 | 6 | 4 | 3 | 4 | 2 | 3 | 6 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |  |
|  | 7 | 4 | 2 | 5 | 2 | 9 | 4 | 8 | 9 | 2 | 5 | 6 | 6 | 7 | 5 | 1 | 2 | 3 | 4 | 5 | 8 | 9 |  |
|  | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |  |
| <b>INTEGUMENTARY SYSTEM</b>                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Mammary gland                              | 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 |   |   |   |   |   |   |   |  |
| Scapula, squamous cell carcinoma, multiple |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |  |
| <b>MUSCULOSKELETAL SYSTEM</b>              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Bone                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| Skeletal muscle                            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Hindlimb, hemangiosarcoma                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>NERVOUS SYSTEM</b>                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Brain                                      | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| <b>RESPIRATORY SYSTEM</b>                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Lung                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| Alveolar/bronchiolar adenoma               |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X | X |   |   |   | X | X | X |  |
| Alveolar/bronchiolar adenoma, multiple     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |  |
| Alveolar/bronchiolar carcinoma             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Alveolar/bronchiolar carcinoma, multiple   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Lymphoma malignant histiocytic             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |  |
| Lymphoma malignant mixed                   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Squamous cell carcinoma, metastatic, skin  |   |   |   |   |   |   |   | X |   |   |   |   |   | X |   |   |   |   |   |   |   |   |  |
| Nose                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| Trachea                                    | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |  |
| <b>SPECIAL SENSES SYSTEM</b>               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Harderian gland                            | + | M | + | + | + | + | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + |  |
| Adenoma                                    |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   | X |   |  |
| Bilateral, adenoma                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |  |
| <b>URINARY SYSTEM</b>                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| 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                             | 1 | 0 | 5 |    |
|--|---|---|---|----|
| CARCASS ID                                 | 1 | 3 3 3 4 4 4 4 4 5 5 5 5 5 5 5 5 5 6 6 6 6 6 6 7 | 1 |    |
| TOTAL TISSUES TUMORS                       |   |   |   |    |
| <b>INTEGUMENTARY SYSTEM</b>                |   |   |   |    |
| Mammary gland                              | M   | M   | M   | 11 |
| Skin                                       | +   | +   | +   | 50 |
| Squamous cell carcinoma                    |   |   |   | 1  |
| Back, squamous cell carcinoma              |   |   | X   | 4  |
| Scapula, basosquamous tumor malign         | X   |   |   | 2  |
| Scapula, squamous cell carcinoma           |   | X   | X   | 10 |
| Scapula, squamous cell carcinoma, multiple |   |   | X   | 2  |
| <b>MUSCULOSKELETAL SYSTEM</b>              |   |   |   |    |
| Bone                                       | +   | +   | +   | 50 |
| Skeletal muscle                            |   |   | +   | 1  |
| Hindlimb, hemangiosarcoma                  |   |   | X   | 1  |
| <b>NERVOUS SYSTEM</b>                      |   |   |   |    |
| Brain                                      | +   | +   | +   | 50 |
| <b>RESPIRATORY SYSTEM</b>                  |   |   |   |    |
| Lung                                       | +   | +   | +   | 50 |
| Alveolar/bronchiolar adenoma               | X   |   |   | 8  |
| Alveolar/bronchiolar adenoma, multiple     |   |   |   | 1  |
| Alveolar/bronchiolar carcinoma             |   | X   |   | 1  |
| Alveolar/bronchiolar carcinoma, multiple   |   |   |   | 1  |
| Lymphoma malignant histiocytic             |   |   | X   | 1  |
| Lymphoma malignant mixed                   |   |   |   | 1  |
| Squamous cell carcinoma, metastatic, skin  |   |   |   | 2  |
| Nose                                       | +   | +   | +   | 50 |
| Trachea                                    | +   | +   | +   | 50 |
| <b>SPECIAL SENSES SYSTEM</b>               |   |   |   |    |
| Harderian gland                            | +   | +   | +   | 42 |
| Adenoma                                    | X   |   | X   | 6  |
| Bilateral, adenoma                         |   |   |   | 1  |
| <b>URINARY SYSTEM</b>                      |   |   |   |    |
| Kidney                                     | +   | +   | +   | 50 |
| Lymphoma malignant mixed                   |   |   |   | 1  |
| Squamous cell carcinoma, metastatic, skin  |   |   |   | 2  |
| Urinary bladder                            | +   | +   | +   | 48 |





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

| WEEKS ON STUDY                                       | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |  |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|--|
| CARCASS ID   | 0 | 0 | 0 | 0 | 0 | 3 | 3 | 5 | 6 | 6 | 7 | 7 | 7 | 7 | 8 | 8 | 8 | 8 | 8 | 8 | 8 | 9 | 9 | 9 | 9 | 9 |  |
|  | 1 | 1 | 1 | 1 | 5 | 6 | 2 | 5 | 9 | 3 | 3 | 5 | 5 | 6 | 8 | 1 | 2 | 5 | 7 | 8 | 8 | 0 | 0 | 0 | 0 | 0 |  |
|  | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |  |
|  | 5 | 6 | 6 | 9 | 8 | 7 | 9 | 8 | 4 | 9 | 5 | 7 | 8 | 5 | 6 | 4 | 8 | 8 | 5 | 6 | 6 | 7 | 7 | 7 | 7 |   |  |
|  | 9 | 5 | 8 | 2 | 8 | 1 | 4 | 9 | 4 | 1 | 1 | 3 | 5 | 2 | 7 | 1 | 2 | 0 | 5 | 4 | 6 | 0 | 2 | 4 | 8 |   |  |
|  | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |   |  |
| <b>INTEGUMENTARY SYSTEM</b>                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| 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 |   |  |
| <b>MUSCULOSKELETAL SYSTEM</b>                        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Bone   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |  |
| Skeletal muscle                                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | M | + |   |  |
| Diaphragm, squamous cell carcinoma, metastatic, skin |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>NERVOUS SYSTEM</b>                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Brain  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |  |
| <b>RESPIRATORY SYSTEM</b>                            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Lung   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |  |
| Alveolar/bronchiolar adenoma                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   | X |   |  |
| Alveolar/bronchiolar carcinoma                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |  |
| Squamous cell carcinoma, metastatic, skin            |   |   |   |   |   |   |   | X |   |   | X |   |   | X |   |   |   |   |   |   |   |   | X | X |   |   |  |
| Nose   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |  |
| Trachea  | + | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |   |  |
| <b>SPECIAL SENSES SYSTEM</b>                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Harderian gland                                      | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | M | + | + | + | + | + | + |   |  |
| Adenoma  |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Carcinoma  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| Lymphoma malignant lymphocytic                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| <b>URINARY SYSTEM</b>                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |  |
| 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                                       | 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1 1 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | TOTAL: TISSUES TUMORS |   |    |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|-----------------------|---|----|
|  | 9 9 9 9 9 9 9 9 9 9 9 9 0 0 0 0 0 0 0 0 0 0 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                       |   |    |
| CARCASS ID   | 0 1 2 4 6 7 8 9 9 9 9 9 0 0 0 0 1 2 2 2 2 2 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                       |   |    |
|  | 2 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                       |   |    |
| <b>INTEGUMENTARY SYSTEM</b>                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                       |   |    |
| Mammary gland  | 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                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                       |   | 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                     | X | 27 |
| Scapula, squamous cell carcinoma, multiple           |   |   |   | X | X |   |   |   |   | X | X | X | X |   | X |   |   |   |   |   | X                     | X | 12 |
| <b>MUSCULOSKELETAL SYSTEM</b>                        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                       |   |    |
| Bone   | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +                     | + | 49 |
| Skeletal muscle                                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                       |   | 1  |
| Diaphragm, squamous cell carcinoma, metastatic, skin |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |                       |   | 1  |
| <b>NERVOUS SYSTEM</b>                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                       |   |    |
| Brain  | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +                     | + | 50 |
| <b>RESPIRATORY SYSTEM</b>                            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                       |   |    |
| Lung   | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +                     | + | 50 |
| Alveolar/bronchiolar adenoma                         |   |   |   |   |   |   |   |   |   |   |   |   | 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 |                       |   | 16 |
| Nose   | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +                     | + | 50 |
| Trachea  | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +                     | + | 49 |
| <b>SPECIAL SENSES SYSTEM</b>                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                       |   |    |
| Harderian gland                                      | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +                     | + | 48 |
| Adenoma  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |                       | X | 3  |
| Carcinoma  |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |                       |   | 1  |
| Lymphoma malignant lymphocytic                       | X   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                       |   | 1  |
| <b>URINARY SYSTEM</b>                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                       |   |    |
| Kidney   | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +                     | + | 50 |
| Lymphoma malignant lymphocytic                       |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                       |   | 1  |
| Squamous cell carcinoma, metastatic, skin            |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 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           |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|--|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
|  | 5 0 0 5 4 4 0 0 2 5 5 5 5 5 5 7 9 9 0 1 1 2 2 3 3 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CARCASS ID   | 3 4 4 3 3 4 3 3 3 4 3 3 4 4 4 3 3 3 3 3 3 3 3 3 3 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 6 1 1 8 7 0 6 7 7 1 6 7 1 1 1 6 8 9 6 7 9 8 8 9 7 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>ALIMENTARY SYSTEM</b>   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Esophagus  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Gallbladder  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intestine large  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intestine large, cecum   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intestine large, colon   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intestine large, rectum  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 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   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Salivary glands  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stomach  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stomach, forestomach   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Stomach, glandular   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin                        | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Tooth  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>CARDIOVASCULAR SYSTEM</b>                                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood vessel   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Heart  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin                        | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>ENDOCRINE SYSTEM</b>  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adrenal gland  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Capsule, adenoma   | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adrenal gland, cortex  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Medulla, squamous cell carcinoma, metastatic, skin               | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adrenal gland, medulla   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Islets, pancreatic   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Parathyroid gland  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pituitary gland  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thyroid gland  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>GENERAL BODY SYSTEM</b>                                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Tissue, NOS  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>GENITAL SYSTEM</b>  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Epididymis   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Preputial gland  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Prostate   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Testes   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Interstitial cell, adenoma                                       | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>HEMATOPOIETIC SYSTEM</b>                                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone marrow  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 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   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 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   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |







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

| WEEKS ON STUDY  | 0         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   | TOTAL TISSUES TUMORS |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|---|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|---|----------------------|--|----|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
|   | 3 3 3 4 4 4 4 5 5 5 7 7 8 9 0 1 1 1 2 2 3 3 3 3 3 3 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CARCASS ID  | 3 4 3 3 3 3 3 3 3 3 3 3 3 3 3 4 4 3 3 3 3 3 3 4     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | 9 0 8 8 6 9 9 9 7 9 9 8 7 8 8 8 0 0 7 9 6 7 6 6 0   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 4 3 3 7 3 1 8 6 7 7 9 5 8 2 1 9 2 4 0 5 5 2 2 4 0 |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>INTEGUMENTARY SYSTEM</b>                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mammary gland   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Skin  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma                                 |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Scapula, basosquamous tumor malign                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Scapula, squamous cell carcinoma                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Scapula, squamous cell carcinoma, multiple              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| M + M M M + M |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 4  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 50 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 1  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 3  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X X   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 37 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X X   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 5  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>MUSCULOSKELETAL SYSTEM</b>                           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 50 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>NERVOUS SYSTEM</b>                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Brain   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 50 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>RESPIRATORY SYSTEM</b>                               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lung  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Alveolar/bronchiolar adenoma                            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Alveolar/bronchiolar carcinoma                          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Basosquamous tumor malignant, metastatic, skin          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant histiocytic                          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Nose  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Trachea   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 50 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 2  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 1  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 3  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 1  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 20 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 50 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 50 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>SPECIAL SENSES SYSTEM</b>                            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Harderian gland   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenoma   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + + + + + + + + M + + + + + + + + + + + + + + + + + + + |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 42 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X X   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 4  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>URINARY SYSTEM</b>                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kidney  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Basosquamous tumor malignant, metastatic, skin          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Urinary bladder   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  |    |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 50 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 2  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| X X   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |   |                      |  | 5  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| + 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 |
|---|-----------------|--------------|-------------|-------------|
| <b>Adrenal Gland Capsule: Adenoma</b>             |                 |              |             |             |
| 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    |
| <b>Harderian Gland: Adenoma</b>                   |                 |              |             |             |
| 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     |
| <b>Harderian Gland: Adenoma or Carcinoma</b>      |                 |              |             |             |
| 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     |
| <b>Liver: Hepatocellular Adenoma</b>              |                 |              |             |             |
| 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    |
| <b>Liver: Hepatocellular Carcinoma</b>            |                 |              |             |             |
| 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    |
| <b>Liver: Hepatocellular Adenoma or Carcinoma</b> |                 |              |             |             |
| 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 |
|--|-----------------|--------------|-------------|-------------|
| <b>Lung: Alveolar/Bronchiolar Adenoma</b>  |                 |              |             |             |
| 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    |
| <b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b>                               |                 |              |             |             |
| 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    |
| <b>Skin (Application Site): Basosquamous Tumor Malignant</b>                         |                 |              |             |             |
| 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     |
| <b>Skin (Application Site): Basosquamous Tumor Malignant or Basal Cell Carcinoma</b> |                 |              |             |             |
| 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     |
| <b>Skin (Application Site): Squamous Cell Carcinoma</b>                              |                 |              |             |             |
| 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     |
| <b>Skin (All Sites): Squamous Cell Carcinoma</b>                                     |                 |              |             |             |
| 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 |
|--|-----------------|--------------|-------------|-------------|
| <b>Circulatory System: Hemangioma</b>                    |                 |              |             |             |
| 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    |
| <b>Circulatory System: Hemangiosarcoma</b>               |                 |              |             |             |
| 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    |
| <b>Circulatory System: Hemangioma or Hemangiosarcoma</b> |                 |              |             |             |
| 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    |
| <b>Hematopoietic System: Lymphoma, All Malignant</b>     |                 |              |             |             |
| 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    |
| <b>All Sites: Benign Tumors</b>                          |                 |              |             |             |
| 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    |
| <b>All Sites: Malignant Tumors</b>                       |                 |              |             |             |
| 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 |
|---------------------------------|-----------------|--------------|-------------|-------------|
| <b>All Sites: All Tumors</b>    |                 |              |             |             |
| 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<sub>1</sub> MICE (a)**

| Study  | Incidence in Controls |                |                        |
|--|-----------------------|----------------|------------------------|
|  | Papilloma             | Carcinoma      | Papilloma or Carcinoma |
| <b>Historical Incidence in Dermal Studies Using Acetone as a Vehicle (b)</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%)           |
| <b>Overall Historical Incidence for Untreated Controls</b>                   |                       |                |                        |
| 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%                  |
| <b>Range (e)</b>   |                       |                |                        |
| 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          |
| <b>ALIMENTARY SYSTEM</b>                                  |                 |              |            |             |
| 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%)         |              |            |             |
| <b>CARDIOVASCULAR SYSTEM</b>                              |                 |              |            |             |
| 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 |
|---|-----------------|--------------|------------|-------------|
| <b>CARDIOVASCULAR SYSTEM</b>                  |                 |              |            |             |
| 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%)      |
| <b>ENDOCRINE SYSTEM</b>                       |                 |              |            |             |
| 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%)     |             |
| <b>GENERAL BODY SYSTEM</b>                    |                 |              |            |             |
| None  |                 |              |            |             |
| <b>GENITAL SYSTEM</b>                         |                 |              |            |             |
| 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 |
|---|-----------------|--------------|------------|-------------|
| <b>GENITAL SYSTEM (Continued)</b>                           |                 |              |            |             |
| Testes  | (50)            | (50)         | (50)       | (50)        |
| Infarct   | 1 (2%)          |              |            |             |
| Inflammation, chronic, focal                                |                 | 1 (2%)       |            |             |
| Seminiferous tubule, atrophy                                |                 |              | 1 (2%)     |             |
| <b>HEMATOPOIETIC SYSTEM</b>                                 |                 |              |            |             |
| 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%)      |
| <b>INTEGUMENTARY SYSTEM</b>                                 |                 |              |            |             |
| 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 |
|--|-----------------|--------------|------------|-------------|
| <b>INTEGUMENTARY SYSTEM</b>                    |                 |              |            |             |
| 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%)    |
| <b>MUSCULOSKELETAL SYSTEM</b>                  |                 |              |            |             |
| Bone   | (50)            | (50)         | (49)       | (50)        |
| Artery, femur, thrombus                        |                 |              |            | 1 (2%)      |
| Cranium, proliferation                         | 1 (2%)          |              |            |             |
| Tibia, inflammation, acute                     |                 |              |            | 1 (2%)      |
| <b>NERVOUS SYSTEM</b>                          |                 |              |            |             |
| 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%)          |              |            |             |
| <b>RESPIRATORY SYSTEM</b>                      |                 |              |            |             |
| 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%)          |              |            |             |
| Interstitialium, inflammation, chronic         |                 | 2 (4%)       | 1 (2%)     | 1 (2%)      |
| <b>SPECIAL SENSES SYSTEM</b>                   |                 |              |            |             |
| 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%)     |
| <b>URINARY SYSTEM</b>                          |                 |              |            |             |
| 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

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**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          |
| <b>ALIMENTARY SYSTEM</b>                                |                 |              |            |             |
| 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 |
|--|-----------------|--------------|------------|-------------|
| <b>ALIMENTARY SYSTEM (Continued)</b>                     |                 |              |            |             |
| 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%)       |            |             |
| <b>CARDIOVASCULAR SYSTEM</b>                             |                 |              |            |             |
| 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%)     | 1 (2%)      |
| Squamous cell carcinoma, metastatic, skin                |                 |              |            | 2 (4%)      |
| <b>ENDOCRINE SYSTEM</b>                                  |                 |              |            |             |
| 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%)     |             |
| <b>GENERAL BODY SYSTEM</b>                               |                 |              |            |             |
| Tissue, NOS  | *(50)           | *(50)        | *(50)      | *(50)       |
| Osteosarcoma, metastatic, metastatic                     | 1 (2%)          |              |            |             |
| <b>GENITAL SYSTEM</b>                                    |                 |              |            |             |
| 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 |
|--|-----------------|--------------|------------|-------------|
| <b>GENITAL SYSTEM</b>                                      |                 |              |            |             |
| 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%)      |
| <b>HEMATOPOIETIC SYSTEM</b>                                |                 |              |            |             |
| 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 |
|--|-----------------|--------------|------------|-------------|
| <b>HEMATOPOIETIC SYSTEM</b>                              |                 |              |            |             |
| 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%)     |             |
| <b>INTEGUMENTARY SYSTEM</b>                              |                 |              |            |             |
| 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 |
|---|-----------------|--------------|------------|-------------|
| <b>INTEGUMENTARY SYSTEM</b>                                       |                 |              |            |             |
| Skin (Continued)  | (50)            | (50)         | (50)       | (50)        |
| Sebacous gland, adenocarcinoma                                    |                 | 1 (2%)       |            |             |
| Subcutaneous tissue, fibrosarcoma                                 |                 |              | 1 (2%)     |             |
| Subcutaneous tissue, scapula, squamous cell carcinoma, metastatic |                 |              | 1 (2%)     |             |
| <b>MUSCULOSKELETAL SYSTEM</b>                                     |                 |              |            |             |
| 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%)      |
| <b>NERVOUS SYSTEM</b>   |                 |              |            |             |
| Brain   | (50)            | (50)         | (50)       | (50)        |
| Lymphoma malignant lymphocytic                                    |                 |              |            | 1 (2%)      |
| <b>RESPIRATORY SYSTEM</b>   |                 |              |            |             |
| 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%)          |              |            |             |
| <b>SPECIAL SENSES SYSTEM</b>                                      |                 |              |            |             |
| 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 |
|--|-----------------|--------------|------------|-------------|
| <b>URINARY SYSTEM</b>  |                 |              |            |             |
| 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%)     |             |
| <b>SYSTEMIC LESIONS</b>  |                 |              |            |             |
| 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%)     |             |
| <b>ANIMAL DISPOSITION SUMMARY</b>                              |                 |              |            |             |
| 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               |              |            |             |
| Accidentally killed  | 1               |              |            |             |
| Drowned  | 1               | 1            |            |             |
| Scheduled sacrifice  | 10              | 10           | 10         | 12          |
| <b>TUMOR SUMMARY</b>   |                 |              |            |             |
| 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                                   | 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  | 1 5 6 6 6 7 7 8 8 8 9 9 9 0 0 0 0 0 0 0 0 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| CARCASS ID                                       | 0 6 3 5 5 2 2 7 2 5 5 5 7 7 0 0 1 2 3 3 3 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  | 0 1 1 0 0 0 0 1 0 0 0 0 0 1 0 1 0 0 0 0 0 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 9 0 0 6 8 8 9 0 7 9 6 9 9 8 0 7 1 7 8 8 6        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 3 6 1 2 7 0 2 8 0 4 7 7 8 3 5 6 0 5 5 1 1        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 1        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>ALIMENTARY SYSTEM</b>                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 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 |   |   |   |   |   |   |   |   |   |   |   |   |
| Hepatocellular adenoma                           |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   | X |   |   | X |
| Hepatocellular adenoma, multiple                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Lymphoma malignant lymphocytic                   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |
| Lymphoma malignant mixed                         |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   | X |   |   |   |
| Mesentery  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Hemangioma                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Lymphoma malignant lymphocytic                   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |
| Lymphoma malignant undifferentiated cell type    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Osteosarcoma, metastatic uncertain primary site  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Pancreas   | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant mixed                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Lymphoma malignant undifferentiated cell type    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Osteosarcoma, metastatic, uncertain primary site |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Salivary glands                                  | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach  | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Stomach forestomach                              | +   | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Papilloma squamous                               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |
| Stomach glandular                                | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adenoma  |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |
| <b>CARDIOVASCULAR SYSTEM</b>                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Blood vessel                                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Heart  | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant mixed                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Lymphoma malignant undifferentiated cell type    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |   |
| <b>ENDOCRINE SYSTEM</b>                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Adrenal gland                                    | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Capsule adenoma                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Capsule lymphoma malignant lymphocytic           |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |
| Adrenal gland cortex                             | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Adrenal gland medulla                            | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Islets, pancreatic                               | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Parathyroid gland                                | +   | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + | + | M | M | + |
| Pituitary gland                                  | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Pars distalis, adenoma                           |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |
| Pars intermedia adenoma                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X | X |
| Thyroid gland                                    | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | M | + | + |
| Follicular cell adenoma                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>GENERAL BODY SYSTEM</b>                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Tissue, NOS                                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Osteosarcoma, metastatic metastatic              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>GENITAL SYSTEM</b>                            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Clitoral gland                                   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Ovary  | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Cystadenoma                                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Luteoma  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Lymphoma malignant lymphocytic                   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |
| Lymphoma malignant mixed                         |   |   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |
| Uterus   | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Hemangioma                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 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                                   | 1 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | TOTAL TISSUES TUMORS |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----------------------|
|  | 0 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| CARCASS ID                                       | 5 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
|  | 6 6 7 7 7 7 7 7 7 8 8 8 8 8 9 9 9 9 9 9 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 8                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 9                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 3                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 4                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 7                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 8                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 9                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 4                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 6                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 8                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 9                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 0                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 5                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 6                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 9                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 0                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 3                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 4                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 7                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 9                    |
|  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| <b>ALIMENTARY SYSTEM</b>                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| 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                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 7                    |
| Hepatocellular adenoma, multiple                 | X                                       | X |   |   |   |   |   |   |   |   |   |   | X | X |   |   |   |   | X |   | 1                    |
| Lymphoma malignant lymphocytic                   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 5                    |
| Lymphoma malignant mixed                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| 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                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Lymphoma malignant undifferentiated cell type    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Osteosarcoma, metastatic, uncertain primary site |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Salivary glands                                  | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |
| Stomach  | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |
| Stomach, forestomach                             | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49                   |
| Papilloma squamous                               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 3                    |
| Stomach, glandular                               | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |
| Adenoma  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| <b>CARDIOVASCULAR SYSTEM</b>                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| Blood vessel                                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Heart  | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |
| Lymphoma malignant mixed                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Lymphoma malignant undifferentiated cell type    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| <b>ENDOCRINE SYSTEM</b>                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| Adrenal gland                                    | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |
| Capsule, adenoma                                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
| Capsule, lymphoma malignant lymphocytic          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Adrenal gland, cortex                            | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |
| Adrenal gland, medulla                           | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |
| Islets, pancreatic                               | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49                   |
| Parathyroid gland                                | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 45                   |
| Pituitary gland                                  | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49                   |
| Pars distalis, adenoma                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 17                   |
| Pars intermedia, adenoma                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
| Thyroid gland                                    | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49                   |
| Follicular cell, adenoma                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
| <b>GENERAL BODY SYSTEM</b>                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| Tissue, NOS                                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Osteosarcoma, metastatic, metastatic             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| <b>GENITAL SYSTEM</b>                            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| Clitoral gland                                   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Ovary  | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |
| Cystadenoma                                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Luteoma  | X                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Lymphoma malignant lymphocytic                   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
| Lymphoma malignant mixed                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |
| Uterus   | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |
| Hemangioma                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Lymphoma malignant lymphocytic                   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Lymphoma malignant mixed                         |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Polyp stromal                                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |

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

| WEEKS ON STUDY   | 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1 1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|--|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
|  | 1 5 6 6 6 7 7 8 8 8 9 9 0 0 0 0 0 0 0 0 0 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CARCASS ID   | 0 6 3 5 5 2 7 2 5 5 5 7 7 0 0 1 2 3 3 5 5 5 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 0 1 1 0 0 0 0 1 0 0 0 0 0 0 1 0 1 0 0 0 0 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 9 0 0 6 8 8 9 0 7 9 6 9 9 8 0 7 1 7 8 8 6 6 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 3 6 1 2 7 0 2 8 0 4 7 7 8 3 5 6 0 5 5 1 1 3 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>HEMATOPOIETIC SYSTEM</b>                                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Blood  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone marrow  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hemangioma   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mast cell tumor, NOS                                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lumbar, lymphoma malignant lymphocytic                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mediastinal, lymphoma malignant lymphocytic                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mediastinal, lymphoma malignant mixed                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mandibular                                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mesenteric                                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant undifferentiated cell type              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Spleen   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hemangioma   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hemangiosarcoma, metastatic                                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant undifferentiated cell type              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Osteosarcoma, metastatic, uncertain primary site           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thymus   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant undifferentiated cell type              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>INTEGUMENTARY SYSTEM</b>                                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mammary gland  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenocarcinoma   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Inguinal, lymphoma malignant mixed                         |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Skin   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hemangioma   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hemangiosarcoma  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>MUSCULOSKELETAL SYSTEM</b>                              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Skeletal muscle  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Abdominal lymphoma malignant lymphocytic                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>NERVOUS SYSTEM</b>                                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Brain  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>RESPIRATORY SYSTEM</b>                                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lung   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Alveolar/bronchiolar adenoma                               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Alveolar/bronchiolar carcinoma                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hepatocellular carcinoma, metastatic liver                 |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Osteosarcoma, metastatic, uncertain primary site           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mediastinum, lymphoma malignant undifferentiated cell type |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Nose   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Trachea  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>SPECIAL SENSES SYSTEM</b>                               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Harderian gland  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenoma  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>URINARY SYSTEM</b>                                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kidney   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant undifferentiated cell type              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Osteosarcoma, metastatic, uncertain primary site           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Urinary bladder  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

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

| WEEKS ON STUDY   | 1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | TOTAL TISSUES TUMORS |
|--|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|----------------------|
|  | 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| CARCASS ID   | 5 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
|  | 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
|  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
|  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| <b>HEMATOPOIETIC SYSTEM</b>                                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Blood  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Bone marrow  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Hemangioma   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Mast cell tumor, NOS                                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Lymph node   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 49                   |
| Lumbar, lymphoma malig lymphocytic                         |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Mediastinal, lymphoma malignant lymphocytic                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2                    |
| Mediastinal, lymphoma malig mixed                          |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Lymph node, mandibular                                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 48                   |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2                    |
| Lymphoma malignant mixed                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 3                    |
| Lymph node, mesenteric                                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 6                    |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Lymphoma malignant mixed                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Lymphoma malignant undifferentiated cell type              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Spleen   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Hemangioma   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2                    |
| Hemangiosarcoma, metastatic                                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 3                    |
| Lymphoma malignant mixed                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 9                    |
| Lymphoma malignant undifferentiated cell type              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 3                    |
| Osteosarcoma, metastatic, uncertain primary site           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Thymus   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 42                   |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Lymphoma malignant mixed                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2                    |
| Lymphoma malignant undifferentiated cell type              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| <b>INTEGUMENTARY SYSTEM</b>                                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Mammary gland  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Adenocarcinoma   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 44                   |
| Inguinal, lymphoma malignant mixed                         |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Skin   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Hemangioma   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Hemangiosarcoma  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| <b>MUSCULOSKELETAL SYSTEM</b>                              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Bone   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Skeletal muscle  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Abdominal, lymphoma malignant lymphocytic                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| <b>NERVOUS SYSTEM</b>                                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Brain  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| <b>RESPIRATORY SYSTEM</b>                                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Lung   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Alveolar/bronchiolar adenoma                               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Alveolar/bronchiolar carcinoma                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 3                    |
| Hepatocellular carcinoma, metastatic, liver                |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Lymphoma malignant mixed                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2                    |
| Osteosarcoma, metastatic, uncertain primary site           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Mediastinum, lymphoma malignant undifferentiated cell type |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2                    |
| Nose   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Trachea  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| <b>SPECIAL SENSES SYSTEM</b>                               |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Harderian gland  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Adenoma  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 43                   |
| <b>URINARY SYSTEM</b>                                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Kidney   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                      |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                   |
| Lymphoma malignant mixed                                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2                    |
| Lymphoma malignant undifferentiated cell type              |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 3                    |
| Osteosarcoma, metastatic, uncertain primary site           |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |
| Urinary bladder  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 49                   |
| Lymphoma malignant lymphocytic                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                    |



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

| WEEKS ON STUDY  | 0               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | TOTAL TISSUES TUMORS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----------------------|
|   | 5               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
|   | CARCASS ID<br>1 1 1 1 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| <b>ALIMENTARY SYSTEM</b>                              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| 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   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 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                    |
| Peridental tissue, histiocytic sarcoma, metastatic    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| <b>CARDIOVASCULAR SYSTEM</b>                          |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| Blood vessel  | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 1                    |
| Heart   | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |
| <b>ENDOCRINE SYSTEM</b>                               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| 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 |   |   |   |   |   |   | 16                   |
| Thyroid gland   | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49                   |
| Lymphoma malignant lymphocytic                        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| Follicular cell, adenoma                              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |
| <b>GENERAL BODY SYSTEM</b>                            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| None  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| <b>GENITAL SYSTEM</b>                                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |
| 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  | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 49                   |
| Histiocytic sarcoma                                   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | M | 2                    |
| Polyp stromal   |   |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   | 1                    |

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

| WEEKS ON STUDY                                   | 0 0 0 0 0 0 0 0 0 0 0 0 1 1 1 1 1 1 1 1 1 1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|--|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
|  | 0 2 3 6 6 6 6 7 7 8 8 9 0 0 0 0 0 0 0 0 0 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CARCASS ID                                       | 5 8 1 0 2 6 9 4 9 0 3 2 1 2 2 2 2 2 4 5 5 5 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | 2 1 1 2 2 2 2 1 2 1 2 2 2 1 1 2 2 1 2 1 1 1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 3 8 8 1 4 1 2 9 2 8 0 0 0 8 9 0 1 9 1 8 8 8      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 3 4 1 8 0 9 6 6 8 7 9 5 1 3 8 2 0 2 2 2 5 6      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 1      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>HEMATOPOIETIC SYSTEM</b>                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone marrow                                      | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Femoral, hemangiosarcoma                         | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node                                       | + + + + I + + + + + + + + + + + + + + + + + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lumbar, histiocytic sarcoma, metastatic          | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mediastinal, lymphoma malignant lymphocytic      | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mediastinal, lymphoma malignant mixed            | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pancreatic, lymphoma malignant mixed             | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mandibular                           | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                   | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed                         | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin        | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mesenteric                           | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Histiocytic sarcoma, metastatic                  | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                   | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Spleen   | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hemangiosarcoma                                  | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Histiocytic sarcoma, metastatic, metastatic      | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed                         | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Capsule, histiocytic sarcoma, metastatic         | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thymus   | + M + + M + + + + M + M + + + M + + + + + + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                   | + M + + M + + + + M + M + + + M + + + + + + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed                         | + M + + M + + + + M + M + + + M + + + + + + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>INTEGUMENTARY SYSTEM</b>                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mammary gland                                    | + M M + M + + + M + + + + + + + + + + + +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenocarcinoma                                   | + M M + M + + + M + + + + + + + + + + + +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Skin   | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                   | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Back, lymphoma malignant lymphocytic             | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Back, squamous cell carcinoma                    | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Scapula, lymphoma malignant lymphocytic          | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Scapula, squamous cell carcinoma                 | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Scapula, squamous cell carcinoma, multiple       | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Sebaceous gland, adenocarcinoma                  | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>MUSCULOSKELETAL SYSTEM</b>                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone   | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>NERVOUS SYSTEM</b>                            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Brain  | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>RESPIRATORY SYSTEM</b>                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lung   | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenocarcinoma, metastatic, mammary gland        | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Alveolar/bronchiolar adenoma                     | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Alveolar/bronchiolar carcinoma                   | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hepatocellular carcinoma, metastatic, liver      | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Hepatocellular carcinoma, metastatic, metastatic | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Histiocytic sarcoma, metastatic, metastatic      | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                   | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed                         | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin        | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Nose   | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Trachea  | + + M + + + + + + + + + + + + + + + + + + + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>SPECIAL SENSES SYSTEM</b>                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Harderian gland                                  | M M + + + + + + + + + + + + + + + + + + +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenoma  | M M + + + + + + + + + + + + + + + + + + +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Carcinoma  | M M + + + + + + + + + + + + + + + + + + +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                   | M M + + + + + + + + + + + + + + + + + + +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>URINARY SYSTEM</b>                            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Kidney   | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Histiocytic sarcoma, metastatic, metastatic      | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant lymphocytic                   | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Urinary bladder                                  | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Histiocytic sarcoma, metastatic                  | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed                         | + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |



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

| WEEKS ON STUDY                                   | 1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | TOTAL: TISSUES TUMORS |
|--|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|-----------------------|
|  | 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                       |
| CARCASS ID                                       | 5 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                       |
|  | 1 1 1 1 1 1 2 2 2 2 2 2 2 2 2 2 2 2 2 2 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                       |
|  | 9 9 9 9 9 9 0 0 0 0 0 0 0 0 0 0 0 0 0 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                       |
|  | 1 3 4 5 7 9 0 3 4 6 7 8 1 3 4 5 6 7 0 1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                       |
|  | 1 |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                       |
| <b>HEMATOPOIETIC SYSTEM</b>                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                       |
| Bone marrow                                      | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                    |
| Femoral, hemangiosarcoma                         | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                     |
| Lymph node                                       | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 49                    |
| Lumbar, histiocytic sarcoma, metastatic          | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                     |
| Mediastinal, lymphoma malignant lymphocytic      | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                     |
| Mediastinal, lymphoma malig mixed                | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X                     |
| Pancreatic, lymphoma malignant mixed             | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X                     |
| Lymph node, mandibular                           | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 49                    |
| Lymphoma malignant lymphocytic                   | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2                     |
| Lymphoma malignant mixed                         | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X                     |
| 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                     |
| Capsule, histiocytic sarcoma, metastatic         | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                     |
| Thymus   | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 45                    |
| Lymphoma malignant lymphocytic                   | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                     |
| Lymphoma malignant mixed                         | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X                     |
| <b>INTEGUMENTARY SYSTEM</b>                      |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                       |
| Mammary gland                                    | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 41                    |
| Adenocarcinoma                                   | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | M                     |
| 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                     |
| Scapula, squamous cell carcinoma, multiple       | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X                     |
| Sebacous gland, adenocarcinoma                   | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X                     |
| <b>MUSCULOSKELETAL SYSTEM</b>                    |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                       |
| Bone   | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                    |
| <b>NERVOUS SYSTEM</b>                            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                       |
| Brain  | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                    |
| <b>RESPIRATORY SYSTEM</b>                        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                       |
| Lung   | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                    |
| Adenocarcinoma, metastatic, mammary gland        | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                     |
| Alveolar/bronchiolar adenoma                     | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X                     |
| Alveolar/bronchiolar carcinoma                   | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 5                     |
| Hepatocellular carcinoma, metastatic, liver      | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 4                     |
| Hepatocellular carcinoma, metastatic, metastatic | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                     |
| Histiocytic sarcoma, metastatic, metastatic      | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X                     |
| Lymphoma malignant lymphocytic                   | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                     |
| Lymphoma malignant mixed                         | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 2                     |
| Squamous cell carcinoma, metastatic, skin        | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X                     |
| Nose   | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                     |
| Trachea  | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                    |
| <b>SPECIAL SENSES SYSTEM</b>                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                       |
| Harderian gland                                  | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 46                    |
| Adenoma  | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | M                     |
| Carcinoma  | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X                     |
| Lymphoma malignant lymphocytic                   | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X                     |
| <b>URINARY SYSTEM</b>                            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |                       |
| Kidney   | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 50                    |
| Histiocytic sarcoma, metastatic, metastatic      | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                     |
| Lymphoma malignant lymphocytic                   | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                     |
| Urinary bladder                                  | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 49                    |
| Histiocytic sarcoma, metastatic                  | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | 1                     |
| Lymphoma malignant mixed                         | +                                       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  | X                     |

**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<br>STUDY                                     | 0  |
|---|--|
|   | 0 0 0 5 6 6 6 7 7 8 8 8 8 8 8 8 8 9 9 9 9 9 9 9 9  |
| CARCASS<br>ID   | 1 1 7 8 3 5 7 1 1 1 1 2 2 3 3 4 5 6 7 3 6 6 7 7 8 8  |
|   | 3<br>1 3 2 0 3 3 2 2 4 3 2 1 1 2 2 3 0 5 2 0 4 4 0 4 0<br>4 4 2 1 7 6 1 0 9 8 6 6 2 4 3 2 4 0 8 5 5 7 2 1 9<br>1 |
| <b>ALIMENTARY SYSTEM</b>                              |  |
| Esophagus   | +  |
| Gallbladder   | +  |
| Lymphoma malignant histiocytic                        |  |
| Sarcoma, metastatic                                   |  |
| 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  |  |
| Hemangiosarcoma                                       |  |
| Hepatocellular carcinoma                              |  |
| Hepatocellular adenoma                                |  |
| Histiocytic sarcoma, metastatic, metastatic           |  |
| Lymphoma malignant histiocytic                        | X  |
| Mesentery   |  |
| Sarcoma, metastatic                                   |  |
| Pancreas  | +  |
| Histiocytic sarcoma, metastatic, metastatic           |  |
| Lymphoma malignant histiocytic                        | X  |
| Lymphoma malignant undifferentiated cell type         |  |
| Salivary glands                                       | +  |
| Lymphoma malignant histiocytic                        |  |
| Stomach   | +  |
| Stomach, forestomach                                  | +  |
| Papilloma squamous                                    |  |
| Stomach, glandular                                    | +  |
| Lymphoma malignant mixed                              |  |
| <b>CARDIOVASCULAR SYSTEM</b>                          |  |
| Blood vessel  | +  |
| Heart   |  |
| Histiocytic sarcoma, metastatic, metastatic           | X  |
| Squamous cell carcinoma, metastatic, skin             |  |
| <b>ENDOCRINE SYSTEM</b>                               |  |
| Adrenal gland   | +  |
| Leukemia granulocytic                                 |  |
| Bilateral capsule, adenoma                            |  |
| Capsule, adenoma                                      |  |
| 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                                |  |
| Pars distalis, carcinoma                              | X  |
| Thyroid gland   | +  |
| Follicular cell, adenoma                              |  |
| <b>GENERAL BODY SYSTEM</b>                            |  |
| None  |  |
| <b>GENITAL SYSTEM</b>                                 |  |
| Ovary   | +  |
| Granulosa cell tumor malignant                        |  |
| Granulosa cell tumor benign                           |  |
| Histiocytic sarcoma, metastatic, metastatic           | X  |
| Lymphoma malignant mixed                              |  |
| Mixed tumor benign                                    | 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  | 0         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|---|---|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|--|
|   | 0 0 0 5 6 6 6 7 7 8 8 8 8 8 8 8 8 8 9 9 9 9         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| CARCASS ID  | 1 1 7 8 3 5 7 1 1 1 2 2 3 3 4 5 6 7 3 6 6 7 7 8 8   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|   | 3         |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 1 3 2 0 3 3 2 2 4 3 2 1 1 2 2 3 0 5 2 0 4 4 0 4 0                 |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 4 4 2 1 7 6 1 0 9 8 6 6 2 4 3 2 4 0 8 5 5 7 2 1 9                 |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 1                   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>HEMATOPOIETIC SYSTEM</b>                                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 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   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lumbar, lymphoma malignant mixed                                  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mediastinal, lymphoma malignant histiocytic                       | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mediastinal, lymphoma malignant mixed                             |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mediastinal, lymphoma malignant undifferentiated cell type        |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mediastinal, squamous cell carcinoma, metastatic, skin            | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Pancreatic, lymphoma malignant histiocytic                        | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Renal, lymphoma malignant histiocytic                             | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Renal, lymphoma malignant mixed                                   | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mandibular  | + M + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Histiocytic sarcoma, metastatic                                   | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant histiocytic                                    | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Squamous cell carcinoma, metastatic, skin                         | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymph node, mesenteric  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant histiocytic                                    | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant mixed  | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Spleen  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Lymphoma malignant histiocytic                                    | 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       |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Thymoma benign  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>INTEGUMENTARY SYSTEM</b>                                       |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Mammary gland   | M + M + + + M + + M M + + X + + + + + + + + M + + + |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Adenocarcinoma  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| 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   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Scapula, squamous cell carcinoma, multiple                        | X X X X X X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Subcutaneous tissue, fibrosarcoma                                 |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Subcutaneous tissue, scapula, squamous cell carcinoma, metastatic |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>MUSCULOSKELETAL SYSTEM</b>                                     |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Bone  | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Osteosarcoma  |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Skeletal muscle   | +   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Back, sarcoma, metastatic   | X   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Intercostal, squamous cell carcinoma, metastatic, skin            |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| <b>NERVOUS SYSTEM</b>   |   |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Brain   | +     |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

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

| WEEKS ON STUDY  | 0 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | TOTAL TISSUES TUMORS |   |   |   |    |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----------------------|---|---|---|----|
|   | 9 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |    |
| CARCASS ID  | 9 0 1 1 3 4 4 4 4 4 5 5 5 5 5 5 5 5 5 5           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | TOTAL TISSUES TUMORS |   |   |   |    |
|   | 3           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |    |
|   | 1 4 2 1 1 3 3 3 4 4 0 0 0 0 1 1 1 3 2 2 3 4 4 4   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |    |
|   | 3 6 5 0 8 1 5 3 2 3 3 6 7 8 1 5 7 9 0 7 9 9 0 4 8 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |    |
|   | 1           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |    |
| <b>HEMATOPOIETIC SYSTEM</b>                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |    |
| Bone marrow   | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +                    | + | + | + | 50 |
| Lymph node  | +   | + | + | + | + | + | M | + | + | + | + | + | + | + | + | + | + | M | + | + | +                    | + | + | + | 47 |
| Squamous cell carcinoma, metastatic                               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   | 1  |
| Squamous cell carcinoma, metastatic, metastatic                   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   | 1  |
| Axillary, adenocarcinoma, metastatic, mammary gland               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   | 1  |
| Axillary, squamous cell carcinoma, metastatic, skin               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X                    |   |   |   | 1  |
| Lumbar, lymphoma malign histiocytic                               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   | 2  |
| Lumbar, lymphoma malignant mixed                                  |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   | 1  |
| Mediastinal, lymphoma malignant histiocytic                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   | 2  |
| Mediastinal, lymphoma malign 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                                    |   |   |   |   | X |   |   |   |   |   |   |   |   |   | X |   |   |   |   |   |                      |   |   |   | 2  |
| Lymphoma malignant mixed  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   | 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 | + | +                    | + | + | + | 33 |
| Thymoma benign  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   | X | 1  |
| <b>INTEGUMENTARY SYSTEM</b>                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |    |
| Mammary gland   | +   | + | + | + | + | 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  |
| <b>MUSCULOSKELETAL SYSTEM</b>                                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |    |
| Bone  | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +                    | + | + | + | 49 |
| Osteosarcoma  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      | X |   |   | 1  |
| Skeletal muscle   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   | 2  |
| Back, sarcoma, metastatic   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   | 1  |
| Intercostal, squamous cell carcinoma, metastatic, skin            |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   | 1  |
| <b>NERVOUS SYSTEM</b>   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |    |
| Brain   | +   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | +                    | + | + | + | 50 |

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

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



**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 | 2 | 2 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 | 6 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |
| CARCASS ID   | 1 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|  | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| <b>ALIMENTARY SYSTEM</b>                                 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 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                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 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  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>CARDIOVASCULAR SYSTEM</b>                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Blood vessel   | + | + |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Heart  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant lymphocytic                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |
| Squamous cell carcinoma, metastatic                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |
| Squamous cell carcinoma, metastatic, skin                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>ENDOCRINE SYSTEM</b>                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Adrenal gland  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Capsule, adenoma   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |
| Capsule, carcinoma                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |
| 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  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| <b>GENERAL BODY SYSTEM</b>                               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| None   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| <b>GENITAL SYSTEM</b>                                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Ovary  | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Granulosa cell tumor malignant                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Granulosa cell tumor benign                              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| Lymphoma malignant lymphocytic                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |
| Mixed tumor benign                                       |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |
| Uterus   | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Lymphoma malignant lymphocytic                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | X |
| Polyp stromal  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |







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

| WEEKS ON STUDY   | 0 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | TOTAL TISSUES TUMORS |   |   |   |   |
|--|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|----------------------|---|---|---|---|
|  | 7 7 7 7 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |   |
| CARCASS ID   | 8 9 9 9 0 0 1 3 3 3 3 3 3 3 5 5 5 5 5 5 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |   |
|  | 4 |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |   |
| <b>HEMATOPOIETIC SYSTEM</b>                              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |   |
| 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        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 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 | + | + | + | + | + | 33                   |   |   |   |   |
| Squamous cell carcinoma, metastatic                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | M | +                    | 1 |   |   |   |
| <b>INTEGUMENTARY SYSTEM</b>                              |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |   |
| Mammary gland  | +                                       | M | M | I | + | + | M | + | + | + | + | + | + | + | + | + | + | + | + | + | 39                   |   |   |   |   |
| Adenocarcinoma   |   |   |   |   |   |   |   | X | X |   | X |   |   |   |   |   |   |   | X | M | +                    | + | + | + | 4 |
| Skin   | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |   |   |   |   |
| Lymphoma malignant lymphocytic                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |   |   |   |   |
| Squamous cell carcinoma                                  |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   | 2                    |   |   |   |   |
| Squamous cell carcinoma, multiple                        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 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               |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 10                   |   |   |   |   |
| Scapula, squamous cell carcinoma, metastatic             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |   |   |   |   |
| Scapula, squamous cell carcinoma, metastatic, multiple   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |   |   |   |   |
| <b>MUSCULOSKELETAL SYSTEM</b>                            |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |   |
| Bone   | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |   |   |   |   |
| Skeletal muscle  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |   |   |   |   |
| Intercostal, squamous cell carcinoma, metastatic, skin   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |   |   |   |   |
| Neck, lymphoma malignant lymphocytic                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |   |   |   |   |
| <b>NERVOUS SYSTEM</b>                                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |   |
| Brain  | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |   |   |   |   |
| Lymphoma malignant lymphocytic                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |   |   |   |   |
| <b>RESPIRATORY SYSTEM</b>                                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |   |
| Lung   | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |   |   |   |   |
| Adenocarcinoma, metastatic, mammary gland                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |   |   |   |   |
| Alveolar/bronchiolar adenoma                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 6                    |   |   |   |   |
| Alveolar/bronchiolar carcinoma                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |   |   |   |   |
| Granulosa cell tumor malignant, metastatic, ovary        |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |   |   |   |   |
| Lymphoma malignant lymphocytic                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |   |   |   |   |
| Squamous cell carcinoma, metastatic                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 2                    |   |   |   |   |
| Squamous cell carcinoma, metastatic, skin                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 18                   |   |   |   |   |
| Bronchiole, adenocarcinoma, metastatic                   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |   |   |   |   |
| Nose   | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |   |   |   |   |
| Trachea  | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |   |   |   |   |
| <b>SPECIAL SENSES SYSTEM</b>                             |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |   |
| Hardenian gland  | +                                       | + | + | + | + | + | + | I | + | + | + | + | + | + | + | + | + | + | + | + | 45                   |   |   |   |   |
| Adenoma  |   |   |   |   |   |   |   |   | X |   |   |   |   |   |   |   |   |   |   |   | 8                    |   |   |   |   |
| Lymphoma malignant lymphocytic                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |   |   |   |   |
| <b>URINARY SYSTEM</b>                                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |                      |   |   |   |   |
| Kidney   | +                                       | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | 50                   |   |   |   |   |
| Lymphoma malignant lymphocytic                           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |   |   |   |   |
| Squamous cell carcinoma                                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 1                    |   |   |   |   |
| Squamous cell carcinoma, metastatic                      |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   | 3                    |   |   |   |   |
| 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 |
|--|-----------------|--------------|------------|-------------|
| <b>Adrenal Gland Capsule: Adenoma</b>              |                 |              |            |             |
| 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     |
| <b>Adrenal Gland Capsule: Adenoma or Carcinoma</b> |                 |              |            |             |
| 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     |
| <b>Harderian Gland: Adenoma</b>                    |                 |              |            |             |
| Overall Rates (a)                                  | 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     |
| <b>Harderian Gland: Adenoma or Carcinoma</b>       |                 |              |            |             |
| Overall Rates (a)                                  | 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     |
| <b>Liver: Hepatocellular Adenoma</b>               |                 |              |            |             |
| 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    |
| <b>Liver: Hepatocellular Carcinoma</b>             |                 |              |            |             |
| 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 |
|--|-----------------|--------------|-------------|-------------|
| <b>Liver: Hepatocellular Adenoma or Carcinoma</b>      |                 |              |             |             |
| 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    |
| <b>Lung: Alveolar/Bronchiolar Adenoma</b>              |                 |              |             |             |
| 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     |
| <b>Lung: Alveolar/Bronchiolar Carcinoma</b>            |                 |              |             |             |
| 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    |
| <b>Lung: Alveolar/Bronchiolar Adenoma or Carcinoma</b> |                 |              |             |             |
| 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     |
| <b>Mammary Gland: Adenocarcinoma</b>                   |                 |              |             |             |
| 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     |
| <b>Ovary: Granulosa Cell Tumor</b>                     |                 |              |             |             |
| 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 |
|--|-----------------|--------------|-------------|-------------|
| <b>Ovary: Granulosa Cell Tumor or Malignant Granulosa Cell Tumor</b>                               |                 |              |             |             |
| 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     |
| <b>Ovary: Benign Mixed Tumor</b>   |                 |              |             |             |
| 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     |
| <b>Ovary: Luteoma, Granulosa Cell Tumor, or Benign Mixed Tumor</b>                                 |                 |              |             |             |
| 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     |
| <b>Ovary: Luteoma, Granulosa Cell Tumor, Benign Mixed Tumor, or Malignant Granulosa Cell Tumor</b> |                 |              |             |             |
| 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     |
| <b>Pituitary Gland/Pars Distalis: Adenoma</b>  |                 |              |             |             |
| 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    |
| <b>Pituitary Gland/Pars Distalis: Adenoma or Carcinoma</b>   |                 |              |             |             |
| 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 |
|--|-----------------|--------------|--------------|-------------|
| <b>Skin (Application Site): Squamous Cell Carcinoma</b>  |                 |              |              |             |
| 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     |
| <b>Skin (All Sites): Squamous Cell Carcinoma</b>         |                 |              |              |             |
| 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     |
| <b>Forestomach: Squamous Papilloma</b>                   |                 |              |              |             |
| 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    |
| <b>Circulatory System: Hemangioma</b>                    |                 |              |              |             |
| 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    |
| <b>Circulatory System: Hemangioma or Hemangiosarcoma</b> |                 |              |              |             |
| 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    |
| <b>Hematopoietic System: Lymphoma, All Malignant</b>     |                 |              |              |             |
| 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 |
|------------------------------------|-----------------|--------------|--------------|-------------|
| <b>All Sites: Benign Tumors</b>    |                 |              |              |             |
| 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    |
| <b>All Sites: Malignant Tumors</b> |                 |              |              |             |
| 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     |
| <b>All Sites: All Tumors</b>       |                 |              |              |             |
| 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<sub>1</sub> MICE (a)**

| Study  | Incidence in Controls |                |                        |
|--|-----------------------|----------------|------------------------|
|  | Papilloma             | Carcinoma      | Papilloma or Carcinoma |
| <b>Historical Incidence in Dermal Studies Using Acetone as a Vehicle (b)</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%)            |
| <b>Overall Historical Incidence for Untreated Controls</b>                   |                       |                |                        |
| TOTAL  | 2/1,689 (0.1%)        | 2/1,689 (0.1%) | 4/1,689 (0.2%)         |
| SD (c)   | 0.49%                 | 0.49%          | 0.84%                  |
| <b>Range (d)</b>   |                       |                |                        |
| 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<sub>1</sub> MICE (a)**

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

| Study  | Incidence in Controls |                 |                      |
|--|-----------------------|-----------------|----------------------|
|  | Adenoma               | Carcinoma       | Adenoma or Carcinoma |
| <b>Historical Incidence in Dermal Studies Using Acetone as a Vehicle (b)</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%)          |
| <b>Overall Historical Incidence for Untreated Controls</b>                   |                       |                 |                      |
| TOTAL  | 73/1,676 (4.4%)       | 35/1,676 (2.1%) | 107/1,676 (6.4%)     |
| SD (c)   | 3.35%                 | 1.68%           | 3.76%                |
| <b>Range (d)</b>   |                       |                 |                      |
| 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          |
| <b>ALIMENTARY SYSTEM</b>                 |                 |              |            |             |
| 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 |
|---|-----------------|--------------|------------|-------------|
| <b>CARDIOVASCULAR SYSTEM</b>                  |                 |              |            |             |
| 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%)     |             |
| <b>ENDOCRINE SYSTEM</b>                       |                 |              |            |             |
| 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%)    |             |
| <b>GENERAL BODY SYSTEM</b>                    |                 |              |            |             |
| None  |                 |              |            |             |
| <b>GENITAL SYSTEM</b>                         |                 |              |            |             |
| 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 |
|---|-----------------|--------------|------------|-------------|
| <b>GENITAL SYSTEM (Continued)</b>                     |                 |              |            |             |
| 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%)    |
| <b>HEMATOPOIETIC SYSTEM</b>                           |                 |              |            |             |
| 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%)     |             |
| <b>INTEGUMENTARY SYSTEM</b>                           |                 |              |            |             |
| 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 |
|--|-----------------|--------------|------------|-------------|
| <b>INTEGUMENTARY SYSTEM</b>                        |                 |              |            |             |
| 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%)          |              |            |             |
| <b>MUSCULOSKELETAL SYSTEM</b>                      |                 |              |            |             |
| Bone   | (50)            | (50)         | (49)       | (50)        |
| Humerus, proliferation                             |                 |              | 1 (2%)     |             |
| Skeletal muscle                                    | (1)             |              | (2)        | (2)         |
| Abdominal, inflammation, acute                     | 1 (100%)        |              |            |             |
| <b>NERVOUS SYSTEM</b>                              |                 |              |            |             |
| 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%)     |             |
| <b>RESPIRATORY SYSTEM</b>                          |                 |              |            |             |
| 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%)      |
| Interstitial, inflammation, chronic                | 1 (2%)          |              |            |             |
| Nose   | (50)            | (50)         | (50)       | (50)        |
| Glands, inflammation, acute                        |                 |              |            | 1 (2%)      |
| Nerve, nares, inflammation, subacute               |                 |              |            | 1 (2%)      |
| <b>SPECIAL SENSES SYSTEM</b>                       |                 |              |            |             |
| Harderian gland                                    | (43)            | (46)         | (42)       | (45)        |
| Hyperplasia  | 1 (2%)          |              |            |             |
| Hyperplasia, nodular                               |                 |              |            | 1 (2%)      |
| Inflammation, necrotizing                          |                 |              |            | 1 (2%)      |
| Inflammation, subacute                             |                 |              | 2 (5%)     | 3 (7%)      |
| <b>URINARY SYSTEM</b>                              |                 |              |            |             |
| 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

|   | PAGE |
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| TABLE E1 MURINE ANTIBODY DETERMINATIONS FOR RATS AND MICE IN THE TWO-YEAR DERMAL STUDIES OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE | 191  |

# APPENDIX E. SENTINEL ANIMAL PROGRAM

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## 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<sub>1</sub> 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:

|      | <u>Hemagglutination<br/>Inhibition</u>   | <u>Complement<br/>Fixation</u>  | <u>ELISA</u>   |
|------|--|---|--|
| Mice | PVM (pneumonia virus of mice)<br>Reo 3 (reovirus type 3)<br>GDVII (Theiler's encephalomyelitis virus) (6,18 mo)<br>Poly (polyoma virus)<br>MVM (minute virus of mice)<br>Ectro (infectious ectromelia)<br>Sendai | M. Ad. (mouse adenovirus)<br>LCM (lymphocytic choriomeningitis virus) | MHV (mouse hepatitis virus)<br>GDVII (24 mo)   |
| Rats | PVM (6,12,18 mo)<br>KRV (Kilham rat virus)<br>H-1 (Toolan's H-1 virus)<br>Sendai (6,12,18 mo)  | RCV (rat coronavirus) (6 mo)  | RCV/SDA (sialodacryoadenitis virus) (12,18,24 mo)<br><i>M. pul.</i> ( <i>Mycoplasma pulmonis</i> ) (24 mo)<br>PVM (24 mo)<br>Sendai (24 mo)<br><i>M. arth.</i> ( <i>Mycoplasma arthritidis</i> ) (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 |
|-------------------|-------------------|---------------------------------|
| <b>RATS</b>       |                   |                                 |
| 6                 | (b)               | None positive                   |
| 12                | 4/10              | PVM                             |
| 18                | (b)               | None positive                   |
| 24                | 7/10<br>5/8       | PVM<br><i>M. arth.</i>          |
| <b>MICE</b>       |                   |                                 |
| 6                 | 9/10              | MHV                             |
| 12                | (c)               | --                              |
| (d) 18            | 3/10<br>10/10     | PVM<br>MHV                      |
| 24                | 2/10<br>10/10     | PVM<br>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)

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**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                                    |
|---|---------------|---|
| <b>Vitamins</b>                         |               |   |
| A                                       | 5,500,000 IU  | Stabilized vitamin A palmitate or acetate |
| D <sub>3</sub>                          | 4,600,000 IU  | D-activated animal sterol                 |
| K <sub>3</sub>                          | 2.8 g         | Menadione                                 |
| <i>d</i> - $\alpha$ -Tocopheryl acetate | 20,000 IU     |   |
| Choline                                 | 560.0 g       | Choline chloride                          |
| Folic acid                              | 2.2 g         |   |
| Niacin                                  | 30.0 g        |   |
| <i>d</i> -Pantothenic acid              | 18.0 g        | <i>d</i> -Calcium pantothenate            |
| Riboflavin                              | 3.4 g         |   |
| Thiamine                                | 10.0 g        | Thiamine mononitrate                      |
| B <sub>12</sub>                         | 4,000 $\mu$ g |   |
| Pyridoxine                              | 1.7 g         | Pyridoxine hydrochloride                  |
| Biotin                                  | 140.0 mg      | <i>d</i> -Biotin                          |
| <b>Minerals</b>                         |               |   |
| 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 $\pm$ Standard Deviation | Range        | Number of Samples |
|--|-------------------------------|--------------|-------------------|
| Protein (percent by weight)                          | 23.07 $\pm$ 1.06              | 21.3-26.3    | 26                |
| Crude fat (percent by weight)                        | 5.20 $\pm$ 0.66               | 3.3-6.5      | 26                |
| Crude fiber (percent by weight)                      | 3.49 $\pm$ 0.52               | 2.8-5.6      | 26                |
| Ash (percent by weight)                              | 6.63 $\pm$ 0.34               | 6.1-7.3      | 26                |
| <b>Amino Acids (percent of total diet)</b>           |                               |              |                   |
| Arginine   | 1.32 $\pm$ 0.072              | 1.310-1.390  | 5                 |
| Cystine  | 0.319 $\pm$ 0.088             | 0.218-0.400  | 5                 |
| Glycine  | 1.146 $\pm$ 0.063             | 1.060-1.210  | 5                 |
| Histidine  | 0.571 $\pm$ 0.026             | 0.531-0.603  | 5                 |
| Isoleucine   | 0.914 $\pm$ 0.030             | 0.881-0.944  | 5                 |
| Leucine  | 1.946 $\pm$ 0.056             | 1.850-1.990  | 5                 |
| Lysine   | 1.280 $\pm$ 0.067             | 1.200-1.370  | 5                 |
| Methionine   | 0.436 $\pm$ 0.165             | 0.306-0.699  | 5                 |
| Phenylalanine  | 0.938 $\pm$ 0.158             | 0.665-1.05   | 5                 |
| Threonine  | 0.855 $\pm$ 0.035             | 0.824-0.898  | 5                 |
| Tryptophan   | 0.277 $\pm$ 0.221             | 0.156-0.671  | 5                 |
| Tyrosine   | 0.618 $\pm$ 0.086             | 0.564-0.769  | 5                 |
| Valine   | 1.108 $\pm$ 0.043             | 1.050-1.170  | 5                 |
| <b>Essential Fatty Acids (percent of total diet)</b> |                               |              |                   |
| Linoleic   | 2.290 $\pm$ 0.313             | 1.83-2.52    | 5                 |
| Linolenic  | 0.258 $\pm$ 0.040             | 0.210-0.308  | 5                 |
| <b>Vitamins</b>                                      |                               |              |                   |
| Vitamin A (IU/kg)                                    | 12,269 $\pm$ 4,639            | 4,100-24,000 | 26                |
| Vitamin D (IU/kg)                                    | 4,450 $\pm$ 1,382             | 3,000-6,300  | 4                 |
| $\alpha$ -Tocopherol (ppm)                           | 43.58 $\pm$ 6.92              | 31.1-48.0    | 5                 |
| Thiamine (ppm)                                       | 17.89 $\pm$ 3.9               | 12.0-27.0    | 26                |
| Riboflavin (ppm)                                     | 7.6 $\pm$ 0.85                | 6.10-8.2     | 5                 |
| Niacin (ppm)   | 97.8 $\pm$ 31.68              | 65.0-150.0   | 5                 |
| Pantothenic acid (ppm)                               | 30.06 $\pm$ 4.31              | 23.0-34.0    | 5                 |
| Pyridoxine (ppm)                                     | 7.68 $\pm$ 1.31               | 5.60-8.8     | 5                 |
| Folic acid (ppm)                                     | 2.62 $\pm$ 0.89               | 1.80-3.7     | 5                 |
| Biotin (ppm)   | 0.254 $\pm$ 0.053             | 0.19-0.32    | 5                 |
| Vitamin B <sub>12</sub> (ppb)                        | 24.21 $\pm$ 12.66             | 10.6-38.0    | 5                 |
| Choline (ppm)  | 3,122 $\pm$ 416.8             | 2,400-3,430  | 5                 |
| <b>Minerals</b>                                      |                               |              |                   |
| Calcium (percent) (a)                                | 1.30 $\pm$ 0.15               | 0.95-1.63    | 25                |
| Phosphorus (percent)                                 | 0.96 $\pm$ 0.06               | 0.87-1.10    | 26                |
| Potassium (percent)                                  | 0.900 $\pm$ 0.098             | 0.772-0.971  | 3                 |
| Chloride (percent)                                   | 0.513 $\pm$ 0.114             | 0.380-0.635  | 5                 |
| Sodium (percent)                                     | 0.323 $\pm$ 0.043             | 0.258-0.371  | 5                 |
| Magnesium (percent)                                  | 0.167 $\pm$ 0.012             | 0.151-0.181  | 5                 |
| Sulfur (percent)                                     | 0.304 $\pm$ 0.064             | 0.268-0.420  | 5                 |
| Iron (ppm)   | 410.3 $\pm$ 94.04             | 262.0-523.0  | 5                 |
| Manganese (ppm)                                      | 90.29 $\pm$ 7.15              | 81.7-99.4    | 5                 |
| Zinc (ppm)   | 52.78 $\pm$ 4.94              | 46.1-58.2    | 5                 |
| Copper (ppm)   | 10.72 $\pm$ 2.76              | 8.09-15.39   | 5                 |
| Iodine (ppm)   | 2.95 $\pm$ 1.05               | 1.52-3.82    | 4                 |
| Chromium (ppm)                                       | 1.85 $\pm$ 0.25               | 1.44-2.09    | 5                 |
| Cobalt (ppm)   | 0.681 $\pm$ 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                |
| <i>E. coli</i> (MPN/g)                   | 3.0                       |               | 26                |
| Total nitrosamines (ppb) (f)             | 5.65 ± 5.66               | 1.8-30.9      | 26                |
| <i>N</i> -Nitrosodimethylamine (ppb) (f) | 4.61 ± 5.68               | 0.8-30.0      | 26                |
| <i>N</i> -Nitrosopyrrolidine (ppb) (f)   | 1.04 ± 0.24               | 0.81-1.7      | 26                |
| <b>Pesticides (ppm)</b>                  |                           |               |                   |
| 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

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## APPENDIX G. FIVE-DAY DERMAL STUDY

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### 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<sub>1</sub> 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, sub-optimal, 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<sup>6</sup> 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<sub>1</sub> 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<br>(per 10 <sup>6</sup> viable nucleated<br>spleen cells) | 1,394 ± 79.4    | 1,502 ± 166.3 | 1,090 ± 101.7 | **723 ± 98.5 |
| Plaque-forming cells<br>(×10 <sup>-3</sup> 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<sup>3</sup>/mm<sup>3</sup>, 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<sup>3</sup>/mm<sup>3</sup>. 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

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# 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  $\pm 10\%$  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   |
|---|---|---|
| <b>Preparation</b><br>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 |
| <b>Maximum Storage Time</b><br>7 d  | 16 d  | 14 d  |
| <b>Storage Conditions</b><br>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

## APPENDIX H. GAVAGE STUDIES

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### 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<sub>1</sub> 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<sub>1</sub> 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  |
|--|--|--|
| <b>EXPERIMENTAL DESIGN</b>   |  |  |
| <b>Size of Study Groups</b><br>5 males and 5 females of each species   | 5 males and 5 females of each species  | 10 males and 10 females of each species  |
| <b>Doses</b><br>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   |
| <b>Date of First Dose</b><br>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)   |
| <b>Date of Last Dose</b><br>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)  |
| <b>Duration of Dosing</b><br>Single dose   | 12 doses over 16 d   | 5 d/wk for 13 wk   |
| <b>Type and Frequency of Observation</b><br>Observed 2 × d; weighed initially  | Observed 2 × d; weighed initially and 1 × wk thereafter  | Same as 16-d studies   |
| <b>Necropsy, Histologic Examinations, and Supplemental Analyses</b><br>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 on 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 |
| <b>ANIMALS AND ANIMAL MAINTENANCE</b>  |  |  |
| <b>Strain and Species</b><br>F344/N rats; B6C3F <sub>1</sub> mice  | F344/N rats; B6C3F <sub>1</sub> mice   | F344/N rats; B6C3F <sub>1</sub> mice   |
| <b>Animal Source</b><br>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  |
|--|--|--|
| <b>ANIMALS AND ANIMAL MAINTENANCE (Continued)</b>  |  |  |
| <b>Study Laboratory</b><br>Battelle Columbus Laboratories  | Battelle Columbus Laboratories   | Battelle Columbus Laboratories   |
| <b>Method of Animal Identification</b><br>Toe clip   | Toe clip   | Toe clip   |
| <b>Time Held Before Study</b><br>14 d  | Rats--12 d; mice--13 d   | Rats--14 or 15 d; mice--22 or 23 d   |
| <b>Age When Placed on Study</b><br>Rats--7 wk; mice--8 wk  | Rats--6 wk; mice--7 wk   | Rats--6-7 wk; mice--9 wk   |
| <b>Age When Killed</b><br>Rats--9 wk; mice--10 wk  | Rats--9 wk; mice--10 wk  | Rats--19-20 wk; mice--22 wk  |
| <b>Necropsy Dates</b><br>4/3/81  | 6/12/81  | Rats--12/3/81-12/4/81;<br>mice--12/1/81-12/2/81                                |
| <b>Method of Animal Distribution</b><br>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  |
| <b>Diet</b><br>NIH 07 Rat and Mouse Ration (Zeigler Bros., Inc., Gardners, PA); available ad libitum   | Same as single-administration studies  | Same as single-administration studies  |
| <b>Bedding</b><br>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)                         |
| <b>Water</b><br>Automatic watering system (Edstrom Industries, Waterford, WI); available ad libitum  | Same as single-administration studies  | Same as single-administration studies  |
| <b>Cages</b><br>Polycarbonate (Lab Products, Inc., Rochelle Park, NJ)  | Same as single-administration studies  | Same as single-administration studies  |
| <b>Cage Filters</b><br>Spun-bonded polyester, Dupont 2024® (Snow Filtration, Cincinnati, OH)   | Same as single-administration studies  | Same as single-administration studies  |
| <b>Animals per Cage</b><br>5   | 5  | 5  |
| <b>Other Chemicals on Study in the Same Room</b><br>None   | None   | None   |
| <b>Animal Room Environment</b><br>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 |

# APPENDIX H. GAVAGE STUDIES

## 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<br>(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<sub>50</sub> by Spearman-Kärber 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) |         |            | Final Weight Relative to Vehicle Controls (percent) |
|---------------|--------------|---------------------------|---------|------------|---|
|               |              | Initial (b)               | Final   | Change (c) |   |
| <b>MALE</b>   |              |                           |         |            |   |
| 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)   |
| <b>FEMALE</b> |              |                           |         |            |   |
| 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  |
|---------------|-----------------|-------------|-------------|-------------|--------------|
| <b>MALE</b>   |                 |             |             |             |              |
| 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   |
| <b>FEMALE</b> |                 |             |             |             |              |
| 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

# APPENDIX H. GAVAGE STUDIES

## 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<br>(mg/kg) | Survival (a) | Mean Body Weights (grams) |          |            | Final Weight Relative<br>to Vehicle Controls<br>(percent) |
|-----------------|--------------|---------------------------|----------|------------|---|
|                 |              | Initial (b)               | Final    | Change (c) |   |
| <b>MALE</b>     |              |                           |          |            |   |
| 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  |
| <b>FEMALE</b>   |              |                           |          |            |   |
| 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   |
|-----------------|-----------------|-------------|-------------|-------------|---------------|---------------|
| <b>MALE</b>     |                 |             |             |             |               |               |
| 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  |
| <b>FEMALE</b>   |                 |             |             |             |               |               |
| 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  |
|-------------------|-----------------|--------------|--------------|--------------|--------------|--------------|
| <b>MALE</b>       |                 |              |              |              |              |              |
| 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 |
| <b>FEMALE</b>     |                 |              |              |              |              |              |
| 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<sup>7</sup> 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  |
|---|-----------------|---------------|--------------|----------------|----------------|--------------|
| <b>MALE</b>                                 |                 |               |              |                |                |              |
| Number examined (b)                         | 7               | 8             | 8            | 8              | 7              | 5            |
| Leukocytes (10 <sup>3</sup> /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 <sup>3</sup> /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 <sup>3</sup> /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 <sup>3</sup> /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 <sup>3</sup> /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 <sup>3</sup> )   | 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 <sup>3</sup> /μl)             | 539 ± 18.3      | 570 ± 13.4    | 553 ± 11.9   | 534 ± 13.4     | 537 ± 21.0     | 590 ± 22.0   |
| Erythrocytes (10 <sup>6</sup> /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   |
| <b>FEMALE</b>                               |                 |               |              |                |                |              |
| Number examined (b)                         | 8               | 10            | 7            | 9              | 8              | 2            |
| Leukocytes (10 <sup>3</sup> /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 <sup>3</sup> /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 <sup>3</sup> /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 <sup>3</sup> /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 <sup>3</sup> /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 <sup>3</sup> )   | 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 <sup>3</sup> /μl)             | 555 ± 11.2      | 547 ± 13.7    | 597 ± 15.0   | 562 ± 10.0     | *601 ± 9.5     | 554 ± 16.5   |
| Erythrocytes (10 <sup>6</sup> /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

# APPENDIX H. GAVAGE STUDIES

## 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<br>(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<sub>50</sub> by probit analysis: 1,862 mg/kg (95% confidence interval 1,080-3,194 mg/kg)

(b) LD<sub>50</sub> 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<br>(mg/kg) | Survival (a) | Mean Body Weights (grams) |             |             | Final Weight Relative<br>to Vehicle Controls<br>(percent) |
|-----------------|--------------|---------------------------|-------------|-------------|---|
|                 |              | Initial (b)               | Final       | Change (c)  |   |
| <b>MALE</b>     |              |                           |             |             |   |
| 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)   |
| <b>FEMALE</b>   |              |                           |             |             |   |
| 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 |
|----------------|-----------------|--------------|-------------|-------------|-------------|
| <b>MALE</b>    |                 |              |             |             |             |
| 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  |
| <b>FEMALE</b>  |                 |              |             |             |             |
| 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

## APPENDIX H. GAVAGE STUDIES

### 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<br>(mg/kg) | Survival (a) | Mean Body Weights (grams) |            |             | Final Weight Relative<br>to Vehicle Controls<br>(percent) |
|-----------------|--------------|---------------------------|------------|-------------|---|
|                 |              | Initial (b)               | Final      | Change (c)  |   |
| <b>MALE</b>     |              |                           |            |             |   |
| 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  |
| <b>FEMALE</b>   |              |                           |            |             |   |
| 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     |
|--------------------|-----------------|---------------|--------------|---------------|--------------|-----------------|
| <b>MALE</b>        |                 |               |              |               |              |                 |
| 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    |
| <b>FEMALE</b>      |                 |               |              |               |              |                 |
| 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

|          |  | PAGE |
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**TABLE 11. 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    |
|---------------|-----------------|--------------|--------------|-------------|--------------|
| <b>MALE</b>   |                 |              |              |             |              |
| 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   |
| <b>FEMALE</b> |                 |              |              |             |              |
| 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 12. 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    |
|-----------------|-----------------|-------------|-------------|-------------|--------------|--------------|
| <b>MALE</b>     |                 |             |             |             |              |              |
| 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 |
| <b>FEMALE</b>   |                 |             |             |             |              |              |
| 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    |
|-------------------|-----------------|--------------|--------------|--------------|--------------|--------------|
| <b>MALE</b>       |                 |              |              |              |              |              |
| 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 |
| <b>FEMALE</b>     |                 |              |              |              |              |              |
| 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<sup>7</sup> 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    |
|---|-----------------|--------------|--------------|-----------------|--------------|--------------|
| <b>MALE</b>                                       |                 |              |              |                 |              |              |
| 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 <sup>6</sup> /mm <sup>3</sup> )  | 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 <sup>3</sup> /mm <sup>3</sup> ) | 109 ± 10.7      | 111 ± 12.6   | 117 ± 13.4   | 88 ± 8.3        | 104 ± 13.8   | 115 ± 15.8   |
| Leukocytes (10 <sup>3</sup> /mm <sup>3</sup> )    | 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   |
| <b>FEMALE</b>                                     |                 |              |              |                 |              |              |
| 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 <sup>6</sup> /mm <sup>3</sup> )  | 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 <sup>3</sup> /mm <sup>3</sup> ) | 150 ± 190       | 125 ± 21.8   | 112 ± 11.2   | 121 ± 13.3      | 129 ± 14.6   | 99 ± 16.2    |
| Leukocytes (10 <sup>3</sup> /mm <sup>3</sup> )    | 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 15. 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 |
|----------------|-----------------|-------------|-------------|-------------|---------------|--------------|--------------|
| <b>MALE</b>    |                 |             |             |             |               |              |              |
| 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   |
| <b>FEMALE</b>  |                 |             |             |             |               |              |              |
| 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 16. 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   |
|-----------------|-----------------|----------------|---------------|---------------|---------------|---------------|
| <b>MALE</b>     |                 |                |               |               |               |               |
| 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    |
| <b>FEMALE</b>   |                 |                |               |               |               |               |
| 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

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**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    |
|-----------------|-----------------|-------------|--------------|
| <b>MALE</b>     |                 |             |              |
| 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   |
| <b>FEMALE</b>   |                 |             |              |
| 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       |
|--|-----------------|-------------|-----------------|
| <b>MALE</b>  |                 |             |                 |
| Number examined  | 10              | 10          | 10              |
| Leukocytes (10 <sup>3</sup> /mm <sup>3</sup> )             | 5.37 ± 0.54     | 5.57 ± 0.26 | 5.02 ± 0.44     |
| Lymphocytes (10 <sup>3</sup> /mm <sup>3</sup> )            | 3.17 ± 0.47     | 3.38 ± 0.22 | 2.81 ± 0.29     |
| Segmented neutrophils (10 <sup>3</sup> /mm <sup>3</sup> )  | 2.11 ± 0.18     | 2.12 ± 0.09 | 2.14 ± 0.21     |
| Eosinophils (10 <sup>3</sup> /mm <sup>3</sup> )            | 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 <sup>3</sup> )                  | 50.9 ± 0.55     | 51.3 ± 0.54 | 51.9 ± 0.48     |
| Nucleated erythrocytes (10 <sup>3</sup> /mm <sup>3</sup> ) | 0.90 ± 0.50     | 1.80 ± 0.68 | 0.90 ± 0.35     |
| Platelets (10 <sup>3</sup> /mm <sup>3</sup> )              | 485 ± 37.6      | 457 ± 21.7  | 424 ± 33.1      |
| Erythrocytes (10 <sup>6</sup> /mm <sup>3</sup> )           | 8.89 ± 0.13     | 9.14 ± 0.11 | 8.87 ± 0.26     |
| Reticulocytes (10 <sup>6</sup> /mm <sup>3</sup> )          | 0.19 ± 0.02     | 0.17 ± 0.02 | 0.17 ± 0.01     |
| <b>FEMALE</b>  |                 |             |                 |
| Number examined (b)  | 9               | 10          | 10              |
| Leukocytes (10 <sup>3</sup> /mm <sup>3</sup> )             | 2.82 ± 0.15     | 2.75 ± 0.17 | 3.40 ± 0.36     |
| Lymphocytes (10 <sup>3</sup> /mm <sup>3</sup> )            | 1.71 ± 0.09     | 1.83 ± 0.08 | 2.02 ± 0.12     |
| Segmented neutrophils (10 <sup>3</sup> /mm <sup>3</sup> )  | 1.03 ± 0.09     | 0.87 ± 0.09 | 1.29 ± 0.27     |
| Eosinophils (10 <sup>3</sup> /mm <sup>3</sup> )            | 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 <sup>3</sup> )                  | 53.4 ± 0.47     | 53.7 ± 0.26 | 54.3 ± 1.25     |
| Nucleated erythrocytes (10 <sup>3</sup> /mm <sup>3</sup> ) | 1.11 ± 0.26     | 2.50 ± 0.81 | 2.60 ± 1.14     |
| Platelets (10 <sup>3</sup> /mm <sup>3</sup> )              | 381 ± 17.0      | 410 ± 24.0  | 397 ± 32.7      |
| Erythrocytes (10 <sup>6</sup> /mm <sup>3</sup> )           | 8.23 ± 0.08     | 8.24 ± 0.11 | 7.48 ± 0.57     |
| Reticulocytes (10 <sup>6</sup> /mm <sup>3</sup> )          | 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    |
|-----------------|-----------------|-----------------|--------------|----------------|
| <b>MALE</b>     |                 |                 |              |                |
| 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     |
| <b>FEMALE</b>   |                 |                 |              |                |
| 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     |
|---|-----------------|---------------|----------------|-----------------|
| <b>MALE</b>   |                 |               |                |                 |
| Leukocytes (10 <sup>3</sup> /mm <sup>3</sup> )            | 3.92 ± 0.409    | 4.26 ± 0.358  | 4.52 ± 0.517   | **11.34 ± 2.734 |
| Lymphocytes (10 <sup>3</sup> /mm <sup>3</sup> )           | 2.95 ± 0.286    | 3.14 ± 0.280  | 3.18 ± 0.323   | *5.06 ± 0.717   |
| Segmented neutrophils (10 <sup>3</sup> /mm <sup>3</sup> ) | 0.90 ± 0.149    | 0.98 ± 0.124  | 1.25 ± 0.230   | *5.93 ± 2.277   |
| Eosinophils (10 <sup>3</sup> /mm <sup>3</sup> )           | 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 <sup>3</sup> )                 | 44.2 ± 0.36     | 43.5 ± 0.40   | 44.0 ± 0.26    | 44.7 ± 1.14     |
| Platelets (10 <sup>3</sup> /mm <sup>3</sup> )             | 864 ± 15.3      | 828 ± 46.0    | 831 ± 50.2     | 927 ± 66.8      |
| Erythrocytes (10 <sup>6</sup> /mm <sup>3</sup> )          | 9.83 ± 0.133    | 10.38 ± 0.221 | 10.18 ± 0.138  | **7.83 ± 0.484  |
| Reticulocytes (10 <sup>6</sup> /mm <sup>3</sup> )         | 0.20 ± 0.019    | 0.19 ± 0.024  | 0.19 ± 0.015   | **0.46 ± 0.067  |
| <b>FEMALE</b>   |                 |               |                |                 |
| Leukocytes (10 <sup>3</sup> /mm <sup>3</sup> )            | 4.08 ± 0.347    | 3.34 ± 0.221  | 2.98 ± 0.338   | 3.86 ± 0.702    |
| Lymphocytes (10 <sup>3</sup> /mm <sup>3</sup> )           | 3.12 ± 0.289    | 2.44 ± 0.144  | **2.19 ± 0.217 | **2.13 ± 0.120  |
| Segmented neutrophils (10 <sup>3</sup> /mm <sup>3</sup> ) | 0.83 ± 0.065    | 0.82 ± 0.093  | 0.72 ± 0.151   | 1.61 ± 0.706    |
| Eosinophils (10 <sup>3</sup> /mm <sup>3</sup> )           | 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 <sup>3</sup> )                 | 44.0 ± 0.42     | 45.3 ± 0.26   | 44.2 ± 0.47    | 45.0 ± 0.47     |
| Platelets (10 <sup>3</sup> /mm <sup>3</sup> )             | 669 ± 50.9      | 661 ± 30.2    | 726 ± 53.4     | 714 ± 19.4      |
| Erythrocytes (10 <sup>6</sup> /mm <sup>3</sup> )          | 10.21 ± 0.090   | 9.84 ± 0.110  | 9.88 ± 0.150   | *9.37 ± 0.400   |
| Reticulocytes (10 <sup>6</sup> /mm <sup>3</sup> )         | 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

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## APPENDIX K. CHEMICAL CHARACTERIZATION

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### 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*-configured stereoisomers were present at a concentration of approximately 2:1 relative to the *syn*-configured 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.

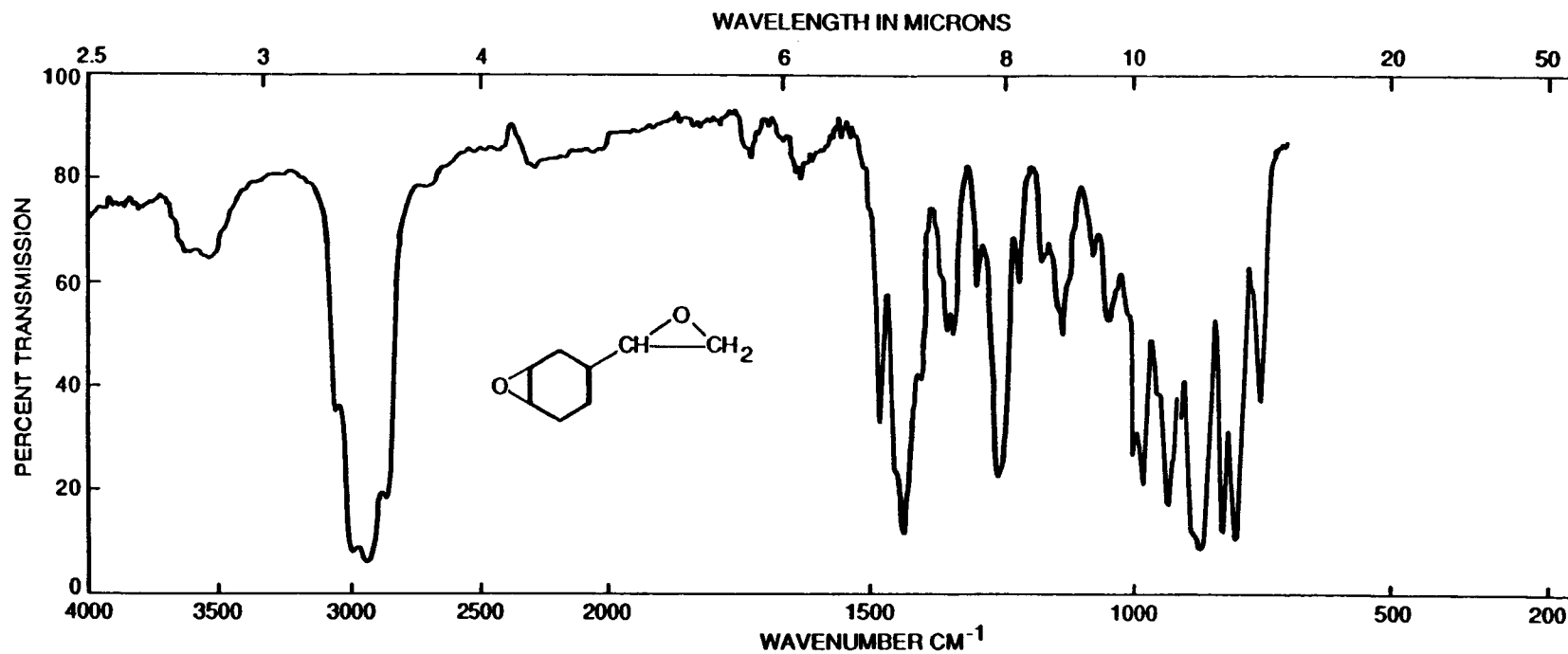


FIGURE K1. INFRARED ABSORPTION SPECTRUM OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (LOT NO. TF3-91614)

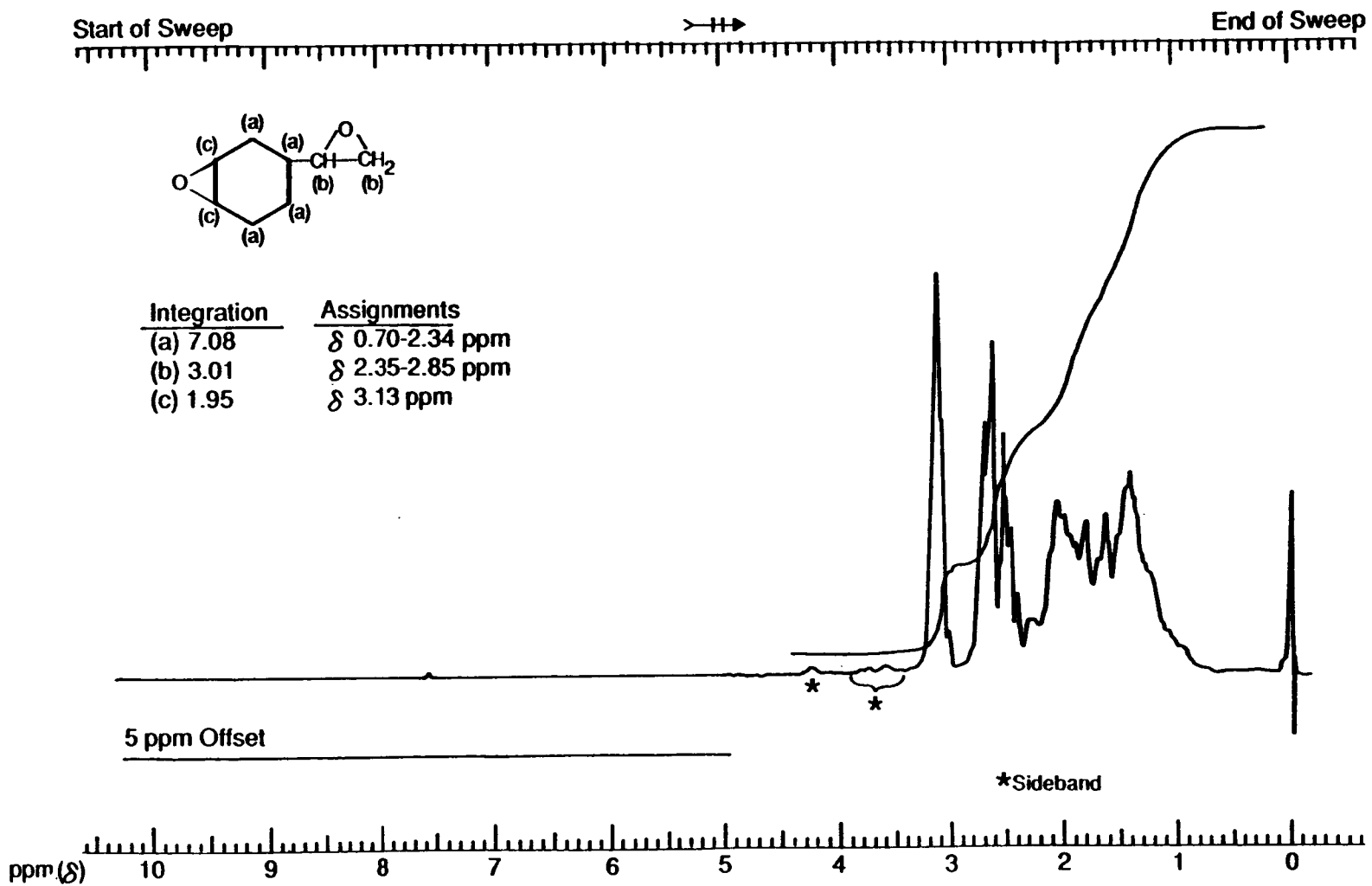


FIGURE K2. NUCLEAR MAGNETIC RESONANCE SPECTRUM OF 4-VINYL-1-CYCLOHEXENE DIEPOXIDE (LOT NO. TF3-91614)

# APPENDIX K. CHEMICAL CHARACTERIZATION

## 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  $\pm 10\%$  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  $\pm 10\%$  of the target concentrations approximately 93% (39/42) of the time throughout the studies; the three samples outside the  $\pm 10\%$  were within  $\pm 13\%$  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     |
|--|--|--|--|
| <b>Preparation</b><br>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. |
| <b>Maximum Storage Time</b><br>2 wk  | 2 wk                                   | 2 wk                                   | 2 wk                                   |
| <b>Storage Conditions</b><br>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

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# APPENDIX L. GENETIC TOXICOLOGY

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## 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  $6 \times 10^6$  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,  $3 \times 10^6$  cells were plated in medium and soft agar supplemented with Tft for selection of Tft-resistant cells (TK<sup>+/+</sup>), 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.

## APPENDIX L. GENETIC TOXICOLOGY

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*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 ( $21 \pm 2$  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.

## APPENDIX L. GENETIC TOXICOLOGY

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

(b) Revertants are presented as mean  $\pm$  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 TRIFLUOROTHYMININE 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) |
|---------------------------------|-----------------------|------------------------------|---------------------------------|---------------------|---------------------|
| <b>Trial 1</b>                  |                       |                              |                                 |                     |                     |
| 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                 |
| <b>Trial 2</b>                  |                       |                              |                                 |                     |                     |
| 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 ( $6 \times 10^5$ /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,  $3 \times 10^6$  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  $1 \times 10^6$  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  $1 \times 10^6$  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) |
|-----------------------------------|--------------|-------------|--------------------|-------------|-----------------|-----------|---------------|----------------------------------|
| <b>- S9 (c) Summary: Positive</b> |              |             |                    |             |                 |           |               |                                  |
| 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                            |
| <b>+ S9 (e) Summary: Positive</b> |              |             |                    |             |                 |           |               |                                  |
| 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<br>(µg/ml)                 | Total<br>Cells | No. of<br>Abs | Abs/<br>Cell | Percent<br>Cells<br>with Abs | Dose<br>(µg/ml)                 | Total<br>Cells | No. of<br>Abs | Abs/<br>Cell | Percent<br>Cells<br>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                              | 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

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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

## APPENDIX M. AUDIT SUMMARY

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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.